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Case Report

Invasive biliary cystic tumor without ovarian-like stroma

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Presented herein is a rare case of invasive biliary cystic tumor without an ovarian-like stroma, and the apparent sequence underlying its malignant transformation, which was identified on detailed histological examination. A 54-year-old woman was incidentally diagnosed as having a cystic tumor in segment VIII of the liver, and central bisegmentectomy was performed. Macroscopically the tumor measured 4.6 × 3.5 cm; and unilocular cystic and solid areas were seen on cut surface. Microscopically the tumor showed three types of neoplasia: adenoma and tubulopapillary adenocarcinoma in the cystic area, and invasive adenocarcinoma in the solid area. The relative area of the tumor occupied by each of these histological types was approximately 3%, 50% and 47%, respectively. Moreover, transitional zones between adenoma and tubulopapillary adenocarcinoma, and between tubulopapillary adenocarcinoma and invasive adenocarcinoma were noted. The immunohistochemical expression of Ki-67 and p53 increased gradually from adenoma through to tubulopapillary adenocarcinoma, and was highest in invasive adenocarcinoma. MUC1 was positive, and MUC2 and MUC5AC were both negative. No ovarian-like stroma or communication with the bile ducts around the tumor was found in any area of the specimen. On the basis of the World Health Organization histological classification and these pathological findings, the present case was diagnosed as invasive-type biliary cystadenocarcinoma.

Key words: biliary cystadenocarcinoma, biliary cystic tumor, intraductal papillary mucinous neoplasm, invasion, Ki-67, liver, MUC, p53

Biliary cystic tumors of the liver are rare.[1–3] According to the World Health Organization (WHO) histological classification of tumors of the liver and intrahepatic bile ducts,[3] biliary malignant cystic tumor is classified only as biliary cystadenocarcinoma (BCAC), which is defined as a usually multilocular tumor lined by mucus-secreting epithelium forming papillary folds and containing mucoid fluid but distinguished from tumors arising in a background of cystic congenital malformation, parasitic infection or hepatolithiasis. However, because the histological definition of biliary cystic tumor is not well defined, it is not useful for making a clear pathological diagnosis, especially in cases of advanced malignant biliary cystic tumor of the liver. Nakajima *et al.* classified BCAC into two subtypes: invasive and non-invasive.[4] Although several cases of invasive-type BCAC have been reported,[4–8] the detailed pathological features and pathogenesis have not yet been described, and therefore the criteria for diagnosis of biliary cystic tumor are still unclear.

Here we report a rare case of invasive biliary cystic tumor with a detailed description of the histological findings.

CLINICAL SUMMARY

A 54-year-old woman was found to have a cystic tumor in the right lobe of the liver incidentally during follow-up abdominal ultrasonography for hypertension at a local hospital, and was admitted to National Cancer Center, Tokyo, Japan. She had no symptoms. Laboratory data indicated that her serum levels of total bilirubin, alkaline phosphatase, glutamic oxaloacetic transaminase, glutamic pyruvate transaminase, CEA and AFP were all within normal limits, and only the serum level of carbohydrate antigen 19–9 was elevated (1003 U/mL). Serum markers of hepatitis A, B and C were negative. Enhanced abdominal CT showed a low-density cystic mass with wall enhancement in segment VIII of the liver. The cystic mass contained a large and prominent watery, enhancing, soft-tissue mass with calcification (Fig. 1a). No dilatation of the intrahepatic bile ducts was detected. A preoperative diagnosis of BCAC or mucin-producing cholangiocellular carcinoma (CCC) was made, and the patient underwent central

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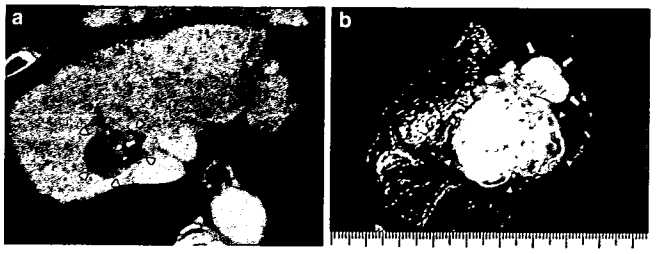

Figure 1 (**a**) Abdominal CT showing a low-density cystic mass with an enhancing wall (white arrowhead) and calcification (blue arrow) in segment VIII of the liver, but no sign of dilatation of the intrahepatic bile ducts. (**b**) Gross appearance of the tumor, showing a cystic area (white arrowhead) and a solid area (yellow arrow).

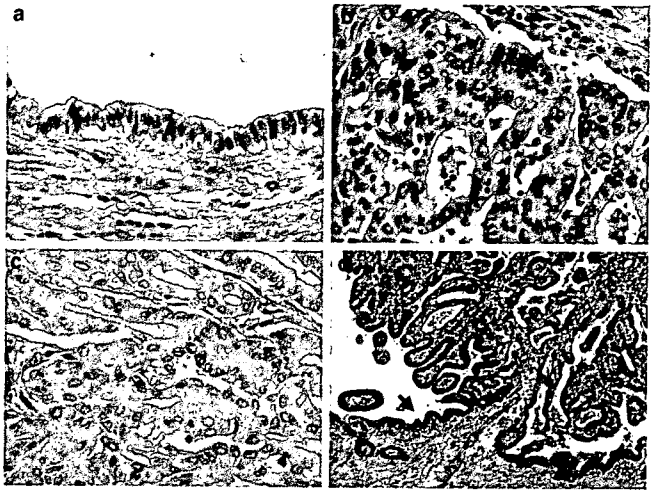

Figure 2 Microscopically, the tumor shows three types of neoplasia: (**a**) adenoma, (**b**) tubulopapillary adenocarcinoma, and (**c**) invasive adenocarcinoma. (**d**) Transitional zone between adenoma (black arrow) and tubulopapillary adenocarcinoma (*). (a–d, HE).

bisegmentectomy. At the time of writing, 21 months after surgery, the patient remained well without any evidence of tumor recurrence.

PATHOLOGICAL FINDINGS

Macroscopically the resected tumor measured 4.6 × 3.5 cm, and cystic and solid areas were seen on cut surface (Fig. 1b).

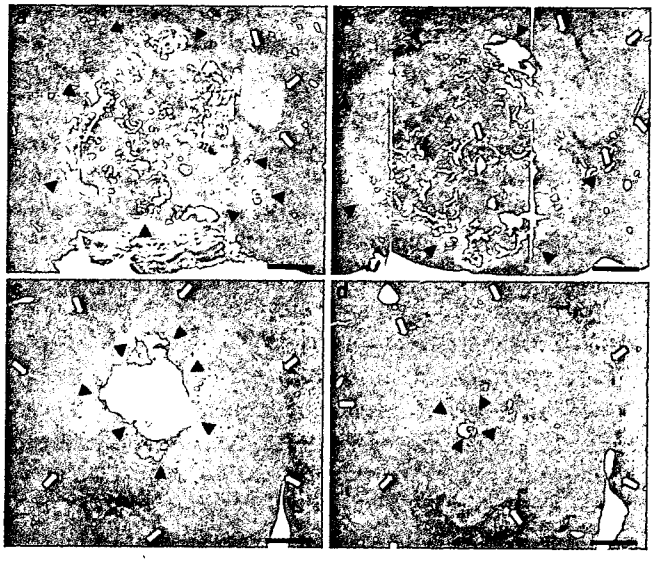

Figure 3 (**a–d**) Low-magnification view of the tumor. The cystic area (black arrowhead) and solid area (white arrow) can be identified. (**b**) Calcification (blue arrow) and overt tumor invasion through the cyst wall into the neighboring liver parenchyma are evident (HE). Bars, 5 mm.

