

Received: 2013.08.25  
Accepted: 2014.01.23  
Published: 2014.03.22

# When hepatic-side ductal margin is positive in N+ cases, additional resection of the bile duct is not necessary to render the negative hepatic-side ductal margin during surgery for extrahepatic distal bile duct carcinoma

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

ABCDEFG **Yukihiro Iso**  
E **Junji Kita**  
E **Masato Kato**  
E **Mitsugi Shimoda**  
ACDEG **Keiichi Kubota**

Department of Gastroenterological Surgery, Dokkyo Medical University, Mibu, Tochigi, Japan

**Corresponding Author:** Yukihiro Iso, e-mail: karinaiso@yahoo.co.jp  
**Source of support:** Departmental sources

**Background:** The current standard treatment for extrahepatic distal bile duct carcinoma (EDBDC) is surgical resection, as no effective alternative treatment exists. In this study, we investigated the treatment strategies and outcomes for 90 cases of EDBDC at our department.

**Material/Methods:** Between April 2000 and March 2013, 90 pancreatoduodenectomies (PDs) were performed for EDBDC. The mean patient age was 69.1±9.8 years, and there were 59 males and 31 females. Extended lymph adenectomy including lymph nodes around the common hepatic artery and celiac axis was performed in all patients. The mean operation time was 537.1±153.8 min and the mean operative blood loss was 814.0±494.0 ml. There were no operation-related deaths. The overall 1-, 3-, and 5-year survival rates were 90.0%, 51.2%, and 45.0%, respectively.


**Results:** Lymph node metastasis was present in 28 patients (N+; 31.1%), and it was absent in 62 (N-; 68.9%). The 5-year survival rate was 20.0% for N+ patients and 52.4% for N- patients, which is significantly higher ( $P=0.03$ ). Nine cases (10.0%) showed hepatic-side ductal margin (HM) positivity for carcinoma. The 5-year survival rate was 18.7% for HM-positive patients and 48.3% for HM-negative patients, which is significantly higher ( $P=0.005$ ). In multivariate analysis, N+ was the strongest adverse prognostic factor. Subclass analysis of 62 cases (excluding 28 N+ cases) revealed 7 patients with positive HMs (11.3%) and 55 patients with negative HMs (88.7%). The 5-year survival rate was 47.6% for HM-positive patients and 49.8% for HM-negative patients ( $P=0.73$ ).

Thirty-five cases (38.9%) recurred: there were 19 cases of local recurrence (21.1%), 11 cases of liver metastasis (12.2%), 4 cases of distant recurrence (4.4%), and 1 case of para-aortic lymph node metastasis (1.1%).

**Conclusions:** In conclusion, when HM is positive in N+ cases, additional resection of the bile duct is not necessary to render the HM negative for carcinoma.

**MeSH Keywords:** **Bile Duct Neoplasms • Lymphatic Metastasis • Bile Ducts, Extrahepatic • Pancreaticoduodenectomy**

**Full-text PDF:** <http://www.medscimonit.com/download/index/idArt/889714>

 1321

 2

 7

 28

## Background

The current standard treatment for extrahepatic distal bile duct carcinoma (EDBDC) is surgical resection, as no effective alternative treatment exists [1]. Pancreatoduodenectomy (PD) has been established as a standard procedure, and PD with hepatectomy (HPD) is the extended procedure in cases of invasion to major blood vessels, nerves or lymphatics, or extensive progression along the long axis of the bile duct [2]. Given the surgical stress and radicality of these treatments, EDBDC is often characterized by difficulty in determining the rational extent of resection.

We reviewed our experiences of standard PD with extended lymph node dissection (D2) [3] for EDBDC and assessed the available treatment strategies.

## Material and Methods

Between April 2000 and March 2013, 90 PDs were performed for EDBDC at our department. The standard procedure was PD with extended lymph node dissection (D2 dissection). LN was defined in accordance with the General Rules for Surgical and Pathological Studies on Cancer of the Biliary Tract [3]. Nodes around the bile duct (N1), peripancreatic nodes, and nodes around the hepato-duodenal ligament excluding N1 (N2) were dissected routinely (D2) [3]. We performed surgery with removal of the semi-circular nerve plexus around the superior mesenteric artery. Extended lymph adenectomy, including lymph nodes along the common hepatic artery and celiac axis, was performed in all patients. In cases of portal vein invasion, we performed PD with portal vein resection (PDPVR). In cases of superficial spread of the carcinoma along the bile duct toward the hilar bile duct, we performed HPD with 2-stage pancreateojejunostomy [4].

