Indications for Extended Hepatectomy in the Management of Stage IV Hilar Cholangiocarcinoma

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Hypothesis: In operations for hilar cholangiocarcinoma, simultaneous extended hepatectomy and removal of extrahepatic bile ducts are considered curative resection. However, the effect of extended operations for stage IV hilar cholangiocarcinoma on survival is still unclear.


Patients and Methods: Fifty-seven patients with stage IVA or IVB hilar cholangiocarcinoma were enrolled. Thirty-three of these patients underwent extended hepatectomy to achieve macroscopic radical resection (surgical group). A self-expandable metallic biliary stent (EMBS) was implanted in 24 patients (EMBS group) in whom radical treatment was judged to be impossible.

Main Outcome Measure: Survival in patients with stage IV hilar cholangiocarcinoma treated by means of extended operation or stenting.

Results: Survival was 25.7±40.9 months in the surgical group vs 6.5±5.8 months in the EMBS group (P=.03). In the surgical group, radical resection results were macroscopically and histologically successful in 21 patients (64%). In patients with stage IVB disease, survival did not differ between the surgical and EMBS groups.

Conclusions: In patients with stage IVA disease, radical extended hepatectomy should be performed after excluding patients who have extensive invasion of the hepatic artery or portal vein. However, in patients with stage IVB disease, with carcinomatous peritonitis or distant metastasis, there is little possibility of achieving long-term survival with surgery, and stent implantation should be the first choice.

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Hilar cholangiocarcinoma shows less of an association with carcinomatous peritonitis and distant metastasis and is relatively localized when compared with intrahepatic cholangiocarcinoma. If adequate local treatment (ie, extended hepatectomy including the caudate lobe) is performed in patients without cirrhosis, long-term survival might be attained. However, stage IV hilar cholangiocarcinoma tends to invade the portal vein and the hepatic arteries and also metastasizes to lymph nodes or liver; therefore, extended hepatectomy, including excision of involved vessels and reconstruction, and extended lymph node dissection are essential for radical surgery to ensure that no residual cancer remains at the local site. Although surgeons tend to recommend an extended operation to achieve radical resection, some patients have a better quality of life with stenting of the bile duct alone, when the risk of surgery, extent of invasion, and severity of symptoms are considered.

We treated 96 patients with hilar cholangiocarcinoma in the Wakayama Medical University Hospital between 1981 and 2001, and 73 of these patients had stage IVA or IVB disease according to the TNM classification (International Classification of Diseases for Oncology code C24.0-12) of the Union Internationale Contre le Cancer. Thirty-eight patients with stage IV disease underwent surgery. Although 5 patients had palliative tumor resection or biliary drainage alone, 33 underwent extended hepatectomy with the aim of macroscopic radical resection. Of these 33 patients, 2 died in the hospital within 30 days after surgery. They had portal vein reconstruction but developed acute portal vein thrombosis and postoperative hemorrhage. A self-expandable metallic biliary stent (EMBS) was implanted in 24 of 35 patients in whom radical treatment was judged impossible on the basis of imaging data. The remaining 11 patients were treated before 1990 and underwent tube stenting after percutaneous transhepatic biliary drainage because EMBS was still being developed at that time. In this study,

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survival was compared between the 33 patients with stage IV disease who underwent extended hepatectomy and the 24 patients who underwent only EMBS implantation.

The diagnostic procedure for hilar cholangiocarcinoma at our department was as follows: Ultrasonography or computed tomography was performed to localize the tumor and to verify distant metastasis to the liver or other sites, presence of ascites, and extent of lymph node metastasis. If jaundice (a total bilirubin level of 5 mg/dL [85.5 µmol/L] or more) was present, percutaneous transhepatic biliary drainage was performed. Angiography was also performed to confirm the anatomic characteristics of the blood vessels and determine the presence of tumor invasion into the hepatic arteries and portal vein. Intrahepatic metastasis was studied by means of computed tomographic angiography. Cholangiography was performed by injecting contrast medium via the percutaneous transhepatic biliary drainage tube, and endoscopic retrograde cholangiopancreatography was simultaneously performed. Immediately thereafter, helical computed tomography was performed to visualize the bile duct 3-dimensionally. Since invasion of the caudate lobe is especially frequent in patients with hilar cholangiocarcinoma, the presence and severity of invasion into the caudate branch bile ducts was confirmed. In 4 patients in whom extent of invasion was unclear, percutaneous transhepatic cholangiography was performed for the biopsy to assess the actual tumor invasion. Recently, magnetic resonance cholangiography has been used, which allows the bile duct branches to be imaged without drainage.