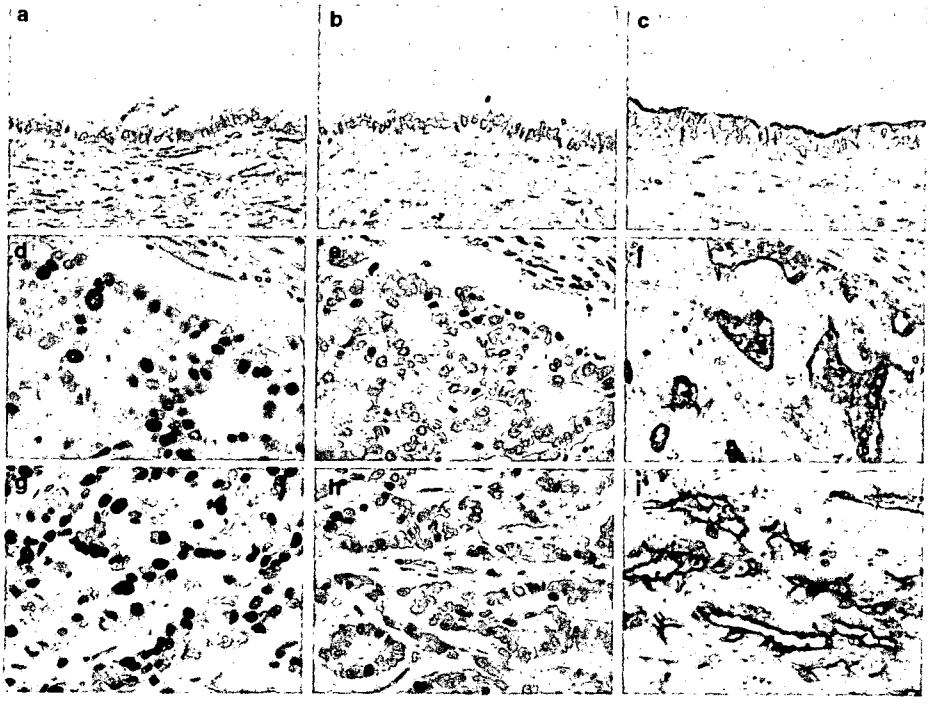

Figure 4 Immunohistochemical expression of (**a**,**d**,**g**) Ki-67 antigen, (**b**,**e**,**h**) anti-p53 protein and (**c**,**f**,**i**) MUC1 core antigen in the (**a–c**) adenoma region, (**d–f**) tubulopapillary adenocarcinoma region and (**g–i**) invasive adenocarcinoma region. The immunohistochemical expression of Ki-67 and p53 increases gradually from adenoma through to tubulopapillary adenocarcinoma, and is highest in invasive adenocarcinoma. MUC1 was positive in all three histological types.

Table 1 Immunohistochemistry

Neoplasia	% positive cells					
	MUC1	MUC2	MUC5AC	MUC6	Ki-67	p-53
Adenoma	70	–	–	–	5	2
Tubulopapillary adenocarcinoma	90	–	–	5	50	25
Invasive adenocarcinoma	100	–	–	–	70	40

–, negative (0%).

The cystic area was unilocular, lined with a smooth fibrous capsule and filled with a soft mass showing a papillary structure and thick mucin. Calcification was found in the lesion. Overt tumor invasion through the cyst wall into the neighboring liver parenchyma was also noted and connected to the solid area, which was gray–white in color.

For pathological examination the surgically resected specimen was fixed in 10% formalin for 3 days at room temperature. The entire tumor was then cut into slices at intervals of 0.7–1.0 cm, and all the tumor-containing sections were routinely processed and embedded in paraffin to examine their histological characteristics. Immunohistochemical studies were carried out on formalin-fixed, paraffin-embedded tissues. The antibodies used included those against Ki-67 antigen (clone MIB-1; Dako Cytomation, Glostrup, Denmark; dilution 1:100), p53 protein (clone DO7; Dako Cytomation; dilution 1:100), MUC1 core (clone Ma552; Novocastra Laboratories, Newcastle-upon-Tyne, UK; dilution 1:100), MUC2 (clone Ccp58; Novocastra Laboratories; dilution 1:200), MUC5AC (clone CLH2; Novocastra Laboratories; dilution 1:200), and MUC6 (clone CLH5; Novocastra Laboratories; dilution 1:100). After deparaffinization and rehydration, the sections were developed using the labeled streptavidin–biotinylated antibody technique and visualized in diaminobenzidine using conventional methods.

Microscopically the tumor had three types of neoplasia: adenoma, tubulopapillary adenocarcinoma, and invasive adenocarcinoma (Fig. 2a–c). Both adenoma and tubulopapillary adenocarcinoma corresponded to the unilocular cystic area, and invasive adenocarcinoma corresponded to the solid area. The relative area of the tumor occupied by each of these histological types was approximately 3%, 50% and 47%, respectively (Fig. 3). In the adenoma area, the cyst wall was lined with epithelial cells showing low-grade atypia, with clear eosinophilic cytoplasm and uniform, small and round nuclei (Fig. 2a). In the areas of tubulopapillary adenocarcinoma the cyst wall was covered by papillary proliferation of atypical columnar epithelial cells with eosinophilic cytoplasm and round nuclei containing multiple small nucleoli, and the tumor cells had grown into the cystic space to form a mass with a tubulopapillary structure (Figs 2b,3a,b). Calcification was seen in this area (Figs 1a,3b). The fibrous capsule had been invaded by the carcinoma cells forming the tubulopapillary mass, and invasion of the adjacent liver parenchyma was also noted (Fig. 3a–d). The areas of invasive adenocarcinoma contained tubular proliferation of atypical columnar epithelial cells with eosinophilic cytoplasm and round nuclei of various sizes (Fig. 2c), and there was evidence of portal vein and middle hepatic vein involvement. Transitional zones between adenoma and tubulopapillary adenocarcinoma (Fig. 2d), and between tubulopapillary adenocarcinoma and invasive adenocarcinoma were also found. No ovarian-like stroma was found in any area of the specimen. None of the different histological areas had any communication with the bile ducts around the tumor. The histological differential diagnosis was CCC with cyst formation or invasive adenocarcinoma derived from intraductal papillary neoplasm of the bile duct (IPN-B).

Immunohistochemistry results are summarized in Table 1. The Ki-67 labeling index was found to increase with increasing histological atypia, from 5% in the adenoma, to 50% in the tubulopapillary adenocarcinoma, and up to 70% in the invasive adenocarcinoma (Fig. 4a,d,g). The percentage of p53-positive cells also increased gradually from 2% in the adenoma to 25% in the tubulopapillary adenocarcinoma, and to 40% in the invasive adenocarcinoma (Fig. 4b,e,h). In all three types of neoplasia, MUC 1 was positive (Fig. 4c,f,i) and both MUC2 and MUC5AC were negative. MUC6 had weak focal positivity only in tubulopapillary adenocarcinoma.

On the basis of the WHO histological classification[3] and the present pathological findings, the current case was diagnosed as invasive biliary cystadenocarcinoma derived from biliary cystadenoma.

DISCUSSION

According to the WHO histological classification of tumors of the liver and intrahepatic bile ducts,[3] malignant biliary cystic tumor is classified only as BCAC. The incidence of BCAC among hepatic malignant epithelial tumors is as low as 0.41%.[1] Many studies have indicated that cystadenocarcinoma develops by malignant transformation of the epithelium of a cystadenoma.[1,9,10] Nakajima *et al.* classified BCAC into two subtypes: invasive and non-invasive.[4] In invasive-type BCAC, carcinoma extends to the liver parenchyma or adjacent organs, whereas in the non-invasive type carcinoma cell proliferation is confined to the cyst wall. On this basis, and in accordance with the WHO classification, the present case was diagnosed as invasive BCAC. Eight cases of invasive

Table 2 Reported cases of invasive-type biliary cystadenocarcinoma

Case Study no.	Age (years)	Sex	Size (cm)	No. cysts	Adenoma lesion	Transitional zone	Ovarian like (mesenchymal) stroma	Outcome
1 Iemoto *et al.*[5]	60	M	14 × 14	Multilocular	–†	+	–	Died 2 year 8 months PO
2 Nakajima *et al.*[4]	47	F	10 × 10	Unilocular	–	–	–	Died 5 months PO
3 Nakajima *et al.*[4]	43	F	9 × 6	Unilocular	–	–	–	Died 1 year PO
4 Nakajima *et al.*[4]	65	F	14 × 14	Multilocular	–†	+	–	Died 10 months PO
5 Stacher *et al.*[6]	77	F	11 × 10 × 14	Multilocular	–	–	ND	Well 8 months PO
6 Bardin *et al.*[7]	43	F	18 × 13.5 × 8	Multilocular	–	–	–	ND
7 Murakami *et al.*[8]	82	F	10 × 10 × 9.5	Multilocular	–	–	–	Died 1 year PO
8 Present study	54	F	4.6 × 3.5	Unilocular	+	+	–	Well 1 year 9 months PO

†Focal benign-appearing epithelium.
+, present; –, absent; ND, not described; PO, postoperatively.

BCAC have been reported in the English-language literature (Table 2). All but one of the patients were women, and their ages ranged from 43 to 82 years (mean, 58.9 years). Multilocular lesions were evident in five cases, and unilocular lesions in two. The tumors ranged in size from 4.6 to 18 cm (mean 11.7 cm). However, these patients had no clear and distinctive clinicopathological characteristics (e.g. age, outcome, tumor size etc.), and because no detailed study of invasive biliary cystic tumor has yet been done, the clinicopathological features remain largely unknown.

