

## Adjuvant surgery for advanced extrahepatic cholangiocarcinoma

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### Abstract

Patients with Stage IV cholangiocarcinoma are currently not considered to be surgical candidates and are typically offered systemic chemotherapy. Recently, several novel systemic chemotherapy regimens have allowed an initially unresectable cholangiocarcinoma to be resectable. The aim of this article is to present the usefulness of adjuvant surgery in a case of advanced cholangiocarcinoma that was successfully treated with gemcitabine. A 72-year-old man was diagnosed with distal cholangiocarcinoma with liver metastases (cT2N0M1, Stage IV). He underwent metal stent placement in the duodenum to alleviate jaundice. After 18 courses of chemotherapy using gemcitabine without severe drug toxicities, a computed tomography scan showed that the liver metastases in S6 and S7 had disappeared. The patient underwent subtotal stomach-preserving pancreaticoduodenectomy and lymph node dissection. The pathological stage was pT2N0M0, Stage I B. The patient underwent 6 cycles of adjuvant chemotherapy using gemcitabine. The patient is alive

and well 6 years and 9 mo after the diagnosis.

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**Key words:** Extrahepatic cholangiocarcinoma; Adjuvant surgery; Conversion surgery; Chemotherapy; Gemcitabine

**Core tip:** Patients with Stage IV cholangiocarcinoma are currently not considered to be surgical candidates and are typically offered systemic chemotherapy. Recently, several novel systemic chemotherapy regimens have allowed an initially unresectable cholangiocarcinoma to be resectable. In a patient with advanced extrahepatic cholangiocarcinoma, gemcitabine (GEM) induced a dramatic reduction of the tumor, which led to curative resection and a long-term survival of 6 years and 9 mo. This result suggests the possibility of advantages of using GEM for the treatment of advanced cholangiocarcinoma, and GEM-based chemotherapy could be performed more often for unresectable cholangiocarcinomas.

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### INTRODUCTION

Cholangiocarcinoma continues to exhibit poor survival rates compared with other gastrointestinal malignancies<sup>[1-4]</sup>. Most cholangiocarcinoma patients are not surgical candidates. Patients with Stage IV cholangiocarcinoma are currently inoperable and are typically offered systemic chemotherapy. The most promising approaches involve

the use of single agents such as gemcitabine (GEM), which has been shown to be effective against cholangiocarcinoma in phase II trials<sup>[5-7]</sup>. In these trials, the response rates for GEM ranged from 8% to 36%, and the overall survival (OS) ranged from 6.3 to 16 mo. We describe a rare case of stage IV cholangiocarcinoma with liver metastases that was initially deemed unresectable and became resectable after GEM chemotherapy and showed a favorable outcome.

## CASE REPORT

The patient was a 72-year-old man referred from a local hospital complaining of jaundice. The laboratory data on admission showed the following elevated values: total bilirubin (T-bil), 6.2 mg/dL (normal range, 0.2-1.2 mg/dL); lactic acid dehydrogenase, 243 U/L (124-232 U/L); alkaline phosphatase 354 U/L (120-320 U/L); and  $\gamma$ -glutamyl transpeptidase, 181 U/L (5-55 U/L). All the tumor markers tested were within the normal limits: carcinoembryonic antigen (CEA), 2.3 ng/mL (normal range, < 5.0 ng/mL), and carbohydrate antigen 19-9, 12.0 U/mL (< 37 U/mL). Abdominal computed tomography (CT) and ultrasonography showed mild dilatation of the common bile duct and bilateral dilation of the intrahepatic bile ducts. Abdominal computed tomography angiography (CTA) detected wall thickening in the distal common bile duct, and the lesion was enhanced by contrast (Figure 1). CT and CTA showed two liver metastases, which measured 8 mm (S6) and 8 mm (S7) in diameter (Figure 2). According to the Union Internationale Contre le Cancer (UICC) guidelines, the patient was diagnosed with lower cholangiocarcinoma (cT2N0M1, Stage IV)<sup>[8]</sup>.

The patient underwent successful placement of a self-expandable metal duodenal stent to relieve jaundice. The patient received a total of 18 cycles of GEM. GEM was administered intravenously at a dose of 800 mg/m<sup>2</sup> per day on days 1, 8, and 15 in a 28-d cycle. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria Grading System (Version 2.0, April 1999)<sup>[9]</sup>. Severe drug toxicities (grade 3 or 4) were not observed.

