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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.


INTRODUCTION
Cholangiocarcinoma continues to exhibit poor survival rates compared with other gastrointestinal malignancies[5-6]. 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[5-7]. 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 γ-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 dilation of the common bile duct and bilateral dilation of the intrahepatic bile ducts. Abdominal computed tomography angiography (CTA) showed a favorable outcome. 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%[11-14]. To overcome this clinical challenge, several strategies, including adjuvant chemotherapy, adjuvant radiotherapy, and adjuvant chemoradiotherapy have been considered for treating cholangiocarcinoma[10-13]. 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 becoming resectable after GEM chemotherapy and showed a favorable outcome.
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 [16]. In 2013, Kato et al. [17] 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 [17-25] (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 α-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 [14,15]. 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 [14].

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...
neutropenia, leukopenia, and anemia were observed with little severe toxicity\textsuperscript{2,3}. The results suggests 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\textsuperscript{25,26}. Valle \textit{et al}\textsuperscript{26} 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\textsuperscript{26}. 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\textsuperscript{27}.

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” (\textit{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.

\textbf{REFERENCES}


\textbf{Table 1 Cases of advanced bile duct cancer treated with adjuvant surgery following effective chemotherapy}

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Diagnosis</th>
<th>Metastasis/invasion</th>
<th>Chemotherapy regimen</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slupski \textit{et al}\textsuperscript{32}</td>
<td>Intrahepatic cholangiocarcinoma</td>
<td>Lung metastases</td>
<td>CDDP, 5-FU, IFN, docorubicin</td>
<td>PR</td>
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<tr>
<td>Shirabe \textit{et al}\textsuperscript{36}</td>
<td>Gallbladder cancer</td>
<td>Para-aortic LNs</td>
<td>GEM, CDDP, 5-FU</td>
<td>PR</td>
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<td>Kitajima \textit{et al}\textsuperscript{39}</td>
<td>Gallbladder cancer</td>
<td>Dissemination</td>
<td>S-1</td>
<td>CR</td>
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<td>Morimoto \textit{et al}\textsuperscript{35}</td>
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<td>GEM</td>
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<td>Kanaji \textit{et al}\textsuperscript{22}</td>
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<td>Kim \textit{et al}\textsuperscript{22}</td>
<td>Intrahepatic cholangiocarcinoma</td>
<td>Portal vein invasion</td>
<td>GEM</td>
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<td>Ohno \textit{et al}\textsuperscript{34}</td>
<td>Ampulla of vater cancer</td>
<td>Liver metastasis</td>
<td>GEM, S-1</td>
<td>PR</td>
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<td>Hasegawa \textit{et al}\textsuperscript{22}</td>
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<td>Hepatic invasion</td>
<td>S-1, para-aortic LN</td>
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<td>Kato \textit{et al}\textsuperscript{27}</td>
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<td>Hepatic vein invasion</td>
<td>GEM</td>
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<td>Arterial invasion</td>
<td>GEM</td>
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<td>Insufficient remnant liver volume</td>
<td>GEM</td>
<td>PR</td>
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CDDP: Cisplatin; 5-FU: Fluorouracil; IFN: Interferon; PR: Partial response; CR: Complete response; GEM: Gemcitabine; LN: Lymph node; SD: Stable disease.


