Topics: Treatment of patients with advanced gallbladder carcinoma with special reference to stage IV

Outcome of radical surgery for stage IV gallbladder carcinoma

KAZUO CHIIWA, MASASHIRO KAI, MOTOAKI NAGANO, MASAHIDE HIYOSHI, JIRO OHUCHIDA, and KAZUHIRO KONDO

First Department of Surgery, Miyazaki University School of Medicine, Miyazaki 889-1692, Japan

Abstract

Background/Purpose. The role of aggressive surgery for patients with stage IV gallbladder carcinoma was examined.

Methods. Cancers were classified according to the TNM system of the Japanese Society of Biliary Surgery. The survival of 37 patients with stage IV cancer (stage IVa, n = 15; stage IVb, n = 22) treated by surgical resection during the period January 1990 to December 2004 was examined and compared with the survival of 41 patients with stage IV disease not treated by surgical resection during the same period.

Results. The postoperative survival rate was significantly better for patients with resected stage IVa cancer than for patients with resected stage IVb disease and for those with nonresected stage IV disease. Survival in patients with N3 lymph node metastasis, liver metastasis, peritoneal dissemination, or vascular invasion was poor, like that in the nonresected group. Surgical resection without residual tumors (curability A and B) yielded a significantly better outcome than that with residual tumor (curability C). There were three 5-year survivors that were treated successfully by curative resection (curability A and B) and all had T4N0 disease.

Conclusions. These results suggest that surgical resection significantly improves survival even in patients with stage IV gallbladder carcinoma when N3 metastasis, liver metastasis, peritoneal dissemination, and vascular invasion are absent. Curative resection can be expected to produce long-term survival in selected patients with stage IV gallbladder carcinoma.

Introduction

The prognosis for gallbladder carcinoma, the most frequent biliary tract cancer, remains dismal even with recent advances in diagnostic modalities and surgical techniques. This is mainly because the disease is usually advanced before it is diagnosed and treated; there is a lack of symptoms and signs in the early stages.

It is generally recognized that surgical resection provides the only hope of long-term survival. The advantage of surgical resection has been reported for advanced gallbladder carcinoma even in the presence of lymph node metastasis. However, Benoist et al. and Bartlett et al. report poor results once lymph node metastasis occurs. The primary tumor (T), lymph node metastasis (N), and stage are well-known prognostic factors, with stage IV being the most advanced disease stage, and characterized by lymph node metastasis, direct liver invasion, vascular involvement, and/or distant metastasis. However, few studies have focused on the role of surgical resection for stage IV gallbladder carcinoma.

The aim of this study was to examine whether surgical resection affects the outcome of patients with stage IV gallbladder carcinoma. Therefore, outcomes and actual 5-year survival after surgical resection were examined. The outcomes and 5-year survival of patients with stage IV cancer who had not undergone surgical resection were examined as a reference.

Patients and methods

Ninety patients with gallbladder carcinoma underwent surgical resection at our University hospital between January 1990 and December 2004. Of these 90 patients, 37 patients with pathologically proven stage IV carcinoma, classified according to the TNM system of the Japanese Society of Biliary Surgery (Table 1) were identified and became the subjects of the study. Their medical records were analyzed, and final follow-up data were obtained in July 2005.

The 37 patients comprised 19 men and 18 women, with a mean age of 65 years (range, 38 to 84 years). Disease was stage IVa in 15 patients and stage IVb in


Table 1. Classification system and disease stages of gallbladder cancer

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Lymph node (N)</th>
<th>Liver (H), peritoneal (P), and distant (M) metastasis</th>
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<tbody>
<tr>
<td>T1: Tumor invasion limited to the mucosa or muscularis propria</td>
<td>N0: No regional lymph node metastasis</td>
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<tr>
<td>T2: Tumor invasion limited to the subserosa</td>
<td>N1: Metastasis in cystic duct and/or pericholedochal lymph node</td>
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<tr>
<td>T3: Tumor perforates the serosa or directly invades the liver &lt;5mm</td>
<td>N2: Metastasis in hepatoduodenal ligament, except N1, posterosuperior pancreatic head, and/or along the common hepatic artery</td>
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<tr>
<td>T4: Tumor extends more than 5 mm into the liver and/or into the hepatoduodenal ligament, portal vein, or hepatic arteries</td>
<td>N3: Metastasis in peripancreatic head (except posterosuperior pancreatic head), celiac, superior mesenteric, and/or paraaortic lymph node</td>
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H(-), P(-), M(-): No evidence of liver metastasis, peritoneal metastasis, or of distant metastasis, other than P and/or H, respectively

