Original Paper

Evaluation of Surgical Resection for Gallbladder Carcinoma at a Japanese Cancer Institute

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ABSTRACT

Background/Aims: Surgical resection is a radical treatment option for gallbladder carcinoma (GBC); however, it is still difficult to cure and patient prognosis is poor. An assessment of the surgical results and chemotherapy options may elucidate effective treatments.

Methodology: We retrospectively examined the demographics, surgical records and outcome in 33 patients with GBC undergoing surgical resection.

Results: Postoperative cancer recurrence was observed in 36% of patients. Mean cancer-free survival time was 84 months, and 3-year cancer-free survival rate was 70% Mean overall survival time was 96 months, and 5-year overall survival rate was 52%. The 3-year cancer-free survival and the 5-year overall survival were significantly different between the final tumor stages ($p<0.001$). Higher CEA and CA19-9 level were significantly related to poor overall survival ($p<0.05$). Macroscopically, papillary type tumor showed significantly better overall survival compared to nodular or flat types ($p<0.05$). Degree of invasion, node metastasis, moderate or poor differentiation, vascular or perineural invasion, and invasion of the liver or hepatoduodenal ligament were significantly associated with poor overall survival ($p<0.05$). A cancer-free margin at the hepatic cut end and dissected periductal structures showed a significantly poor prognosis ($p<0.05$). The overall survival in final curability A was significantly associated with better curability than B or C ($p<0.05$).

Conclusions: Radically extended surgical resection for GBC is necessary to obtain improved patient survival, and new adjuvant chemotherapy would be expected to improve results after surgery.

KEYWORDS: gallbladder carcinoma, tumor markers, stage, curability, survival

ABBREVIATIONS: gallbladder carcinoma (GBC)

INTRODUCTION

Surgical resection is the only effective treatment for gallbladder carcinomas (GBC), although cure rates are still low (1, 2). Concurrent hepatectomy, resection of the extrahepatic bile duct and pancreatic resection are often necessary to accomplish complete (R0) resection, which may improve patient prognosis (1-3). Dissection of extended lymph nodes around the liver, pancreas or aorta is necessary (3, 4) and the postoperative morbidity and mortality rates are still relatively high in cases of extended operation (5, 6). Necessity of extended resections for lymph node resection has become controversial (6, 7). Therefore, the indication of operation for GBC should be carefully decided. In patients who have undergone surgical resection, adjuvant chemotherapy has shown a survival benefit (8). Thus, treatment strategies for GBC should be examined. To estimate the present status regarding surgical treatment for GBC at our institute, we examined our series of GBC in 33 patients at a Japanese cancer institute and we discuss the clinical significance and limitations.

METHODOLOGY

Patients

We experienced 58 patients with GBC administrated in the Division of Surgical Oncology, Department of Translational Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences (NUGSBS) between 1994 and 2008. Of these patients, 33 patients (57%) who underwent surgical resection were analyzed in the present study. In

the other 25 patients, highly advanced GBC such as local extension to the hepatic artery, peritoneal dissemination or distant metastasis were found and radical operation was avoided. The study design was approved by the Human Ethics Review Board of our institution. Informed consent for data collection was obtained by each patient during this period. Anesthetic and patient data were retrieved in the NUGSBS database. Tumor stage and curability were determined based on the *Classification of Biliary Tract Carcinoma* in Japan (9).

Operative procedures and follow-up

Cholecystectomy is a basic surgical option for GBC. In case GBC infiltrated the gallbladder bed of the liver, liver resection was selected. Right hemi-hepatectomy was selected when the GBC involved the hepatic hilum. In case GBC infiltrated the extrahepatic bile duct or node metastasis was observed in the hepatoduodenal ligament, resection of the extrahepatic bile duct was selected and the bile duct was reconstructed with jejunum as the Roux-en Y anastomosis. Lymphadenectomy was basically performed in the Group 2 lymph nodes and lymph nodes at the para-aortic lesion (station number 16a2 and 16b1). In case lymph node metastasis was observed at the para-pancreatic head lesion, pancreaticoduodenectomy was additionally selected and Child's intestinal reconstruction with end-to-side anastomosis of pancreatojejunostomy was performed. In case of tumor involvement in the portal vein, combined vascular resection was performed by the end-to-end anastomosis of vessels. After discharge from the hospital, the patient

status, laboratory data, and disease recurrence were carefully checked every 3 months. Minimum follow-up period after operation was 14 months in the present study.