Recently Zen *et al.* reported that biliary cystic tumor with bile duct communication and without ovarian-like stroma might be a cystic variant of IPN-B rather than a true biliary cystic neoplasm.[11] Several studies have indicated that IPN-B is the counterpart of intraductal papillary mucinous neoplasm of the pancreas (IPMN-P),[12–14] and that the immunophenotypes of IPN-B resemble those of IPMN-P.[15,16] If the term 'biliary cystadenoma' or 'cystadenocarcinoma' is restricted to true cystic neoplasms with an ovarian-like stroma, as in the pancreas, previously reported biliary cystic tumors with an ovarian-like stroma have occurred only in female patients.[17,18] From this viewpoint, the present case was morphologically similar to invasive adenocarcinoma derived from IPN-B, even though bile duct communication was not evident. The present case was of the pancreatobiliary type according to the IPMN-P classification.[19–22] However, the immunohistochemical expression pattern observed was not typical of IPN-B. Most IPN-B have high expression of MUC2 and MUC5AC, but the present case was negative for both.

We consider that in some cases of BCAC, the ovarian-like stroma may disappear during the process of malignant transformation from biliary cystadenoma. Devaney *et al.* reported that non-specific reactive changes were evident in the cyst wall (typically between the ovarian-like zone and the fibrous pseudocapsule),[17] and that ovarian-like stroma was abundant in some cases but focal in others. Similar findings were obtained in other cases we have examined (data not shown). Moreover, most patients with biliary cystadenoma have symptoms of abdominal discomfort and the tumor is large at the time of discovery (mean diameter 15–16 cm).[17,18] These facts suggest that microrupture of the cyst and reactive changes in the cyst wall may occur repeatedly during growth of the tumor, and that symptoms do not become evident until the tumor becomes large. Therefore, the area of ovarian-like stroma may vary. If such events do, in fact, occur, some cases of BCAC derived from cystadenoma may not have an ovarian-like stroma. We consider that the present case may represent this type of BCAC.

On the other hand, the present tumor had invasive solid areas that resembled CCC. Furthermore, there was a cystic component and invasive area lined with epithelial cells showing low-grade atypia that did not communicate with the intrahepatic bile ducts. Features often seen in CCC are dilatation of the intrahepatic bile ducts surrounding the tumor and *in situ* carcinoma in the bile duct epithelium, which are evidence for the theory that CCC arises in the bile duct epithelium. However, we did not detect any such features, and on the basis of the pathological evidence we concluded that the tumor was not CCC.

One of the most interesting features of the present case was that discrete areas of adenoma, tubulopapillary adenocarcinoma and invasive adenocarcinoma were clearly evident within the same specimen. Moreover, transitional zones were also evident between adenoma and tubulopapillary adenocarcinoma, and between tubulopapillary adenocarcinoma and invasive adenocarcinoma. To our knowledge this combination of pathological features has never been reported previously, and we consider that they indicate the sequence underlying the development of invasive biliary cystic tumor. In addition, we found that the immunohistochemical expression of Ki-67 and p53 increased gradually from adenoma lesion through to tubulopapillary adenocarcinoma, and was highest in invasive adenocarcinoma, indicating that the degree of malignancy progressed with increasing histological atypia, from adenoma to invasive adenocarcinoma.[23,24] It was also interesting that high immunohistochemical expression of MUC1 was observed even in adenoma, which shows low histological atypia. MUC1 expression is usually high in invasive-type

intrahepatic bile duct tumors that have a poor prognosis.[25] It is considered that this type of invasive biliary cystic tumor may have a malignant character resembling CCC from as early as the adenoma stage,[26,27] suggesting that the pathogenesis involves the adenoma–cystadenocarcinoma–invasive adenocarcinoma sequence.

In conclusion, we have presented a rare case of invasive biliary cystic tumor without an ovarian-like stroma and have characterized the apparent sequence underlying its malignant transformation, on the basis of detailed histological examination. We believe that the features of the present case are important when considering the pathogenesis or diagnostic criteria of advanced-type biliary cystic tumor.

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Clinical Impact of the Surgical Margin Status in Hepatectomy for Solitary Mass-Forming Type Intrahepatic Cholangiocarcinoma Without Lymph Node Metastases

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Background and Objectives: The clinical impact of the surgical margin status in macroscopic curative hepatectomy for intrahepatic cholangiocarcinoma (ICC) has not yet been fully investigated.

Methods: The data of 57 consecutive patients with mass-forming (MF) type ICC who underwent macroscopic curative hepatectomy during a 10-year period were retrospectively examined, and the relationship between the surgical margin status and patient survival was analyzed.

Results: Lymph node metastases were found to be independently associated with poor survival. The overall 5-year survival rates and the median survival term in the 38 patients without lymph node metastases were 56.8% and 62 months, respectively. Among these 38 patients, the survival rate was better in the negative surgical margin group as compared with that in the positive surgical margin group. However, there was no statistically significant difference between the narrow and wide surgical margin groups.

Conclusions: Negative surgical margin had a definite favorable impact on the survival of patients with a solitary ICC without lymph node metastases. Surgery should be conducted in patients without lymph node metastases even if a wide surgical margin cannot be obtained, but careful attention should be paid not to expose tumors during hepatic dissection.

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KEY WORDS: **mass-forming type; intrahepatic cholangiocarcinoma; hepatectomy; curative resection; surgical margin**

INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) has been considered a rare primary hepatic tumor. Recently, however, the incidence and mortality of ICC have increased [1]. ICCs have been classified into several types based on the macroscopic appearance of the tumors [2–4]. Mass-forming (MF) type ICC, which is the most commonly encountered type in the clinical setting, is a round, potato-shaped lesion with a distinct border in the liver parenchyma, and is sometimes difficult to differentiate from hepatocellular carcinoma and metastatic tumors from other organs [5]. The optimal extent of hepatectomy and the appropriate width of the surgical margin for other hepatic malignancies have been evaluated to improve the surgical outcomes, but the clinical significance of the surgical margin status in

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hepatectomy with MF type ICC has not been fully investigated [6–11].

Curative resection remains one of the most important prognostic factors in patients with ICC [12–14]. However, it is often difficult to obtain a generous surgical margin in cases of ICC because the majority of patients present with large, often centrally located tumors. The most frequent mode of spread into the liver is direct invasion into the adjacent liver parenchyma through the sinusoids [15]. The clinical importance of an adequate surgical margin to ensure removal of the micrometastases in the surrounding liver parenchyma still remains unclear.

In the present study, data of a relatively large number of patients with typical MF type ICC who underwent hepatectomy at one Japanese institution were examined to identify the prognostic factors for survival, with special reference to the status of the surgical margin.

PATIENTS AND METHODS

Between January 1, 1995 and December 31, 2004, 111 patients with ICC underwent macroscopic curative hepatectomy, at the National Cancer Center Hospital, Tokyo, Japan. ICC was defined as the carcinoma arising from second-order or more distal branches of the intrahepatic bile ducts; hilar bile duct cholangiocarcinoma and gallbladder cancer were excluded. The criteria for resectability were absence of peritoneal dissemination, bulky lymph node metastasis, paraaortic lymph node metastasis, and/or intrahepatic metastasis in the remnant liver. Macroscopic curative resection was defined as the absence of apparent tumor residue in the operative field. Based on the macroscopic classification proposed by the Liver Cancer Study Group of Japan, the resected tumors were classified into the MF type (n = 58, 52%), the periductal infiltrating (PI) type (n = 9, 8%), the intraductal growth (IG) type (n = 6, 5%), the MF plus PI type (n = 32, 29%), and the MF plus IG type (n = 6, 5%) [3]. Fifty-eight patients with MF type ICC were enrolled in the present study. There were 33 men and 25 women ranging in age from 44 to 84 years (mean, 65 years).