After 18 cycles of chemotherapy, CT showed that the two liver metastases in S6 and S7 disappeared. The tumor was clinically downstaged to Stage I B (cT2N0M0).

Four weeks after the completion of chemotherapy, the operation was successfully performed. Peritoneal lavage cytology demonstrated no cancer cells in the abdominal cavity. No microscopic invasion of the resected bile duct stump was observed in an intraoperative frozen specimen. The patient underwent curative resection consisting of SSPPD with D2 lymphadenectomy without resecting any other organs.

Tumor cells were detected in the distal bile duct upon microscopic examination (Figure 3). According to the UICC guidelines, the pathological classification of the tumor was cT2N0M0 Stage I B. The patient was discharged on postoperative day 61 in good condition.



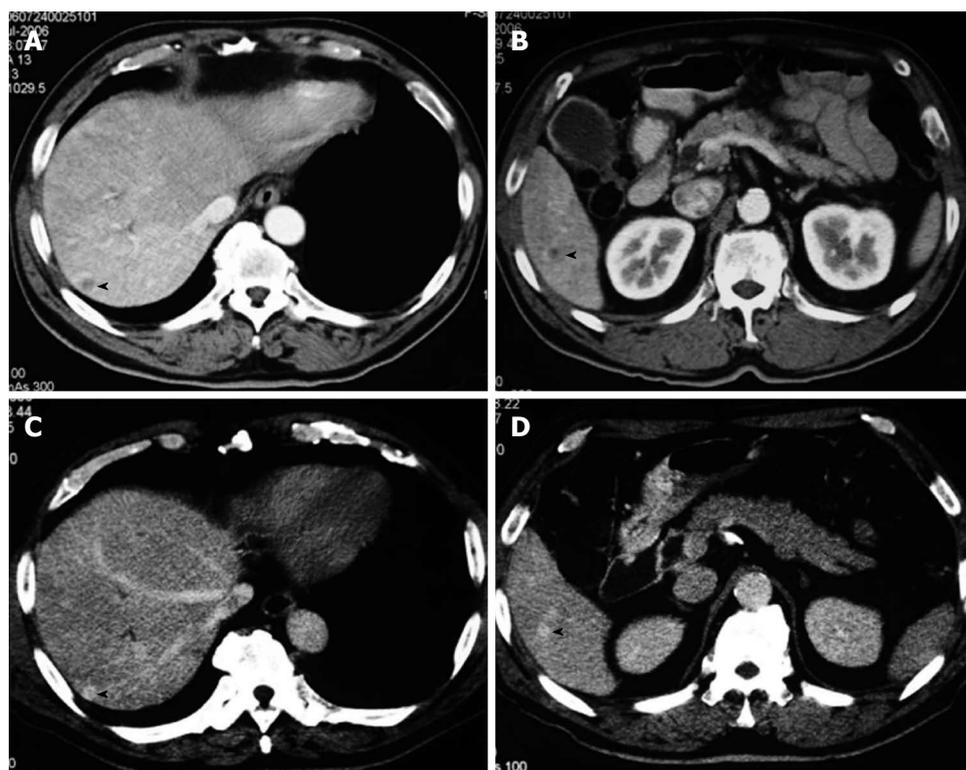
**Figure 1** Abdominal computed tomography angiography image of the common bile duct. Thickening of the wall of the distal common bile duct, which enhances with contrast, was observed (arrowhead).

The patient subsequently received six cycles of adjuvant GEM chemotherapy similar to the preoperative regimen. The patient is alive at 6 years and 9 mo after the diagnosis and 5 years after the surgery.