RESULTS

The patients included 16 men and 17 women with a mean age of 68.8 ± 10.8 years (± SD, range, 35-88 years). These patients underwent liver resection in 13 patients (gallbladder bed resection in nine, resection of Couinaud's segment 4+5 in two, right hemihepatectomy in one and right trisectionectomy in one), resection of extrahepatic bile duct in 16 patients, pancreaticoduodenectomy in two, and combined vascular resection was performed in three. Postoperative bile leakage was observed in three patients (15%) but no other major morbidity was seen. Hospital death was not observed in the present series. Ten patients (30%) underwent postoperative adjuvant chemotherapy including oral administration of 600mg daily of tegafur/uracil (UFT; Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) in three patients, oral administration of 80mg daily of S-1 (TS-1®; Taiho) in two and drip infusion of 1g/m^2 of gemcitabine (Gemzar; Eli Lilly and Co., Indianapolis, IN) in five since 2004.

Macroscopic examination showed a massive type in one patient, a nodular type with an expanding growth pattern in nine, a nodular type with an infiltrating growth pattern in one, a filling type in two, a nodular type with an expanding growth pattern in five, a nodular type with an infiltrating growth pattern in ten, and a flat type with an infiltrating growth pattern in five. The tumor size was over 5cm in ten patients (30%). The tumor was located at a fundus of the gallbladder in 16 patients, body in ten, neck in six and the cystic duct in one. Histological finding showed adenocarcinoma in 31 patients (papillary carcinoma in ten, well-differentiated carcinoma in six, moderately in eight and poorly in four), sarcoma

in one and pure carcinosarcoma in one. Cancer-stroma relationship showed intermediate type-response in 19 patients, medullary type in four and scirrhous in ten. Lymphatic invasion was observed in 24 patients (73%), venous invasion in 29 (76%) and perineural invasion in 12 (36%). Primary tumor invasion was mucosa in four (12%), muscularis propria in two (6%), subserosa in 19 (58%), invasion of the serosa in four (12%) and invasion beyond the serosa in four (12%). Liver invasion was negative in 15 patients (46%), 1a in 13 (39%), 1b in one (3%), 2 in three (9%) and 3 in one (3%). Bile duct invasion was negative in 30 patients (91%), 2 in one (3%), and 3 in two (6%). Portal vein invasion was observed in two patients (6%) and the invasion of hepatic artery was observed in two (6%).

Tumor stage was T1 in 7 patients (21%), 2 in 17 (52%), 3 in three (9%) and 4 in six (18%). Lymph node metastasis was observed in 18 patients (55%). Final stage of tumor was I in seven (21%), II in eight (25%), III in six (18%), IVa in seven (21%) and IVb in five (15%). Positive cancer margin at the hepatic cut end was observed in eight (24%), bile duct cut-end margin in two (3%) and the dissected tissue margin in nine (27%), and positive margin was observed in 18 patients (55%). The final curability was fCur A in 13 patients (39%), B in 16 (49%) and C in four (12%).

Postoperative cancer recurrence was observed in 12 patients (36%), which included peritonitis carcinomatosa in three patients, liver metastasis in seven, local recurrence in three, lymph node recurrence in two and lung metastasis in one. Eleven patients (33%) died after operation, which included cancer-related death in nine and other disease in two.

