Clinical results of intra-arterial adjuvant chemotherapy for prevention of liver metastasis following curative resection of biliary tract cancer

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Abstract
Background. This is a report on the clinical results of intra-arterial adjuvant chemotherapy in the prevention of liver metastasis following curative resection of biliary tract cancer. Methods. Nineteen patients of advanced biliary tract cancer underwent a pathologically radical operation between 2001 and 2006 (8 M and 11 F; mean age 66.2 years). Intra-arterial adjuvant chemotherapy with CDDP and 5-FU was performed selectively for 9 patients. The control group comprised 10 patients. Age, gender, staging of the disease, resection of the portal vein, postoperative radiotherapy, histological liver invasion as demographics and clinical characteristics were compared between the two groups. Results. Demographics and clinical characteristics were similar in the two groups. Liver metastasis occurred in 4 of 9 patients (44.4%) in the chemotherapy group and in 5 of 10 patients (50%) in the control group. There was no difference in the rate of liver metastasis between the two groups. The median survival term was 23.3 months for 9 patients who underwent the intra-arterial adjuvant chemotherapy, whereas the median survival term for 10 patients who were curatively resected without intra-arterial adjuvant chemotherapy was 21.7 months. The median survival term was statistically similar in both groups. Furthermore, in the recurrence-free survival, there was no major difference between the chemotherapy and control groups statistically. Conclusions. In the patients with advanced biliary tract cancer who underwent the curative operation, the intra-arterial adjuvant chemotherapy could not suppress the rate of liver metastasis nor improve cumulative survival.

Key Words: Biliary tract cancer, intra-arterial chemotherapy, adjuvant therapy

Introduction
In addition to the difficulty of early biliary tract cancer diagnosis, even if we could perform a radical operation for patients of biliary tract cancer, patients cannot be guaranteed long-term survival.

In the present conditions, histological curative operation and pertinent chemotherapy in the prevention of early recurrence is important in improving the prognosis of biliary tract cancer patients. This is a report on the clinical results of intra-arterial adjuvant chemotherapy (in the prevention of liver metastasis) with CDDP and 5-FU performed on patients with biliary tract cancer who underwent a radical operation.

Methods
Of 19 patients (8 M and 11 F; mean age 66.2 years; range 45–80 years) with advanced biliary tract cancer who underwent a radical operation between October 2001 and September 2006, 3 had cancer of the Ampulla of Vater, 8 extrahepatic bile duct cancer, and 8 gallbladder cancer.

Diagnosis was confirmed in all patients by histological examination. The clinicopathological features of patients are given in Tables I and II. We performed post-surgery serial observation, i.e. conducting blood examinations, (dynamic) contrast-enhanced CT imaging, and ultrasonography on patients every 4 months. All data were analyzed in accordance with the latest versions of the Japanese classification of Biliary Tract Carcinoma [1].

Lymph node dissection is defined as the D factor, as follows: D0: no dissection of group 1 lymph nodes; D1: dissection of group 1 lymph nodes alone; D2: dissection of groups 1 and 2 lymph nodes; and, D3: dissection of groups 1, 2 and 3 lymph nodes.

According to the JCS, 9 patients had Stage III biliary tract cancer. The other 10 patients were diagnosed as...
Stage IV biliary tract cancer using the Japanese Classification of Biliary Tract Carcinoma. Operative procedures in the 19 patients are given in Tables I and II. All patients had D2 lymph node dissection. In 6 of the 19 patients, the portal vein involved in the biliary tract cancer was resected circularly and reconstructed in end-to-end fashion. Intra-arterial adjuvant chemotherapy was selectively performed for 9 patients who consented to our proposal. Patients who had chronic hepatitis, arterial anomaly and postoperative stenosis of the hepatic artery were excluded. The control group who underwent resection without adjuvant chemotherapy comprised 10 patients. Age, gender, staging of the disease (according to the latest version of the Japanese Classification of Biliary Tract Carcinoma), resection of the portal vein, presence of histological liver invasion, postoperative radiotherapy as demographics and clinical characteristics were compared between the two groups.

**Statistical analysis**

Continuous variables were reported as the mean ± standard deviation and compared using the Mann-Witney U-test. Categorical variables were compared using the Fisher test. A two-sided p-value < 0.05 was considered statistically significant.

**Intra-arterial adjuvant chemotherapy (in the proper hepatic artery)**

Using the Seldinger technique, the catheter was placed in the proper hepatic artery via the right femoral artery 4 weeks after surgery. The catheter was connected to the arterial infuser port, which was buried underneath the skin in the right femoral region. Intra-arterial infusion chemotherapy was started soon afterwards. The protocol of the chemotherapy was as follows: intra-arterial bolus injection of CDDP 10 mg/body and continuous intra-arterial infusion of 5-FU.
500 mg/body for 180 min. We repeated this menu weekly as much as possible throughout the outpatient department.

**Results**

**Toxicity**

There were no local side effects at the site of the arterial infuser port. During the treatment, we observed liver abscess (grade 3 according to Common Terminology/Criteria for Adverse Events (CTCAE)) and anorexia (grades 1 and 2 (CTCAE)) in two patients and bone marrow suppression (grade 1 (CTCAE)) in one.