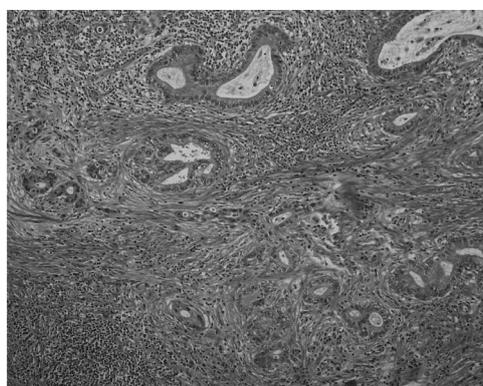
## DISCUSSION

The prognosis of patients with cholangiocarcinoma is poor, with a five-year survival rate of approximately 25% to 55%<sup>[1-4]</sup>. To overcome this clinical challenge, several strategies, including adjuvant chemotherapy, adjuvant radiotherapy, and adjuvant chemoradiotherapy have been considered for treating cholangiocarcinoma<sup>[10-13]</sup>. Few randomized clinical trials have evaluated the utility of adjuvant therapy following R0 resection of cholangiocarcinoma, and most of the current studies are small and retrospective. Therefore, no standard adjuvant modalities have been universally adopted for the treatment of cholangiocarcinoma, and the role of chemotherapy for unresectable cholangiocarcinoma has not been established. Although there has been no standard chemotherapy for cholangiocarcinoma, GEM has been the most actively used agent against cholangiocarcinoma. We treated a patient with advanced extrahepatic cholangiocarcinoma with liver metastases. The patient showed a dramatic response to GEM, which led to curative resection and long-term survival of more than 6 years. GEM may be an effective chemotherapeutic agent for treating cholangiocarcinoma, and a randomized clinical trial needs to be performed.

The feasibility of adjuvant surgery for cholangiocarcinoma has not been determined. Recently, in colorectal, gastric, and pancreatic cancer, several authors have reported “conversion surgery” or “adjuvant surgery”<sup>[14-16]</sup>. Suzuki *et al*<sup>[14]</sup> demonstrated that adjuvant surgery was effective in 20 advanced gastric cancer patients (Stage IV) based on liver or distant lymph node metastasis. The overall survival of patients in the partial response and curative resection groups was prolonged. The survival of patients with H or N factor was also prolonged when they received curative surgery. However, the survival of



**Figure 2** Abdominal computed tomography and computed tomography angiography images at two different levels are shown. A: Computed tomography (CT) showed a low-density mass measuring 8 mm in diameter located in segment 7 of the liver (arrowhead); B: CT showed a low-density mass measuring 8 mm in diameter in segment 6 (arrowhead); C: Computed tomography angiography (CTA) demonstrated an enhancing mass lesion at the same location as in Figure 2A (arrowhead); D: CTA demonstrated an enhancing mass lesion at the same location as in Figure 2B (arrowhead).



**Figure 3** Histopathologic appearance of the cholangiocarcinoma (hematoxylin and eosin,  $\times 200$ ). Tumor cells were detected in the distal bile duct on microscopic examination.

patients with P factor was not prolonged. Locally advanced pancreatic cancer may be a good indication for adjuvant surgery after sustained favorable responses to chemotherapy, even in patients with initially unresectable disease<sup>[6]</sup>. In 2013, Kato *et al*<sup>[17]</sup> reported that eight patients with initially unresectable advanced biliary tract cancer who underwent adjuvant surgery had significantly longer survival than 14 patients who were unable to undergo surgery. Of the eight patients in the surgery group, four patients had gallbladder carcinoma and four patients had intrahepatic cholangiocarcinoma. To our knowledge, from 1983 to 2013, in the field of bile duct cancer, only

16 cases in nine reports underwent adjuvant surgery, including the cases in the report<sup>[17-25]</sup> (Table 1). Of the 16 patients, 10 patients received GEM, 3 received S-1, 2 received GEM and S-1, 1 received GEM combined with cisplatin and fluorouracil, and 1 received cisplatin/interferon  $\alpha$ -2b/doxorubicin/fluorouracil-combination chemotherapy. None of the 16 cases involved extrahepatic cholangiocarcinoma. To the best of our knowledge, this is the first report of adjuvant surgery for extrahepatic cholangiocarcinoma.

Medical oncologists and surgeons have identified surgical candidates among patients with initially unresectable colorectal and gastric cancer who responded favorably to multimodal treatment<sup>[14,15]</sup>. In some cases, the addition of surgery resulted in increased long-term survival. Surgical resection coupled with multimodal treatment is called “adjuvant surgery.” Surgical resection can be classified as curative (no evidence of remaining disease after surgery) or palliative (remaining disease after surgery). Therefore, adjuvant surgery aims to be curative and not palliative after the response to chemotherapy<sup>[14]</sup>.