Figures 1 and 2 show the cancer-free survival and the cancer-related overall survival after operation. Mean cancer-free survival time was 84 months, and 3- and 5-year cancer-free survival rate was 70% and 61%, respectively. Mean overall survival time was 96 months, and 3- and 5-year overall survival rate was 64% and 52%, respectively. By comparison with tumor stage, 3-year cancer-free survivals were significantly different between stages (100% in I, 83% in II, 60% in III, 0% in IVa and 0% in IVb, $p<0.001$). By comparison with tumor stage, 5-year cancer-related overall survival was also significantly different between stages (100% in I, 80% in II, 60% in III, 0% in IVa and 0% in IVb, $p=0.003$). Table 1 shows the relationship between overall 5-year survival rate and clinical parameters. Preoperative CEA and CA19-9 level at the normal cut-off value were significantly related to poor survival rate ($p<0.05$). Tumor size and tumor location were not associated with overall survival. Morphological papillary type tumor showed significantly better survival rate compared to nodular or flat type ($p<0.05$). Postoperative adjuvant chemotherapy was not related to overall survival. Table 2 shows the relationship between overall 5-year survival rate and pathological parameters. Higher T category or deeper invasion, lymph node metastasis, moderately or poorly differentiated adenocarcinoma, major or minor vascular invasion, perineural invasion, and liver or hepatoduodenal ligament invasion were significantly associated with poor overall survival ($p<0.05$). Cancer invasion at hepatic duct cut-end margin and dissected tissue margin showed a significantly poor prognosis ($p<0.05$). The overall survival in final curability A was significantly associated with better curability than B or C ($p<0.05$).

DISCUSSION

Recently, aggressive surgical exploration for GBC has been performed; however, patient prognosis is still not satisfactory for advanced tumors (1, 2, 10). As the techniques and perioperative management have improved remarkably, we have actively performed extended resections for complete tumor resections (R0) during the last 15 years as well. Based on previous reports, the significance of curative resection for GBC has been reported in recent years (1-4, 6, 11, 12). On the other hand, morbidity rate by aggressive resection was not low (5, 6).

In our series, as a modern trend, many patients were older than 70 years. Other reports showed that elderly patients over 80 years can also undergo this major surgery if the patient has no serious complications and a strong performance status (13). Preoperative examinations for GBC and its extension have been dramatically improved and include advanced computed tomography or magnetic resonance image, endoscopic ultrasonography and associated useful diagnostic tools. Diagnosis of lymph node metastasis by these examinations has been improved (14, 15). At our institute, however, the precise evaluation of cancer extension or node metastasis is still difficult before operation at this stage (16). Preoperative diagnosis of node metastasis at the para-aortic region, which may be considered to be a contraindication of surgery, is still difficult by the conventional modalities (17). In our series, a patient was diagnosed with GBC with paraaortic lymph node metastasis. However, histological findings showed a xanthogranuloma of the gallbladder with reactive node swelling in the paraaortic region.

Another patient showed advanced infiltration in the hepatic hilum and extended right hepatectomy was performed. However, GBC actually infiltrated the subserosa (T2 GBC) based on the histological findings. It is still difficult to accurately diagnose the degree of tumor extension. To improve the accuracy of preoperative diagnosis, new diagnostic techniques such as positron emission tomography or fine needle aspiration may be necessary (18). At this stage, we have not performed these examinations.

Although resectability of GBC has been improved, as described above, advanced carcinomas were still found at laparotomy, and eight patients were determined to be inoperable at the time of laparotomy due to peritoneal carcinomatosis or liver metastasis, despite the detailed preoperative image examinations in our series. At this stage, extended hepatectomy, pancreatectomy or hepato-pancreaticoduodenectomy might be aggressively performed in Japan because only surgical exploration in the surrounding tissues, nodes and major vessels can accomplish high curability, because radical resection was thought to be the only effective option (1, 3, 4, 6, 11). In our series, only four cases underwent such an extended resection. Regarding resection of the common bile duct, radical resection is still controversial (4, 19); however, we preferably performed combined resection of the extrahepatic bile duct in the present series because lymphadenectomy seems to be more accomplished by this procedure. Morbidity after resections in GBC were not low (5, 6); however, we have not experienced severe morbidity and mortality after operation yet. As a recent trend, we preferably perform adjuvant chemotherapy

since newly effective drugs have been developed (8, 15). Evidence of the significance of adjuvant chemotherapy has not been clarified (15).

Survival results were similar to those of other reports (1, 2, 5, 6,12); however, we had no 5-year survivors in patients with final tumor stage IV. Regarding stage II and III, satisfactory results were obtained compared to those in other reports (11, 12). We considered that adequate treatment for stage II and III was necessary because of the long survival after surgical treatment, as reported in previous studies (20). We examined the parameters associated with patient prognosis in the present study. Tumor markers CEA and CA19-9 were increased in biliary tract carcinomas, which might reflect tumor size or extent and malignant behavior (21). The present study showed that increases in both markers were associated with postoperative survival as well. Our recent report showed that increased CA19-9 level supported the improvement of diagnostic accuracy for node metastasis in biliary and pancreas carcinomas (16). Preoperative tumor markers were useful for predicting tumor malignant behavior and patient prognosis. As macroscopic findings were associated with postoperative patient prognosis in the bile duct carcinomas (22), the papillary structure of GBC showed better prognosis in comparison with those in nodular or flat type carcinomas in the present study.