The extent of hepatic resection was dependent on tumor size and location. The distribution of the types of hepatectomy was: partial resection (n = 6, 10%), segmentectomy (n = 6, 10%), left lobectomy (n = 15, 26%), right lobectomy (n = 21, 36%), right trisegmentectomy (n = 2, 4%), left trisegmentectomy (n = 6, 10%), and central bisegmentectomy (n = 2, 4%). In 31 patients (53%) suspected to have lymph node involvement based on preoperative imaging or intraoperative findings, lymph node dissection was performed around the hepatoduodenal ligament, posterior to the upper portion of the pancreatic head, and along the common hepatic artery. Resection of the biliary confluence and extrahepatic bile duct, portal vein, and hepatic artery, and combined resection of the inferior vena cava was performed on 13 (22%), 3 (5%), 1 (2%), and 6 patients (10%), respectively. Among the 58 patients, there were no operative or in-hospital deaths. The patients were closely followed up every 3 months at an outpatient clinic with measurement of the serum levels of carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA), chest x-ray, and ultrasonography or computed tomography. The specific sites of first disease recurrence were analyzed. Radiologic evidence of tumor recurrence was considered acceptable even in the absence of biopsy confirmation. When progression of the disease was confirmed by repeated imaging studies, the date of the first suspicious radiologic finding was considered as the date of initial disease recurrence. One patient was lost to follow-up and was excluded from the follow-up analysis. The median follow-up duration of the remaining 57 patients was 19 months (range, 2–115 months).

In these 57 patients, the significance of 14 clinicopathological factors potentially influencing the prognosis was analyzed using the log-rank test. The continuous variables were classified into two groups according to the median value of each factor. Multivariate regression analysis was performed using the Cox proportional hazards model and associations with $P < 0.10$ were entered into the final model adopted. The surgical margin was divided into the following three categories: a wide surgical margin group with a negative surgical margin historically measured as >5 mm in width; a narrow surgical margin group with a negative surgical margin historically measured as ≤5 mm in width; and a positive surgical margin group with a surgical margin involved with cancer cells around non-encapsulated tumors, which was confirmed by microscopic examination. The relationship between the surgical margin status and 10 possible prognostic factors was examined. Trends and differences were tested by the Yates' chi-square test. Survival estimates were calculated by the Kaplan–Meier method and compared using the log-rank test. All statistical analyses were performed using the Software Package for the Social Sciences 11.5J for Windows® (SPSS, Chicago, Illinois). A two sided $P < 0.05$ was considered as denoting significance.

RESULTS

The overall 1- and 5-year survival rates were 73.3% and 43.7%, respectively, in 57 patients with MF type ICC. The mean survival time was compared among the possible predictors (Table I). Lymph node involvement and intrahepatic metastasis were determined to be significantly unfavorable prognostic factors by univariate

TABLE I. Possible Clinical and Pathological Risk Factors for Survival in Patients With MF

Factors		No. of patients	5-year survival rate (%)	Median survival term (months)	*P*-value
Overall		57 (100)	43.7	31	—
Age (median; 65 years)	≤65	30 (53)	45.5	25	0.8653
	>65	27 (47)	41.1	31	
Gender	M	32 (56)	54.4	62	0.5439
	F	25 (44)	35.2	26	
Symptoms	Absent	43 (82)	42.5	31	0.5056
	Present	14 (18)	18.2	26	
Ca19-9 (median: 126 U/ml)	≤126	27 (52)	48.7	30	0.5753
	>126	25 (48)	36.3	31	
CEA (median: 3.0 ng/ml)	≤3.0	35 (61)	48.7	30	0.4893
	>3.0	22 (39)	34.5	31	
Size (median: 5.2 cm)	≤5.2	29 (51)	47.3	30	0.3589
	>5.2	28 (49)	39.1	31	
Intrahepatic metastases	Absent	36 (68)	54.4	62	0.0124
	Present	21 (32)	23.7	14	
Portal vein invasion	Absent	19 (33)	44.6	31	0.6651
	Present	38 (67)	45.5	32	
Hepatic vein invasion	Absent	33 (58)	49.1	32	0.3672
	Present	24 (42)	35.1	22	
Bile duct invasion	Absent	21 (37)	61.3	–	0.2173
	Present	36 (63)	39.5	25	
Histological differentiation	Well	13 (23)	60.6	–	0.1365
	Mod/poor	44 (77)	36.0	26	
Lymph node metastases	Negative	38 (67)	56.8	62	0.0054
	Positive	19 (33)	18.7	17	
Extent of hepatectomy	Segmentectomy and less	12 (21)	12.6	26	0.1578
	Lobectomy and more	45 (79)	53.6	62	
Surgical margin	Negative	44 (77)	56.8	62	0.0621
	Positive	13 (23)	16.7	20	

analysis. Patients with a negative surgical margin tended to have a better survival rate than those with a positive surgical margin. However, the difference was not statistically significant ($P = 0.0621$). When the significant prognostic factors as determined by univariate analysis were assessed by multivariate analysis, only lymph node metastasis was found to be independently associated with poor survival, with a hazard ratio (95% confidence interval) of 2.934 (1.329–6.475: $P = 0.008$).

Figure 1 shows the result of survival analysis in the 57 patients with/without lymph node metastasis and with/without intrahepatic metastasis. The overall 1- and 5-year survival rates in the 26 patients with neither lymph node nor intrahepatic metastasis were 96.1% and 65.3%, respectively. In contrast, nine patients with both lymph node metastasis and intrahepatic metastasis survived for no longer than 25 months, with a median survival time of 17 months.

Figure 2 shows a comparison of the cumulative survival rates by the surgical margin status in the 38 patients with no lymph node metastasis. Compared with the negative (wide and narrow) surgical margin group, survival was significantly poorer in the positive

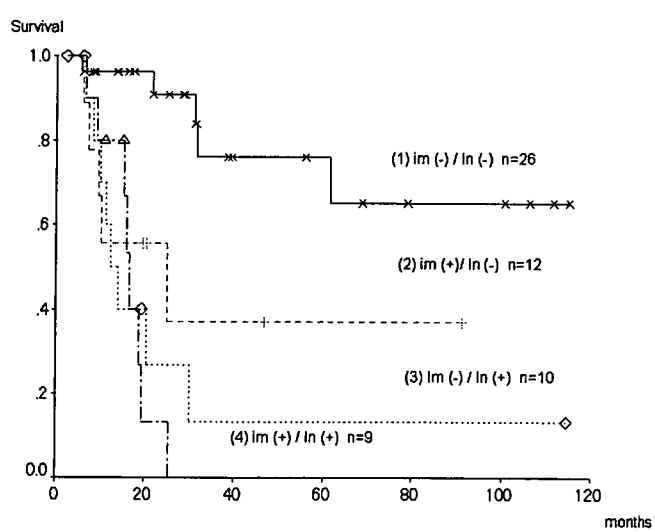

Fig. 1. Overall patient survival rate according to the presence of lymph node metastasis and/or intrahepatic metastasis. ln: lymph node metastasis, im: intrahepatic metastasis. The statistically significant differences revealed were: (1) versus (2), $P = 0.0001$; (1) versus (3), $P < 0.0001$; (1) versus (4), $P = 0.0135$.

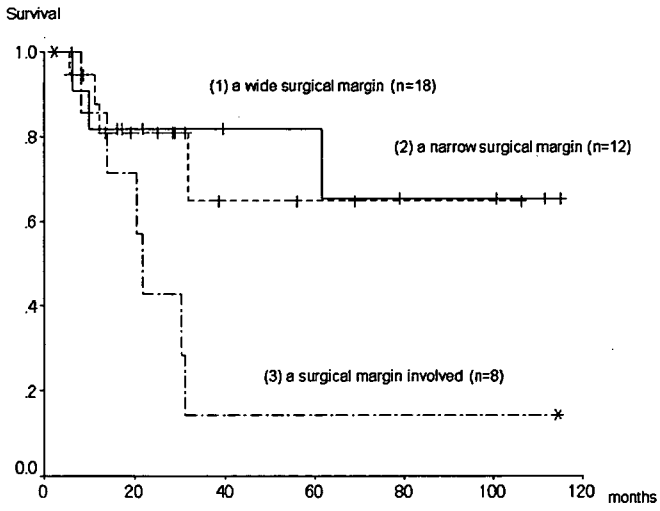

Fig. 2. Overall survival in the 38 patients without lymph node metastasis according to surgical margin status. The statistically significant differences revealed were: (1) versus (2), $P = 0.8252$; (1) versus (3), $P = 0.0396$; (2) versus (3), $P = 0.0373$.

surgical margin group. However, within the group with a negative surgical margin, no difference in survival was observed between the narrow and wide surgical margin subgroups. In contrast in the 19 patients with lymph node metastasis, there was no significant correlation of survival with surgical margin status. In connection with the width of the surgical margin, a narrow resectional margin had no adverse effect on patient survival in cases without either lymph node or intrahepatic metastasis.

Table II shows the relationship between surgical margin status and other clinicopathological factors in the 38 patients with no lymph node metastases. The surgical margin status was significantly associated with intrahepatic metastases ($P = 0.011$) and ICGR15 ($P = 0.036$), respectively.