Our surgical approach to stage IV hilar cholangiocarcinoma consisted of cholecystectomy and extrahepatic cholangiography, extended lobectomy, and caudate lobectomy at the site of substantial hepatic duct invasion and extended lymph node dissection including the para-aortic lymph nodes. If there was similar invasion of both the left and right hepatic ducts, extended right lobectomy was the basic operation. In 3 patients with high risk of postoperative hepatic failure, percutaneous transhepatic portal vein embolization was performed preoperatively and then extended right lobectomy. An EMBS was implanted in 24 patients in whom a radical operation was impossible, including 12 patients with severe invasion of the portal vein and hepatic arteries; 6 patients with carcinomatous peritonitis; and 10 patients with distant metastasis to the liver, lungs, or bone. Two patients had carcinomatous peritonitis with distant metastasis, and 2 had carcinomatous peritonitis with severe invasion of major vessels. Stents were implanted by using the percutaneous transhepatic route via a percutaneous transhepatic biliary drainage fistula or endoscopic retrograde cholangiography via the papilla of Vater. A Wallstent (Boston Scientific Corp, Natick, Mass) that could be bent easily to follow the curvature of the bile duct or a S.M.A.R.T. CONTROL stent (Johnson & Johnson Co, Inc, New Brunswick, NJ) without shortening was used. In patients with obstruction of both the left and right hepatic ducts, 2 stents were combined whenever possible by using the side-by-side method or the stent-through-stent method to avoid incomplete drainage of bile duct branches. Extracorporeal radiotherapy with 6000 rad (60 Gy) was performed in 20 of the 24 patients, excluding those with carcinomatous peritonitis.

The cumulative survival rate was calculated by using the Kaplan-Meier method, and the significance of differences was assessed by using the log-rank test. We also used the χ² square test and t test, with P < .05 considered to indicate statistical significance.

**RESULTS**

Thirty-three patients with extended hepatectomy (surgical group) were compared with 24 patients with EMBS implantation (EMBS group). No sex differences were observed, but the surgical group was younger (mean ± SD, 58 ± 9 years; P = .008). Postoperative hospitalization was 58 ± 32 days in the surgical group, whereas it was 19 ± 11 days in the EMBS group (P < .001). However, survival time was 25.7 ± 40.9 months in the surgical group, which was significantly longer than the 6.5 ± 5.8 months in the EMBS group (P = .03) (Table 1).

The 33 patients in the surgical group consisted of 17 patients undergoing extended left lobectomy; 12, extended right lobectomy; 3, middle bisegmentectomy; and 1, left trisegmentectomy. Five required reconstruction of the hepatic artery and/or portal vein, and 5 also underwent pancreatecodudenectomy. The clinical stage was IVA in 27 patients and IVB in 6 patients. Radical resec-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Surgical Group</th>
<th>EMBS Group</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>No. of patients</td>
<td>33</td>
<td>24</td>
<td>NA</td>
</tr>
<tr>
<td>M/F ratios</td>
<td>19/14</td>
<td>17/7</td>
<td>.38</td>
</tr>
<tr>
<td>Age, y</td>
<td>58 ± 8</td>
<td>69 ± 13</td>
<td>.008</td>
</tr>
<tr>
<td>Postoperative hospitalization, d</td>
<td>58 ± 32</td>
<td>19 ± 11</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Mean ± SD survival, mo (median) [range]</td>
<td>25.7 ± 40.9</td>
<td>6.5 ± 5.8</td>
<td>.03</td>
</tr>
<tr>
<td></td>
<td>[0.6-198.4]</td>
<td>[1.2-63.5]</td>
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Abbreviations: EMBS, self-expandable metallic biliary stent; NA, not applicable.

*Data are given as mean ± SD unless otherwise indicated.

| Table 2. Operations in Patients With Stage IV Hilar Cholangiocarcinoma |
|-----------------------------------------------|----------------|--------------|---------|
| Operation                                      | No. of Patients | Curative Resection | Yes/No | Stage IVA/IVB |
| Extended left lobectomy*                       | 13             | 9/4          | 11/2    |
| Extended left lobectomy, partial resection of the large bowel | 1              | 1/0          | 1/0     |
| Extended left lobectomy, portal vein reconstruction | 1              | 0/1          | 0/1     |
| Extended left lobectomy, pancreaticoduodenectomy, portal vein reconstruction | 1              | 0/1          | 1/0     |
| Extended right lobectomy                       | 8              | 6/2          | 7/1     |
| Extended right lobectomy, removal of extrahepatic bile ducts, portal vein reconstruction | 2              | 2/0          | 2/0     |
| Extended right lobectomy, pancreaticoduodenectomy | 2              | 2/0          | 1/1     |
| Middle bisegmentectomy, removal of extrahepatic bile ducts | 3              | 1/2          | 2/1     |
| Left trisegmentectomy, pancreaticoduodenectomy | 1              | 0/1          | 1/0     |
| **Total**                                      | **33**         | **21/12**    | **27/6** |