By analysis of the histological parameters, various parameters were associated with patient prognosis, as in previous reports (3-5, 12, 19, 23-25). We attempted to perform more extensive surgery to resect surrounding tissues during this period, and complete resection (=R0) resulted in better survival, as in other reports (1, 3, 4, 6, 10, 11). As

described above, we performed aggressive operations such as hepatectomy, pancreatectomy and combined resection of major vessels, as in previous reports (3, 26). However, only surgical removal of the tumor provides effective treatment. In the present series, we performed pancreaticoduodenectomy for node metastasis around the pancreatic head. Unfortunately, postoperative tumor recurrence occurred immediately and the patient survival was limited within 18 months. In case of severe node metastasis, the operative indication for aggressive surgery must be carefully decided. In case of recurrence as liver metastasis, we performed radiofrequency ablation in one case and the patient survived to the 3-year follow-up. Chen et al. also reported significant results with the ablation technique for liver metastasis of GBC as well (27).

Furthermore, adjuvant chemotherapy is necessary to improve prognosis after surgery in patients with or without curable operations; however, such results were not observed in the present study. Since adjuvant chemotherapy using the latest drugs has only recently been used, further long-term follow-up with adjuvant chemotherapy is necessary, using the promising drugs S-1 or cisplatin, combined with novel chemotherapy (28).

In conclusion, aggressive surgical resection was performed in 33 patients with GBC at a single cancer center over the past 15 years. Radical operation was safely performed in many cases. While stage IV GBC showed no survival at 5 years, stage II and III survival could be expected using extended surgical resection to overcome R0 or cancer-negative margin. By considering the poor prognostic parameters by

clinicopathological findings, newly effective adjuvant chemotherapy is expected to improve patient survival.

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Table 1. Comparison between cancer-related overall 5-year survival after resection and clinical and macroscopic parameters and postoperative chemotherapy

Parameters	5-year survival (%)	P value
CEA(ng/ml)		
≤5*	69	0.015
>5	0	
CA19-9 (U/ml)		
≤37*	67	0.045
>37	29	
Tumor size		
<5cm	48	0.85
≥5cm	65	
Anatomy of gallbladder†		
Fundus	52	0.58
Body	75	
Neck	66	
Macroscopic type†		
Nodular type	38	0.006
Papillary type	77	
Flat type	37	
Adjuvant chemotherapy		
No	48	0.31
Yes	61	

*; normal cut-off value

†; Findings according to *Classification of Biliary Tract Carcinoma* in Japan.*(9)*

Table 2. Comparison between overall 5-year survival after resection and pathological parameters

Parameters	5-year survival (%)	P value
T category		
1	100	
2	60	<0.001
3	0	
4	0	
Depth of invasion		
m	100	
mp	88	<0.001
ss	56	
se	0	
si	0	
Lymph node metastases		
0	78	0.050
1	50	
2	19	
Station number 16a2 or 16b1	0	
Histological differentiation or type		0.005
Papillary adenocarcinoma	88	
Well-differentiated adenocarcinoma	70	
Moderately	44	0.048
Poorly	0	
Cancer-stroma relationship		
Intermediate type	62	0.078
Medullary type	67	
Scirrhous type	22	
Lymphatic invasion		
No	80	0.075
Yes	55	
Vascular invasion		
No	86	0.003
Yes	38	
Perineural invasion		
No	80	<0.001
Yes	0	
Liver invasion		
0	72	<0.001
1a	55	
1b	20	
2	0	
3	0	
Biliary invasion		
0	58	0.064

2	0	
3	0	
Major vascular invasion		
No	58	0.003
Yes	0	
Bile duct cut end		
0	49	0.21
2	100	
Hepatic cut end		
0	55	0.012
1	53	
2	0	
Dissected periductal structures		
0	66	<0.001
1	17	
2	0	
Final curability		
A	33	0.031
B	16	
C	0	