Table III lists the sites of recurrence in the 38 patients with no lymph node metastases. The leading site of recurrence was the liver, followed by the lymph nodes; there was no significant correlation with the surgical margin status. No local recurrences were observed in patients with a wide surgical margin, and intrahepatic recurrence was more frequently observed in patients with a narrow surgical margin.

DISCUSSION

Previous articles have reported that lymph node involvement and intrahepatic metastasis are significant poor prognostic factors in patients with ICC undergoing macroscopic curative resection [16–21]. These factors represent completely different modes of spreading in cases with the MF type of ICC: lymph node metastasis spread via lymphatic flow along Glisson's sheath might

TABLE II. Relationship Between Surgical Margin Status and Other Clinicopathological Factors in 38 Patients Without Lymph Node Metastases

Factors	Surgical margin	>5 mm (n = 12)	≤5 mm (n = 18)	Involved (n = 8)	*P*-value
Width	Mean ± S D mm	17 ± 9 mm	3 ± 2 mm	—	<0.001
Age (median: 66 years)	<66 (n = 19)	6 (32)	8 (42)	5 (26)	0.697
	≥66 (n = 19)	6 (32)	10 (53)	3 (15)	
Gender	M (n = 24)	7 (29)	13 (54)	4 (17)	0.509
	F (n = 14)	5 (36)	5 (36)	4 (28)	
Size (median: 5.2 cm)	≤5.2 (n = 19)	9 (47)	7 (37)	3 (16)	0.111
	>5.2 (n = 19)	3 (16)	11 (58)	5 (26)	
Intrahepatic metastases	Absent (n = 26)	10 (38)	14 (54)	3 (8)	0.011
	Present (n = 12)	2 (17)	4 (33)	5 (50)	
Portal vein invasion	Absent (n = 34)	12 (35)	14 (41)	8 (24)	0.083
	Present (n = 4)	0	4 (100)	0	
Hepatic vein invasion	Absent (n = 25)	9 (36)	12 (48)	4 (16)	0.511
	Present (n = 13)	3 (23)	6 (46)	4 (31)	
Bile duct invasion	Absent (n = 16)	5 (31)	7 (44)	4 (25)	0.869
	Present (n = 22)	7 (32)	11 (50)	4 (18)	
Histological differentiation	Well (n = 8)	1 (13)	6 (74)	1 (13)	0.207
	Mod/poor (n = 30)	11 (37)	12 (40)	7 (23)	
ICGR15 (median 8%)	≤8 (n = 20)	10 (50)	7 (35)	3 (15)	0.036
	>8 (n = 18)	2 (11)	11 (61)	5 (28)	
Extent of hepatectomy	Segmentectomy and less (n = 10)	3 (30)	4 (40)	3 (30)	0.711
	Lobectomy and more (n = 28)	9 (32)	14 (50)	5 (18)	

ICGR15: Indocyanine green retention rate at 15 min.

TABLE III. Initial Recurrence Sites and Surgical Margin Status in 38 Patients Without Lymph Node Metastases

Surgical margin	>5 mm	≤5 mm	Involved	*P*-value
Recurrence	6/12 (50%)	8/18 (44%)	6/8 (75%)	0.3460
Sites[a]				
Local recurrence	0	1 (13)	1 (11)	0.7389
Liver	2 (33)	7 (58)	3 (33)	
Lymph nodes	2 (33)	2 (26)	3 (33)	
Peritoneal	0	1 (13)	0	
Lung	1 (16)	1 (13)	1 (11)	
Bone	1 (16)	0	1 (11)	
Skin	1 (16)	0	0	
Solitary recurrence	4 (67)	4 (50)	4 (67)	0.7575
Multiple recurrence	2 (34)	4 (50)	2 (34)	

[a]Sites include multiple organs.

represent non-curable systemic disease, and intrahepatic metastasis might result from spread to the liver via the portal venous system [15,22,23]. In the present study, lymph node metastasis was the only independent prognostic factor predictive of poor survival, and intrahepatic metastasis was revealed to be a significant factor by univariate, but not multivariate analysis.

The prognosis of solitary ICC without lymph node metastases was favorable when microscopic curative resection could be accomplished. In contrast, nine patients who had both lymph node and intrahepatic metastasis survived for no longer than 25 months, with a median survival time of 17 months. If intraoperative ultrasonography confirms the presence of intrahepatic metastases, surgical treatment should be abandoned in patients suspected to have lymph node involvement. As preoperative assessment of lymph node involvement is generally difficult and definitive pathological diagnosis can be obtained only after intraoperative examination, aggressive surgery might be employed with predictable safety even if a small number of metastases are recognized [20,21].

ICCs are usually large and centrally located at the time of diagnosis as compared with other hepatic malignancies, which are initially difficult to detect [1,9,15]. Thirteen of the patients (23%) had a positive surgical margin even after major hepatic resection, which was necessary in 45 patients (79%). One of the major reasons for this might be that a positive surgical margin might not be significantly related with the size of the main tumor itself, but to the presence of intrahepatic metastatic nodules, which might become exposed because of the difficulty in recognizing them during the hepatic dissection. Consistent with this speculation, a positive surgical margin did not function as a negative prognostic factor in patients with intrahepatic metastasis.

Positive surgical margin has previously been reported as another important prognostic factor [12–14], but in the current study, it was not found to be a significant. However, a negative surgical margin may be associated with a significantly better survival rate in patients without lymph node metastases. These results suggest that the role of microscopic curative resection is extremely important in potentially curative condition.

The appropriate width of the surgical margin in patients with ICC has been an important clinical concern among hepatic surgeons. This is because the most frequent modes of the spread of ICC are direct sinusoidal invasion in the absence of a clear tumor capsule and vascular spread with microscopic metastatic deposits in the surrounding liver parenchyma [15]. Cherqui et al. [9] stated that curative resection requires a clear margin of ≥1 cm. Conversely, Valverde et al. [10] and Huang et al. [11] reported that a potentially narrow surgical margin was not a contraindication to resection. The present study indicated that a narrow width of the surgical margin did not adversely influence survival. The presence of possible tiny metastatic deposits around the main tumors might be negligible as compared with the spread of an intrahepatic tumor via the portal venous system in patients with ICC undergoing macroscopic curative hepatectomy. This is because the most frequent site of recurrence was the remnant liver and not local recurrence at the resectional margin.

A negative surgical margin had a definitively favorable impact on survival in patients with a solitary ICC without lymph node metastasis, and careful attention should be paid not to expose tumors at the surgical margin during hepatic dissection. In any event, the surgical outcome in ICC patients without intrahepatic or lymph node metastasis was excellent regardless of the width of the surgical margin.

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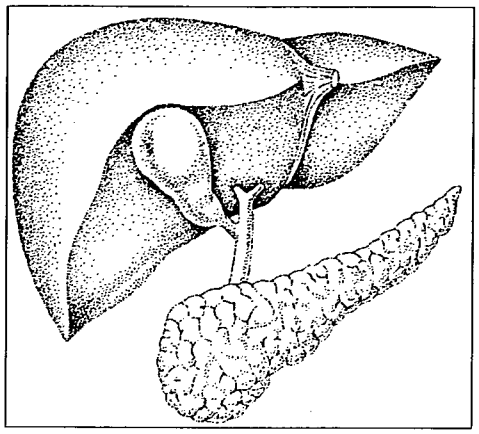

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Changing trends in surgical outcomes after major hepatobiliary resection for hilar cholangiocarcinoma: a single-center experience over 25 years

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Abstract

Background/Purpose. Hepatobiliary resection (HBR) for hilar cholangiocarcinoma (HCCa) remains a technically demanding procedure and is still associated with significant rates of morbidity and mortality. The aim of this study was to characterize changes in surgical outcomes following major HBR for HCCa at a single center over a 25-year period.

Methods. Between 1980 and 2004, 126 patients undergoing preoperative biliary drainage, portal vein embolization, and major HBR were enrolled in this study. The patients were divided into two groups according to the chronological treatment period; i.e., patients who underwent surgery during the initial 20-year period (1980–1999; early group [EG]) and those who underwent surgery during the most recent 5-year period (2000–2004; late group [LG]). Clinicopathological variables were compared retrospectively between the two groups.