*Extended left lobectomy indicates left lobectomy plus partial anterior segmentectomy.
†Extended right lobectomy indicates right lobectomy plus partial internal segmentectomy and partial caudate lobectomy.
tion was achieved according to histologic examination results in 21 (64%) of 33 patients (Table 2).

When the cumulative survival rates in the surgical and self-expandable metallic biliary stent (EMBS) groups were compared with the Kaplan-Meier method, the surgical group showed a significantly longer survival than did the EMBS group (P=.02) (Figure 1).

When the cumulative survival rates in the surgical and EMBS groups were compared with the Kaplan-Meier method, the surgical group showed a significantly longer survival than did the EMBS group (P=.02) (Figure 1).

However, when the cumulative survival rate in patients with stage IVB disease in the surgical group was compared with that in such patients in the EMBS group, survival did not differ significantly (Figure 2).

The therapeutic factors that influenced the prognosis in the surgical group were studied. Twenty-one patients with no residual cancer had significantly longer survival, as compared with survival in 12 patients with residual cancer (P=.007) (Figure 3).

Tumor factors that influenced the prognosis in the surgical group were also studied. No significant difference in long-term prognosis was seen between patients with and those without lymph node metastasis (A) or vascular invasion (B). C, However, among patients with distant metastasis, including carcinomatous peritonitis, there was a significant difference in long-term survival between the 28 patients without distant metastasis with stage IVA disease and the 5 patients with distant metastasis with stage IVB disease (P=.048) (Figure 4).
ied. No significant difference for long-term prognosis was seen between patients with and those without lymph node metastasis or vascular invasion. However, among patients with distant metastasis, including carcinomatous peritonitis, there was a significant difference in long-term survival between the 28 patients with stage IVA disease without distant metastasis and the 5 patients with stage IVB disease with distant metastasis ($P = .048$) (Figure 4).

The stent was implanted in the right hepatic duct alone in 11 patients; there was a percutaneous transhepatic cholangiographic route in 3 patients and an endoscopic retrograde cholangiographic route in 8 patients. Stents were implanted in both the left and right hepatic ducts in 13 patients; there were both endoscopic retrograde cholangiographic and percutaneous transhepatic cholangiographic routes in 7 patients and 2 percutaneous transhepatic cholangiographic routes in 6 patients. Patients with stenting of both the left and right hepatic ducts survived significantly longer, as compared with those who had stenting of the right hepatic duct alone ($P = .03$) (Table 3). When the cumulative survival rate in 18 patients without carcinomatous peritonitis was compared with that in 6 patients with carcinomatous peritonitis, survival was longer in the patients without carcinomatous peritonitis ($P = .007$). However, no significant difference in survival was seen between 14 patients without and 10 patients with distant metastasis ($P = .007$).

Table 3. Stenting in Patients With Stage IV Hilar Cholangiocarcinoma

<table>
<thead>
<tr>
<th>Implantation Site</th>
<th>No. of Patients</th>
<th>Age, Mean ± SD, y</th>
<th>Survival, Mean ± SD, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right hepatic duct (n = 11)</td>
<td>3 8</td>
<td>71 ± 14</td>
<td>107 ± 72</td>
</tr>
<tr>
<td>Left and right hepatic ducts (n = 13)</td>
<td>0 0</td>
<td>67 ± 13</td>
<td>257 ± 208†</td>
</tr>
</tbody>
</table>

Abbreviations: ERC, endoscopic retrograde cholangiography; NA, not applicable; PTC, percutaneous transhepatic cholangiography.
*For all 24 patients who underwent stent implantation, mean ± SD age was 69 ± 13 years and survival was 188 ± 175 days. No stents were placed in the left hepatic duct.
†$P = .03$, as compared with stent implantation in the right hepatic duct alone.