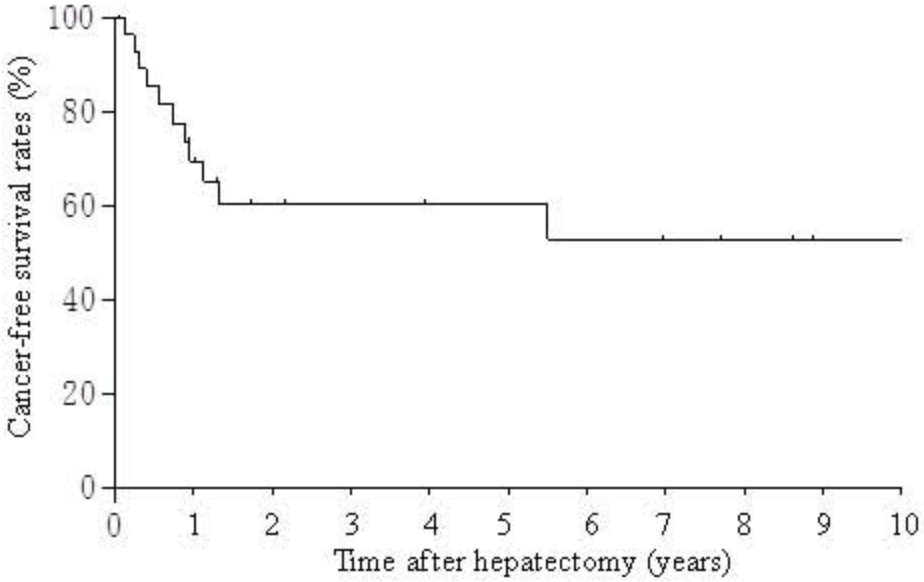
Histological findings according to *Classification of Biliary Tract Carcinoma* in Japan.(9)

Figure legends

Figure 1. Cumulative cancer-free (a) and overall (b) survival after hepatectomy.

Figure 2. Comparison between stages of tumor and cumulative cancer-free (a) and overall (b) survival after hepatectomy.

Figure 1


Cancer-free survival rates (%)
100
80
60
40
20
0
0
1
2
3
4
5
6
7
8
9
10
Time after hepatectomy (years)