Results. The mortality rate improved from 7.9% in the EG to 0% in the LG, but this difference did not reach the level of statistical significance ($P = 0.058$). The overall survival rate at 1, 3, and 5 years was 82.4%, 43.9%, and 35.2%, respectively. The overall survival rate was similar in the two groups ($P = 0.153$). Morbidity was documented in 57.1% of all the patients, and was comparable in the two groups ($P = 0.471$), but the rate of major morbidity was significantly higher in the EG ($P = 0.031$). Red blood cell and fresh frozen plasma transfusion requirements were significantly reduced in the LG, both in regard to the number of patients and the amount of blood product administered. The mean length of postoperative hospital stay was significantly reduced, from 74.4 + −56.3 days in the EG to 29.0 + −11.8 days in the LG ($P < 0.001$). Sixty-nine patients (54.8%) had stage III or IV disease (according to the *General rules for surgical and pathological studies on cancer of the biliary tract* of the Japanese Society of Biliary Surgery), and 55 patients (43.7%) showed positive surgical margins. There were no differences between the two groups in terms of surgical margins or pathological staging.

Conclusions. Improvements were documented in rates of major morbidity, length of hospital stay, and the mortality rate in the LG when compared with the EG. The overall survival rate was similar in the two groups. Blood transfusion requirements were significantly reduced in the LG when compared with the EG. However, the high proportion of patients with positive surgical margins remains a significant problem.

Key words Hilar cholangiocarcinoma · Hepatobiliary resection · Mortality · Blood transfusion · Fresh frozen plasma

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Introduction

Although the use of hepatectomy with caudate lobe resection[1] has increased the resection rate of hilar cholangiocarcinoma (HCCa), major hepatobiliary resection (HBR) for HCCa remains a technically demanding procedure and carries a considerable risk of mortality and serious postoperative morbidity, such as liver failure.[2] Most reports of outcomes following major HBR for HCCa are based on small numbers of patients (i.e., <100 patients),[3–13] and the mortality rate after major HBR is often more than 5% even at high-volume centers.[14–17]

However, recent reports suggest that surgical mortality rates are lower at high-volume centers when compared with low-volume centers.[18–21] At our institution, the number of patients undergoing surgical management of biliopancreatic malignancies has increased markedly since 2000. The standard management strategy for patients with potentially resectable HCCa at our institution consists of appropriate preoperative biliary drainage, preoperative portal vein embolization (PVE),[22–24] and major HBR with caudate lobectomy. The aim of this study was to characterize changes in surgical outcomes following major HBR for HCCa at a single center over a 25-year period.

Patients and methods

Patients

Between January 1980 and December 2004, 175 patients were admitted to our department with a diagnosis of HCCa, including diffuse bile duct carcinoma. Exclusion criteria included patients with intrahepatic cholangiocarcinoma with hilar invasion; patients who did not undergo laparotomy because of highly advanced disease or poor hepatic functional reserve during the preoperative workup; those in whom resection was not possible due to locally advanced status or dissemination; patients who underwent hilar bile duct resection alone; and patients who underwent minor hepatectomy alone. Thus, 126 patients who underwent HBR were enrolled in this study. Medical records, including the hospital charts, operation records, and pathology reports, were retrospectively analyzed.

The patient population consisted of 36 women and 90 men, with a median age of 64 years (range, 33 to 83 years). The patients were divided into two groups according to the chronological treatment period; i.e., patients who underwent surgery during the initial 20-year period (1980–1999; early group [EG]) and those who underwent surgery during the most recent 5-year period (2000–2004; late group [LG]).

Preoperative management and design of surgical procedures

Preoperative evaluation and strategies for management were performed as described previously.[25] Briefly, preoperative workup using image diagnosis included direct cholangiograms, ultrasonography, computed tomography (CT), and conventional abdominal angiography for the assessment of vascular involvement and for the mapping of the vascular anatomy. Concomitantly, patients with obstructive jaundice or obvious cholestatic liver damage principally underwent percutaneous transhepatic biliary drainage (PTBD). The type of hepatectomy was chosen based on the dominant location and extension of the tumor, vascular involvement, and hepatic functional reserve. In patients undergoing right hemihepatectomy or more extensive resection (resected liver volume, estimated using CT-volumetry, >50%), PVE for the resected liver segment was indicated to induce compensatory hypertrophy of the future remnant liver.[22–24]

The indocyanine green (ICG) retention rate at 15 min, after the serum total bilirubin level had decreased to less than 3 mg/dl, was the most reliable key datum for us to evaluate liver functional reserve in our strategy. Definitive surgery was planned 2 to 4 weeks after PVE and was typically performed when the serum total bilirubin level had decreased to less than 2 mg/dl.

Surgery

All the patients underwent hemihepatectomy, bisectionectomy, or more extensive resection with en-bloc resection of the caudate lobe and extrahepatic bile duct, as well as bilio-enterostomy using a Roux-en-Y jejunal limb. Systematic lymphadenectomy for the nodes at the hepatoduodenal ligament and upper part of the retropancreatic and celiac axis was also performed. All liver transections were performed employing the forceps clamp crushing method during hepatic artery and portal vein clamping for 15 min with 5-min intervals (Pringle's maneuver).

The surgical procedures are summarized in Table 1. Right-sided hepatectomy was performed in 63 patients, and left-sided hepatectomy was performed in 62 patients. Only 1 patient underwent central hepatic bisectionectomy. Combined portal vein resection and reconstruction was performed in 18 patients (14.3%), and 2 of these patients underwent concomitant resection and reconstruction of the hepatic artery. Hepatopancreatoduodenectomy (HPD)[26] was performed in 10 patients (7.9%) who had extensive distal bile duct cancer extension, in order to secure the distal bile duct margin. Reconstruction during HPD was conducted by end-to-side pancreaticojejunostomy, using a modified Child's method, in one stage. The amount of blood loss was measured from the volume of blood collected in the suction container plus the weight of gauze soaked with blood.

Blood transfusion strategy[27]

The liberal red blood cell (RBC) transfusion policy employed during the early time periods of this study was significantly restricted in the late 1980s. The most recent criteria consist of RBC transfusion for patients with a hemoglobin concentration of less than 7.5 g/dl during the operation or less than 7.0 g/dl postoperatively. Further, transfusions of fresh frozen plasma (FFP) have undergone a similar shift towards minimization over time. Regardless, FFP transfusion is indicated for patients undergoing extensive liver resection (i.e., >60% of the whole liver), those with poor hepatic functional reserve, or for postoperative hyperbilirubinemia of more than 3.0 to 5.0 mg/dl, at the discretion of the operating surgeon. The volumes of a unit of packed RBC and FFP are 130 ml and 80 ml, respectively.

Definitions of morbidity and mortality

Operative mortality included all in-hospital deaths. In regard to morbidity, all postoperative complications

Table 1. Surgical procedures and operative variables in 126 patients

	EG (1980–1999) (n = 63)	LG (2000–2004) (n = 63)	P value
Type of hepatectomy			
S1,4,5,6,7,8	0	2	
(ext) S1,5,6,7,8	25	36	
S1,2,3,4,5,8,	2	5	
(ext) S1,2,3,4,	36	19	
S1,4,5,8,	0	1	
Right-sided/left-sided	25/38	38/24[a]	0.016
Trisectionectomy	2 (3.2%)	7 (11.1%)	0.084
With PVE	22 (34.9%)	43 (68.3%)	<0.001
With PV	5 (7.9%)	13 (20.6%)	0.073
With PV + HA	2 (3.2%)	2 (3.2%)	1.000
With HA	0	0	1.000
With PD	3 (4.8%)	7 (11.1%)	0.164
Operation time (min)	639 ± 155	689 ± 161	0.212
Blood loss (g)	1480 ± 943	1912 ± 706	<0.001

Numerals indicate Couinaud's segment of the liver
PVE, preoperative portal vein embolization; PV, portal vein resection and reconstruction; HA, hepatic arterial resection and reconstruction; PD, pancreatoduodenectomy
[a] Excluding a patient with central hepatic bisectionectomy

that potentially influenced the outcome or lengthened the hospital stay were considered. Major complications were defined as those that resulted in organ failure or those that required a surgical or interventional radiological procedure. Those complications that could be managed and those that responded to conservative management without intervention or that resolved spontaneously were defined as minor complications.

Final staging of the disease

Histopathological diagnosis of the disease was assessed by pathologists, and the pathological staging of the disease was determined according to the criteria of the International Union Against Cancer (UICC) (sixth edition)[28] and the *General rules for surgical and pathological studies on cancer of the biliary tract* of the Japanese Society of Biliary Surgery (JSBS) (fifth edition).[29]

Statistics

Results are expressed as mean values with SD. Dichotomous variables were evaluated by χ^2 analysis or Fisher's test, as appropriate. The statistical significance of continuous variables was determined by Student's t-test or the Mann-Whitney test. The survival curve for the 126 study patients was generated by the Kaplan-Meier method, and the log-rank test was applied to compare survival between different groups. Results were considered significant when the P values were less than 0.05. All statistical analyses were performed using a statistical analysis software package (SPSS 11.5; SPSS, Chicago, IL, USA).