Figure 5. Tumor factors determining the prognosis in patients with stage IV disease who underwent stenting. A, When the cumulative survival rate in 18 patients without carcinomatous peritonitis was compared with that in 6 patients with carcinomatous peritonitis, survival was longer in the patients without carcinomatous peritonitis ($P = .007$). B, However, no significant difference in survival was seen between 14 patients without and 10 patients with distant metastasis.

Figure 6. Cumulative survival rate in patients with hilar cholangiocarcinoma after single or double stent implantation. Eleven patients with only the right hepatic duct stented had shorter survival, as compared with that in 13 patients with both ducts stented ($P = .007$).

Hilar cholangiocarcinoma extends horizontally along the bile duct and also spreads via the lymphatic vessels around the bile duct and via the nerves, and the boundary between the affected and healthy regions is often unclear. After Longmire et al$^{13}$ reported on right trisegmentec-
otomy in patients with hilar cholangiocarcinoma in 1973, therapeutic results improved a little. At the start of the 1980s, the importance of caudate lobectomy for hilar cholangiocarcinoma was recognized; invasion of the hepatic parenchyma in the caudate lobe and invasion of the caudate bile duct branches occurs in more than 30% of patients with hilar cholangiocarcinoma. Improvement of the long-term prognosis was attained with caudate lobectomy, and the rate of radical resection was also increased with concomitant caudate lobectomy.

When hepatectomy is performed for progressive hilar cholangiocarcinoma, extended right lobectomy is appropriate if the same extent of tumor invasion is observed on both sides. The reasons are reported as follows: (1) It is anatomically easier to perform a long excision of the left hepatic duct than of the right hepatic duct; (2) the junction of the left and right hepatic ducts is located to the right of the hepatic artery, and this region is susceptible to tumor invasion; (3) when excision of the portal vein is necessary, it is possible to obtain a sufficient length of vessel for reconstruction; and (4) percutaneous transhepatic portal vein embolization was useful for compensatory hypertrophy of the left hepatic lobe in performing extended right lobectomy safely. However, when the tumor shows rapid progression in patients with stage IV disease, it is probably more appropriate to perform extended left lobectomy with a small amount of liver as soon as possible.

As our data and that of others show, the prognosis with stage IV hilar cholangiocarcinoma was definitely better in patients undergoing curative resection than in those undergoing palliative surgery. However, even in 21 (64%) of 33 patients with radical resection, the 5-year survival rate was less than 20%. The main reason for this poor survival was that patients with stage IV hilar cholangiocarcinoma and involvement of the bile duct serosa show extensive invasion of the hepatoduodenal ligament and/or invasion of the portal vein and hepatic artery. If an operation is performed that permits vessel preservation by means of dissecting the portal vein and hepatic arteries in the hepatoduodenal ligament, residual cancer cells may invade lymphatic vessels or perineural tissue in the ligament, depending on anatomic characteristics, even if tumor does not invade the blood vessels. However, we found no significant difference in survival between patients with and those without without vascular invasion; long-term survival was possible after aggressive surgery, so extended vascular excision should be performed with the aim of negative surgical margin.

When severe invasion of both the portal vein and hepatic artery occurs in patients with stage IVA hilar cholangiocarcinoma, total hepatoduodenal ligamentectomy and pancreaticoduodenectomy have to be added to extended hepatectomy to achieve negative surgical margin. With such excessive invasion, the postoperative prognosis is tremendously poor, so stenting is selected. However, one should know the limitations of preoperative staging and of surgery experience and expertise involved in the decision to perform resection, even though imaging techniques, including computed tomography, ultrasonography, and magnetic resonance cholangiography, are advanced. Patients with stage IVB disease have both distant metastasis and carcinomatous peritonitis, so stent implantation is the best treatment. To improve quality of life, patients can be discharged after EMBS implantation and undergo outpatient radiotherapy. In a comparison of patients with stage IVC disease undergoing surgery with those undergoing stent implantation, we found no significant difference in survival. Early postoperative recovery was more difficult in the surgical group than in the EMBS group, and hospitalization was also significantly longer; therefore, the optimum therapy for patients with stage IVC disease appears to be immediate EMBS implantation. Unfortunately, there are no accurate data concerning quality of life in the present study; however, it is time we looked at quality of life measurements in judging surgical treatment of malignant disease, including hilar cholangiocarcinoma.

In our study, the most important prognostic factor for EMBS treatment was the presence of carcinomatous peritonitis. If there was no carcinomatous peritonitis, the average survival was 8 months if bilateral stents were implanted and radiotherapy was performed, even in patients with distant metastasis or severe invasion of the large vessels.

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