In a strategy involving adjuvant surgery, adjuvant chemotherapy is considered necessary after the operation. In our patient, the liver metastases showed a surprising complete response without severe toxicity after GEM chemotherapy. Additionally, the patient received adjuvant chemotherapy using GEM as an outpatient and developed no adverse reactions. In previous phase II studies using single-agent GEM, major adverse reactions included

**Table 1** Cases of advanced bile duct cancer treated with adjuvant surgery following effective chemotherapy

Ref.	Diagnosis	Metastasis/invasion	Chemotherapy regimen	Response
Slupski <i>et al</i> <sup>[18]</sup>	IntraHepatic cholangiocarcinoma	Lung metastases	CDDP, 5-FU, IFN, doxorubicin	PR
Shirabe <i>et al</i> <sup>[19]</sup>	Gallbladder cancer	Para-aortic LNs	GEM, CDDP, 5-FU	PR
Kitajima <i>et al</i> <sup>[20]</sup>	Gallbladder cancer	Dissemination	S-1	CR
Morimoto <i>et al</i> <sup>[21]</sup>	Gallbladder cancer	Liver metastasis	GEM	CR
Kanaji <i>et al</i> <sup>[22]</sup>	IntraHepatic cholangiocarcinoma	Dissemination	S-1	CR
Kim <i>et al</i> <sup>[23]</sup>	IntraHepatic cholangiocarcinoma	Portal vein invasion	GEM	PR
Ohno <i>et al</i> <sup>[24]</sup>	Ampulla of Vater cancer	Liver metastasis	GEM, S-1	CR
Hasegawa <i>et al</i> <sup>[25]</sup>	Gallbladder cancer	Hepatic invasion	S-1, para-aortic LN	PR
Kato <i>et al</i> <sup>[17]</sup>	Intrahepatic cholangiocarcinoma	Hepatic vein invasion	GEM	SD
	Intrahepatic cholangiocarcinoma	Hepatic vein invasion	GEM	PR
	Intrahepatic cholangiocarcinoma	Arterial invasion	GEM	SD
	Intrahepatic cholangiocarcinoma	Insufficient remnant liver volume	GEM	PR
	Gallbladder cancer	Arterial invasion	GEM	SD
	Gallbladder cancer	Arterial invasion	GEM	PR
	Gallbladder cancer	Arterial invasion portal vein invasion	GEM	SD
	Gallbladder cancer	Arterial invasion	GEM	SD

CDDP: Cisplatin; 5-FU: Fluorouracil; IFN: Interferon; PR: Partial response; CR: Complete response; GEM: Gemcitabine; LN: Lymph node; SD: Stable disease.

neutropenia, leukopenia, and anemia were observed with little severe toxicity<sup>[5-7]</sup>. The results suggest that GEM is suitable for outpatients because of its mild toxicity.

The UK ABC-02 study defined the standard of care for unresectable advanced biliary tract cancer<sup>[26]</sup>. Valle *et al*<sup>[26]</sup> reported that cisplatin with GEM (GEMC) was associated with a significant survival advantage compared with GEM alone. The median OS was 11.7 mo for GEMC and 8.1 mo for GEM alone<sup>[26]</sup>. A Japanese trial of 83 patients using the same treatment regimens as UK ABC-02 showed the median survival and overall response rate of GEMC *vs* GEM alone were 11.2 mo *vs* 7.7 mo and 19.5% *vs* 11.9%, respectively. These results were consistent with the results of the UK ABC-02 study. GEMC was found to be effective and well tolerated, which indicates that it could also be a standard regimen for Japanese patients<sup>[27]</sup>.

In conclusion, in a patient with advanced extrahepatic cholangiocarcinoma, GEM induced a dramatic reduction of the tumor, which led to curative resection. The patient was still living 6 years and 9 mo after the study. The results suggest possible advantages of using GEM for the treatment of advanced cholangiocarcinoma. GEM-based chemotherapy could be more commonly administered for unresectable cholangiocarcinoma. Furthermore, “adjuvant surgery” (*i.e.*, R0 resection) may significantly contribute to curing cholangiocarcinoma. An evidence-based consensus should be developed on potentially resectable cholangiocarcinoma with liver metastases in each hospital.

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