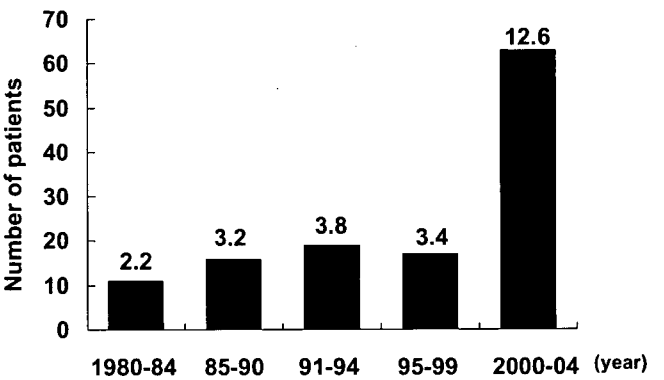

Fig. 1. Numbers of patients who underwent major hepatobiliary resection for hilar cholangiocarcinoma in the indicated 5-year periods. *Numbers above the columns* show the annual numbers of patients during the indicated period

Results

Morbidity, mortality, and survival

The annual number of patients who underwent major HBR for HCCa increased from 3.2 in the EG (1980–1999) to 12.6 in the LG (2000–2004; P = 0.016; Fig. 1). Although the overall in-hospital mortality rate was 3.9% (5/126), all the in-hospital mortalities occurred in the 1980s (Table 2), and the in-hospital mortality rate was 0% in 100 consecutive patients who were enrolled in the study since 1989. The mortality rate improved from 7.9% in the EG to 0% in the LG, but this difference did not reach the level of statistical significance (P = 0.058). The overall survival rates at 1, 3, 5, and 10 years were 82.4%, 43.9%, 35.2%, and 22.2%, respec-

Table 2. Clinical characteristics of patients who died in hospital

Case number	Age (years)	Sex	Type of hepatectomy[a]	POD	Preoperative complication	Main cause of death	Year
1	68	Male	Ext. S1,5,6,7,8	33		Hepatic failure	1981
2	71	Male	Ext. S1,5,6,7,8	95	Schistosomiasis	Hepatic failure	1984
3	66	Male	Ext. S1,5,6,7,8	30	Cholangitis	Sepsis, hepatic failure	1986
4	62	Male	Ext. S1,2,3,4	6		Intraabdominal bleeding, hepatic infarction	1987
5	72	Male	S1,2,3,4,5,8	25		Hepatic failure	1989

POD, postoperative day
[a] Numbers indicate Couinaud's segment of the liver

Table 3 Postoperative course in 126 patients

	EG (1980–1999) ($n = 63$)	LG (2000–2004) ($n = 63$)	P value
Morbidity			
Major	15	6	0.031
Minor	23	28	0.364
Total	38 (60.3%)	34 (54.0%)	0.471
Mortality	5 (7.9%)	0 (0%)	0.058
Postoperative hospital stay (days)	74.4 ± 56.3	29.0 ± 11.8	<0.001
Median [range]	65 [15–429]	26 [23–63]	<0.001

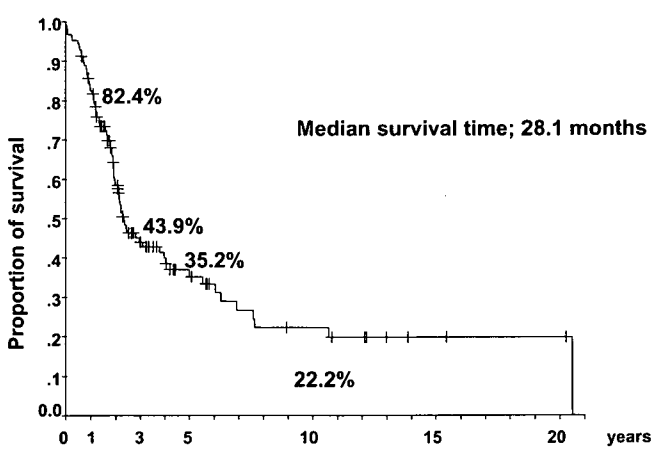

Fig. 2. Cumulative survival of patients with hilar cholangiocarcinoma over a 25-year period at our institution. The overall survival rates at 1, 3, 5, and 10 years were 82.4%, 43.9%, 35.2%, and 22.2%, respectively. The median survival was 28.1 months

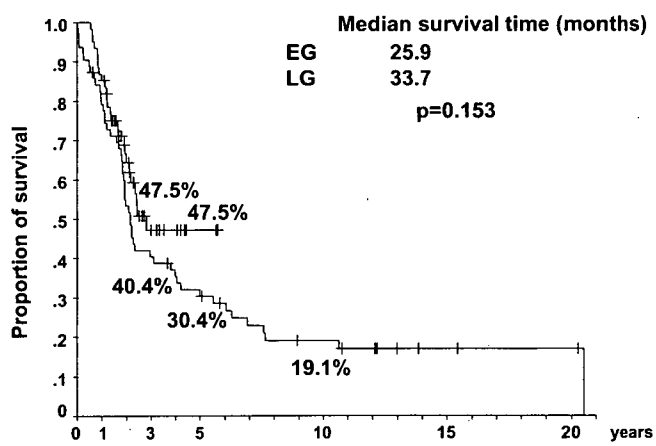

Fig. 3. Cumulative survival according to the chronological treatment period; i.e., the initial 20-year period (early group [*EG*]) and the most recent 5-year period (late group [*LG*]). In the EG, the overall survival rates at 3, 5, and 10 years were 40.4%, 30.4%, and 19.1%, respectively, and the median survival was 25.9 months. In the LG., the overall survival rates at 3 and 5 years were 47.5% and 47.5%, respectively, and the median survival was 33.7 months. The overall survival rate was similar in the two groups ($P = 0.153$)

tively (Fig. 2). The median survival in all patients was 28.1 months (range, 0.17 to 246.1 months), and the overall survival rate was similar in the two groups ($P = 0.153$; Fig. 3). Morbidity was documented in 57.1% of all patients (72/126), and the morbidity rates in the two groups were comparable (60.3% in the EG versus 54.0% in the LG; $P = 0.471$). However, major morbidity was significantly higher in the EG than in the LG ($P = 0.031$; Table 3).

Preoperative variables

Patient characteristics are summarized in Table 4, in which nine clinical variables are compared. The ICG retention value at 15 min was significantly better in the LG than in the EG ($P < 0.001$). Ninety-eight patients (77.8%) underwent preoperative biliary drainage in

Table 4. Characteristics of patients who underwent major hepatobiliary resection

Variables	EG (1980–1999) ($n = 63$)	LG (2000–2004) ($n = 63$)	P value
Sex (male/female)	46/17	44/19	0.693
Age (year)	61.7 ± 9.6	63.2 ± 7.9	0.610
[range]	[39–83]	[33–78]	
Preoperative biliary drainage performed	46 (73.0%)	52 (82.5%)	0.312
ICGR15 (%)	12.1 ± 5.9	8.7 ± 6.8	<0.001
Preoperative serum total bilirubin (mg/dl)	1.4 ± 0.9	1.1 ± 0.5	0.225
Total protein (mg/dl)	7.0 ± 0.6	6.9 ± 0.5	0.193
Albumin (mg/dl)	3.7 ± 0.4	3.7 ± 0.3	0.965
Hemoglobin (g/dl)	12.4 ± 1.4	12.4 ± 1.8	0.596
Platelet ($\times 10^4/\mu l$)	27.4 ± 11.5	24.6 ± 7.2	0.189

ICGR15, indocyanine green retention value at 15 min

Table 5. Blood transfusion data in patients who underwent major hepatobiliary resection

	EG (1980–1999) ($n = 63$)	LG (2000–2004) ($n = 63$)	P value
Blood transfusion			
Packed red blood cells			
Yes	31 (49.2%)	18 (28.6%)	0.019
No	32 (50.8%)	45 (71.4%)	
Mean volume of transfusion (U)	50 ± 8.8	1.3 ± 2.4	0.019
Median [range]	2 [0–56]	0 [0–12]	0.013
Fresh frozen plasma			
Yes	61 (96.8%)	52 (82.5%)	0.002
No	2 (3.2%)	11 (17.5%)	
Mean volume of transfusion (U)	96.6 ± 89.5	51.1 ± 47.2	0.001
Median [range]	70 [0–446]	40 [0–242]	<0.001

total, and there was no difference between the two groups (73.0% in the EG versus 82.5% in the LG; $P = 0.312$). For the other variables, there was no significant difference when comparing the EG and LG.