H(+), P(+), M(+): The presence of liver metastasis, peritoneal metastasis, and distant metastasis other than P and/or H, respectively

Final stage (judged on the basis of surgical and pathological findings)

Stage IVa: T3N2, T4N0, T2N3 without H, P, M
Stage IVb: T3N3, T4N2, T3N4 without H, P, M
Any T any N with H, P, M

According to the Japanese Society of Biliary Surgery

22 patients. The 15 cases of stage IVa were classified pathologically as T4N0 (n = 7), T4N1 (n = 4), T3N2 (n = 2), and T2N3 (n = 2) disease. The 22 cases of stage IVb disease were classified as T3 (n = 3) and T4 (n = 19) disease. Of the 22 patients who underwent surgical resection, 7 had liver metastasis and 2 had peritoneal dissemination. The remaining 13 patients with stage IVb disease had no liver metastasis, peritoneal dissemination, or distant metastasis (T3N3, n = 2; T4N2, n = 8; T4N3, n = 3).

The surgical procedures used in the 37 patients with stage IV disease were cholecystectomy (n = 6), excision of the gallbladder and liver bed (n = 11), anatomical resection of segments IV below and V of the liver (n = 16), and extended right or left hepatic lobectomy (n = 4). The extrahepatic bile duct was excised in 27 patients, and pancreatoduodenectomy was added in 4 patients. In general, anatomical resection of the segments IV below and V of the liver and lymph node dissection were performed as previously described. In brief, lymph node dissection in the hepatoduodenal ligament, below the pancreas head, along the common hepatic artery, and in the paraaortic region was carried out with or without resection of the extrahepatic bile duct. Six of the 37 patients (16%) underwent postoperative chemotherapy; 4 patients were given tegafur-uracil (UFT) orally, and 2 were given 5-fluorouracil (5-FU) + cisplatin (CDDP) intravenously.

An additional 41 patients with stage IV disease not treated by surgical resection were included for comparison. This group comprised 19 men and 22 women, with a mean age of 67 years (range, 37 to 89 years), and they were given “best supportive care.” Laparotomy was performed in 12 of these patients, probe laparotomy in 8 and gastrojejunoscopy or hepaticojejunoscopy in the other 4. Peritoneal dissemination was confirmed in 8 of the 12 patients. Disease stage was determined mainly on the basis of results of clinical imaging, such as direct cholangiography (endoscopic retrograde cholangiography, percutaneous transhepatic cholangiography), computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), or fluorodeoxyglucose-positron emission tomography (FDG-PET). The disease was classified as T4 in all 41 patients. Liver metastasis was present in 20 patients, and peritoneal dissemination was present in 12 patients, and most cancers were classified as stage IVb.

Fifteen patients (37%) in this group received either intravenous 5-FU+CDDP or oral UFT, as in the surgically resected group.

Postoperative survival curves in relation to surgical resection, TN factors, vascular invasion, liver metastasis, peritoneal dissemination, and curability were constructed by the Kaplan-Meier method, and differences in survival were examined by the log-rank test. Curability was classified as A, B, and C, based on the pathological examination. Curability A indicated a cancer-free surgical margin of more than 5 mm and greater extent of lymph node dissection than that of N metastasis. Curability B indicated a cancer-free surgical margin of 5 mm or less and the same extent of lymph node dissection and N metastasis. Curability C was a cancer-positive surgical margin; greater extent of N metastasis than that of lymph node dissection; or the presence of peritoneal dissemination, liver metastasis, or distant metastasis. Probability values less than 0.05 were considered significant.

Results

Postoperative survival of patients with stage IVa and IVb disease

The postoperative survival of patients with stage IV carcinoma who underwent surgical resection and the survival of those who did not undergo surgical resection are shown in Fig. 1. Survival was significantly better