**Demographics and clinical characteristics**

Demographics and clinical characteristics were similar between the two groups, except for resection of the portal vein (Table III). The chemotherapy group had significantly more patients with resection of the portal vein compared to the control group. Liver metastasis occurred in 4 of 9 patients (44%) in the chemotherapy group and in 5 of 10 (50%) in the control group (Table IV). There was no difference statistically between the two groups. In the chemotherapy group, 4 of 9 patients died from liver metastasis and 2 of 9 patients from peritoneal seeding. In the control group, 5 of 10 patients died from liver metastasis and 1 of 10 patients from peritoneal seeding. The causes of death were statistically similar in the two groups (Table V).

**Survival**

Using Kaplan-Meier regression analysis, the median survival term was 23.3 months for 9 patients who underwent intra-arterial adjuvant chemotherapy following curative operation and 21.7 months for 10 patients who were curatively resected without the intra-arterial adjuvant chemotherapy. The difference in cumulative survival rate between the two groups was not statistically significant (Figure 1). In the recurrence-free survival, there was no significant difference statistically between the chemotherapy and control groups (the chemotherapy group, 17.2 months and the control group, 19.2 months) (Figure 2).

**Discussion**

Biliary tract cancer is highly associated with a dismal prognosis and with a 1-year survival rate of 25% [2]. Surgical resection or liver transplantation remains the only curative treatment for biliary tract cancer. However, most patients are candidates for palliative chemotherapy at an initial presentation, because definitive diagnosis is often delayed until most lesions are at an advanced stage [3–6]. Systemic chemotherapy for unresectable biliary tract cancer can improve the quantity and quality of life in those patients [7]. A regimen of 5-FU and platin analogue is effective with response rates ranging from 21% to 40%.

The combination of epirubicin, cisplatin, and continuous infusion of 5-FU is often administered in patients with unresectable biliary tract cancer [8]. Gemcitabine or paclitaxel, new drugs, have demonstrated response rates ranging from 0% to 16%, with a median survival term of approximately 6 months [9]. If we could perform radical operations on patients with advanced biliary tract cancer, most would be guaranteed approximately only 2 years as the median survival term, since local recurrence and distant metastasis frequently occur after radical operation [10,11]. Moreover, many patients who have undergone a radical operation for advanced biliary tract cancer have died from liver metastasis.

<table>
<thead>
<tr>
<th>Demographics and clinical characteristics</th>
<th>Chemotherapy group (n=9)</th>
<th>Control group (n=10)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.1 ± 10.7</td>
<td>66.3 ± 11.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Gender</td>
<td>M: F = 3: 6</td>
<td>M: F = 5: 5</td>
<td>0.9</td>
</tr>
<tr>
<td>Staging (JCS)</td>
<td>Stage III: Stage IV = 3:6</td>
<td>Stage III: Stage IV = 6:4</td>
<td></td>
</tr>
<tr>
<td>Resection of portal vein</td>
<td>+: − = 5:4</td>
<td>+: − = 1:9</td>
<td>0.03</td>
</tr>
<tr>
<td>Postoperative radiation</td>
<td>+: − = 3:6</td>
<td>+: − = 2:8</td>
<td>0.5</td>
</tr>
<tr>
<td>Histological liver invasion</td>
<td>+: − = 4:5</td>
<td>+: − = 3:7</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table IV. Comparison of the rate of liver metastasis between chemotherapy group and control group.

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Chemotherapy group (n=9)</th>
<th>Control group (n=10)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver metastasis</td>
<td>4 (44%)</td>
<td>5 (50%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Peritoneal seeding</td>
<td>2</td>
<td>1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table V. Comparison of the cause of death between chemotherapy group and control group.
In improving the prognosis of patients who undergo radical surgery for biliary tract cancer, prevention of liver metastasis is thought to be important. Administering the anticancer drug directly into the hepatic artery, which supplies blood to the bile duct and gallbladder, has the potential to increase anticancer agent concentration in the cancerous tissue and lead to improved tumor killing in the liver [12–14]. Sullivan et al. may have shown the first instance of recanalization of a completely obstructed common hepatic duct following hepatic arterial infusion of fluoruridine [15]. With hepatic arterial infusion of anticancer drugs, they have a high hepatic extraction and can reach bile canaliculi at high concentration with minimal systemic toxicity. Administration of cisplatin through the hepatic artery provides a high concentration in blood perfusion, whereas the systemic concentration of cisplatin is low [16].

In our study, no grade 4 toxicity was observed; liver metastasis occurred in 4 of 9 patients (44%) in the chemotherapy group and in 5 of 10 patients (50%) in the control group. Intra-arterial adjuvant chemotherapy could not suppress the rate of liver metastasis.

Furthermore, the median survival term was 23.3 months for 9 patients who underwent the intra-arterial adjuvant chemotherapy after surgery. On the contrary, the median survival term was 21.7 months for 10 patients who were curatively resected without the intra-arterial adjuvant chemotherapy. The cumulative survival rate was not improved by the intra-arterial adjuvant chemotherapy. In conclusion, intra-arterial adjuvant chemotherapy for biliary tract cancer is not enough to suppress liver metastasis nor afford long-term survival to patients.

References