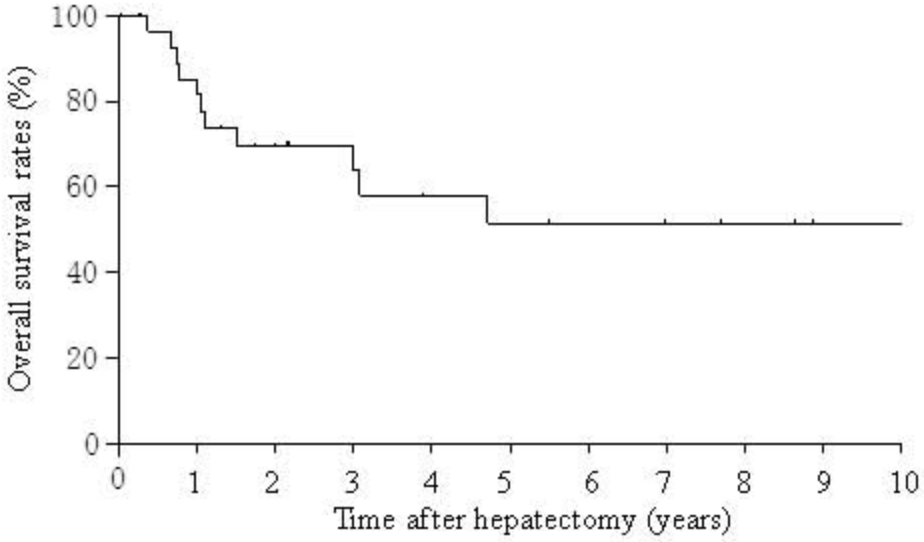
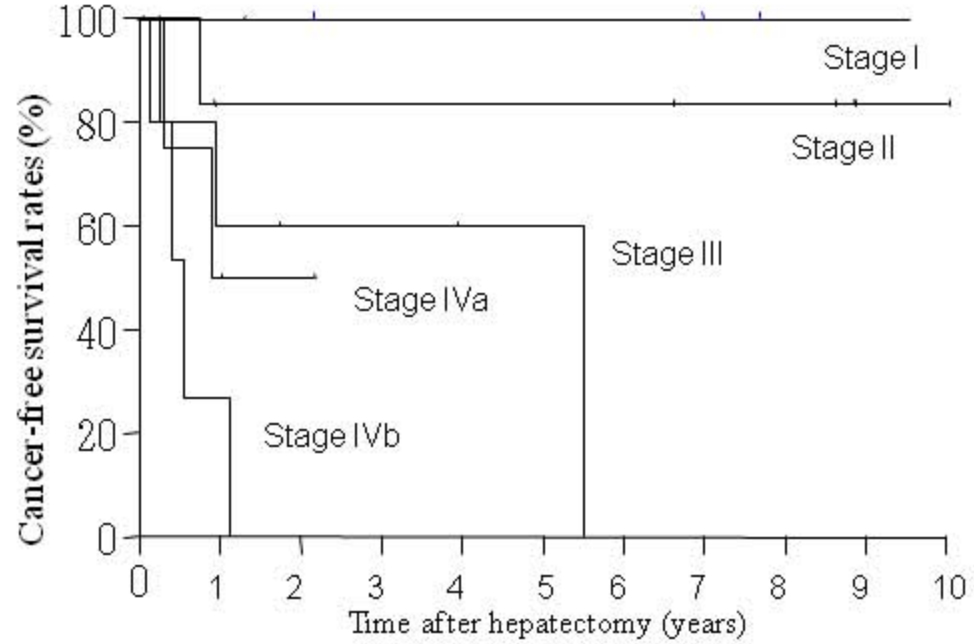
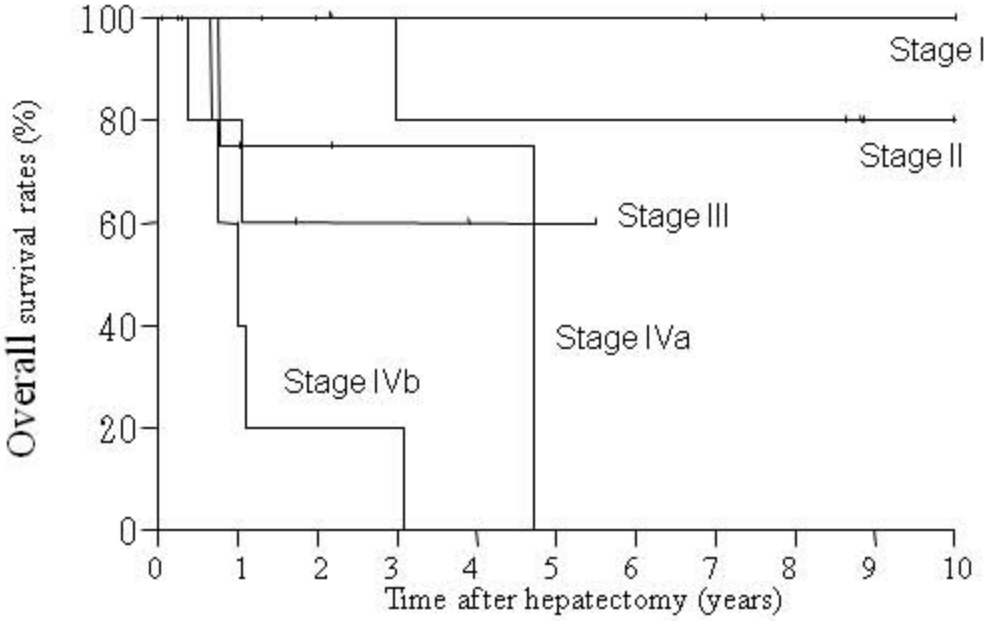

Overall survival rates (%)
100
80
60
40
20
0
0
1
2
3
4
5
6
7
8
9
10
Time after hepatectomy (years)

Figure 2


Cancer-free survival rates (%)
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10
Time after hepatectomy (years)
Stage I
Stage II
Stage III
Stage IVa
Stage IVb


Overall survival rates (%)
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10
Time after hepatectomy (years)
Stage I
Stage II
Stage III
Stage IVa
Stage IVb