Operative variables

Surgical procedures are summarized in Table 1. The proportion of patients who underwent right-sided hepatectomy was significantly higher in the LG ($P = 0.016$), and the proportion of patients with preoperative PVE was also significantly higher in the LG than in the EG ($P < 0.001$). Trisectionectomy and portal vein resection and reconstruction were more frequently indicated in the LG than in the EG, but these differences did not reach the level of statistical significance ($P = 0.084$; and $P = 0.073$, respectively). Although the operation time was comparable in the two groups (689 versus 639 min, $P = 0.212$), intraoperative blood loss was significantly increased in the LG when compared with the EG (1912 versus 1480 ml; $P < 0.001$).

Blood transfusion

As shown in Table 5, RBC transfusion requirements were reduced, from 49.2% in the EG to 28.6% in the LG ($P = 0.019$), and the mean volume of transfused RBC decreased from 5.0 ± 8.8 U in the EG to 1.3 ± 2.4 U in the LG ($P = 0.019$). FFP transfusion requirements also decreased, from 96.8% in the EG to 82.5% in the LG, and the mean volume of transfused FFP decreased from 96.6 ± 89.5 U in the EG to 51.1 ± 47.2 U in the LG ($P = 0.001$).

Histopathological variables (Table 6)

Histologically, 55 patients (43.7%) showed positive surgical margins, including proximal and/or distal bile ducts and excisional margins. Sixty-one patients (48.4%) had lymph node metastasis, and direct tumor invasion to the liver parenchyma was confirmed in 32 patients (25.4%). There were no differences between the two groups in terms of surgical margins, histological grade, lymph

Table 6. Histopathological variables in 126 patients

Variables	EG (1980–1999) ($n = 63$)	LG (2000–2004) ($n = 63$)	P value
Surgical margins			
Positive/negative	27/36	28/35	1.000
Histological grade			
Well, pap/others	29/34	19/44	0.067
Lymph node metastasis			
Present/absent	29/34	32/31	0.593
Invasion to the liver parenchyma			
Present/absent	14/49	18/45	0.414
Staging (JSBS)			
I, II/III, IV	32/31	25/38	0.367
Staging (UICC)			
I, II/III, IV	49/14	52/11	0.656

JSBS, Japanese Society of Biliary Surgery; UICC, International Union Against Cancer

node metastasis, or invasio n into the liver parenchyma. Sixty-nine patients (54.8%) had stage III or IV disease according to the JSBS system, and there was no difference in the histological staging, using the JSBS or the UICC system, when comparing the two groups.

Postoperative hospital stay

The overall mean length of postoperative hospital stay was 50.2 ± 46.2 days (median, 38 days; range, 5–429 days) in all patients, with the mean length being 74.4 ± 56.3 days in the EG, and 29.0 ± 11.8 days in the LG ($P < 0.001$). The mean length of postoperative hospital stay in patients with minor morbidity was 65.4 ± 19.3 days (median, 68 days; range, 30–105 days) in the EG, and 34.1 ± 11.1 days (median, 33 days; range, 19–63 days) in the LG ($P < 0.001$).

Discussion

While the management of liver tumors with hepatectomy is relatively safe, with a mortality rate of less than 5% at most institutions,[30–33] major HBR for HCCa is a technically demanding procedure. The present study demonstrated that the mortality rate following major HBR for HCCa tended to decrease over the past several decades, although this difference did not reach the level of statistical significance. Of note, the mortality rate for major HBR for HCCa was 0% for the most recent 100 patients who had been enrolled since 1989. Because the present treatment strategy of preoperative biliary drainage, preoperative PVE, and major HBR with caudate lobectomy was performed by more than ten attending surgeons throughout the course of this study, it is likely that this is a practical approach for the general population of hepatobiliary surgeons.

The reason for the increase in the number of patients undergoing resection of HCCa at our center since 2000 is unclear, but may be related to the increasing information available to patients and their families regarding disease and hospital capacity, surgical volume, and outcomes. Indeed, as the incidence rate of hepatobiliary malignancies is thought to be lower than that of gastrointestinal malignancies, it seems that the number of patients with hepatobiliary malignancies suitable for resection was likely to be concentrated at a few major centers. Thus, the low rate of mortality in our LG is consistent with the notion that hospital surgical volume is inversely correlated with mortality rates.[18–21]

In recent years, patients with obstructive jaundice have tended to undergo biliary drainage at a low range of serum total bilirubin; consequently, the recovery from cholestatic liver damage may be quite rapid, and this may be the reason that the ICG retention value was better in the LG than in the EG. In tumors that are resectable by either right-sided or left-sided hepatectomy, right-sided resection is the preferred method for patients with a satisfactory functional reserve of the future remnant liver; therefore, right-sided hepatectomy and PVE were more frequently indicated in the LG than in the EG.

Although the operation time was comparable in the two groups in our study, the intraoperative blood loss was approximately 400 ml more in the LG that in the EG. The absolute blood volume loss of 1912 ml in the LG was comparable to that seen in another recent large series of hilar malignancies treated with HBR.[34] The definitive reason for the larger blood loss in the LG remains unclear, but it may be related to extended surgical procedures, including portal vein resection and reconstruction, trisectionectomy, and HPD, which tended to be more frequently indicated in the LG than in the EG.

While the blood transfusion requirement was significantly reduced in the LG when compared with the EG, 28.6% of patients in the LG still underwent RBC transfusion, and 82.5% underwent FFP transfusion; figures that are higher than the transfusion requirement reported in other studies.[34,35] The main purpose of FFP administration is to induce volume expansion without homologous RBC transfusion,[27] which would otherwise be associated with an increased risk of postoperative hyperbilirubinemia[27,34] or immunosuppression.[36] However, the liberal use of FFP results in a higher perioperative cost and a higher risk of transmission of infectious diseases, making minimization of FFP transfusions desirable. Although the proportion of patients receiving FFP decreased, from 96.8% in the EG to 82.5% in the LG, the mean volume of transfused products decreased from 96.6 U in the EG to 51.1 U in the LG. Further minimization of transfusion may help to improve outcomes.

In the present study, the proportion of patients with cancer-positive surgical margins exceeded 40%, which is higher than that reported in another large series, which achieved more than 70% of patients with cancer-negative surgical margins.[4–6,11–13,15–17] Regardless of this finding, the 5-year survival of the patients with positive surgical margins was not necessarily low. Sixty-one patients (48.4%) had lymph node metastasis and more than half of the patients were diagnosed as having stage III or IV disease according to the JSBS system. These data suggest that the patients in this series were not necessarily shifted to an early stage. Thus, the relatively high rate of positive surgical margins in the present study compared with rates in other studies may be attributed either to the strict diagnostic criterion of bile duct margins that we used or to differences in institutional diagnostic criteria.[37] Another possibility is that a positive surgical margin is not a significant prognostic factor.[38] Indeed, several patients in our series have survived for more than 5 years without tumor recurrence, despite having positive surgical margins. Further study to clarify the diagnostic accuracy of bile duct margins and the impact of positive bile duct margins on survival would be of benefit.

In our series, 40% of patients with stage II disease, according to the JSBS system, had positive bile duct margins. Tumor extension in the bile duct consisted of perpendicular and horizontal extensions along the bile duct. While aggressive surgical strategies to combat horizontal extension, such as trisectionectomy or HPD, may be selected, the safety, efficacy, and indications for HPD in patients with biliary cancer remain controversial. In fact, trisectionectomy to minimize future remnant liver volume may be a burden for patients with cholestatic liver damage and may result in serious complications, such as liver failure. When considering patients for trisectionectomy or HPD, we must pay special attention to the safety of such invasive procedures, considering the reported high morbidity and mortality rates associated with HPD for biliary cancer.[26,39,40]

Although overall postoperative morbidity in HBR for HCCa is still high,[2] we found that the rate of major complications and length of hospitalization in patients with minor morbidity was significantly reduced in our LG, which likely accounts for the reduced total length of hospitalization in the LG when compared with the EG.

In summary, improvements were documented in major morbidity rates, length of hospital stay, and the mortality rate in the LG when compared with the EG. The overall survival rate was similar in the two groups. Blood transfusion requirements were significantly reduced in the LG when compared with the EG. However, the high proportion of patients with positive surgical margins remains a significant problem.

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