Follow-up examinations were performed with abdominal ultrasonography, computed tomography, and measurement of the serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels every 3–6 months.

The hepatic-side ductal margin (HM) was defined in accordance with the General Rules for Surgical and Pathological Studies on Cancer of the Biliary Tract [3]. Briefly, HM was defined as the proximal ductal margin. When carcinoma cells were detected on the cut surface of the resected fibromuscular layer margin or the resected mucosal layer, the margin was defined as HM-f-positive and as HM-m-positive, respectively.

## Statistical analysis

Prognostic analysis was performed using the data from 90 patients. The clinicopathologic factors analyzed included age, sex,

**Table 1.** Clinical background factors of the study patients.

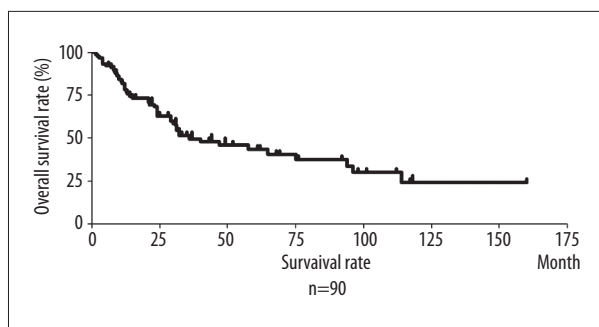
Age	69.1±9.8
Male (%)	59 (65.6)
Female (%)	31 (34.4)
Preoperative biliary drainage (%)	78 (86.7)
HPD (%)	11 (12.2)
PDPVR (%)	5 (5.6)
PD (%)	74 (82.2)
Operation time (min)	537.1±153.8
Intraoperative blood loss (ml)	814.0±494.0
Stage I (%)	5 (5.6)
Stage II (%)	30 (33.3)
Stage III (%)	36 (40.0)
Stage IV (%)	19 (21.1)

HPD – pancreatoduodenectomy with extended hepatectomy; PDPVR – pancreatoduodenectomy with portal vein resection; PD – pancreatoduodenectomy.

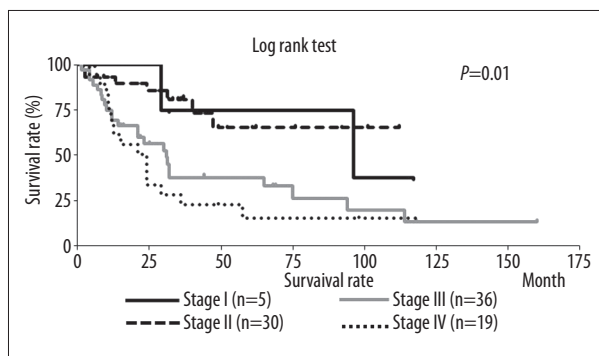
preoperative biliary drainage, the operative procedure, intraoperative blood loss, histopathologic grading (G category in the TNM classification of malignant neoplasms) [5], depth of neoplastic invasion into the bile duct wall (T category), status of lymph node involvement (N category), TNM staging, and HM status. Based on the results of univariate analysis, multivariate analysis was performed. Each parameter was evaluated using chi-squared test, Fisher's exact test, or Student's *t*-test for parametric analysis, and Mann-Whitney U-test for nonparametric analysis. Differences at  $P<0.05$  were considered significant.

## Results

Patient characteristics are shown in Table 1. Mean age was 69.1±9.8 years. There were 59 males (65.6%) and 31 females (34.4%). Preoperative biliary drainage was performed in 78 cases (86.7%). Eleven patients underwent HPD because of hepatic hilar invasion and 5 underwent PDPVR due to portal vein invasion. The remaining 74 patients underwent only PD. The mean operation time was 537.1±153.8 min and the mean operative blood loss was 814.0±494.0 ml. There were no operation-related deaths. Pathological examination revealed that there were 5 cases of stage I, 30 cases of stage II, 36 cases of stage III, and 19 cases of stage IV. The overall 1-, 3-, and 5-year survival rates were 90.0%, 51.2%, and 45.0%, respectively (Figure 1). The 5-year survival rates for patients at stages I, II, III, and IV were 75.0%, 67.2%, 39.7%, and 18.5%, respectively ( $P=0.01$ , Figure 2).



**Figure 1.** Over-all survival rate. The 1-, 3-, and 5-year survival rates were 90.0%, 51.2%, and 45.0%, respectively.

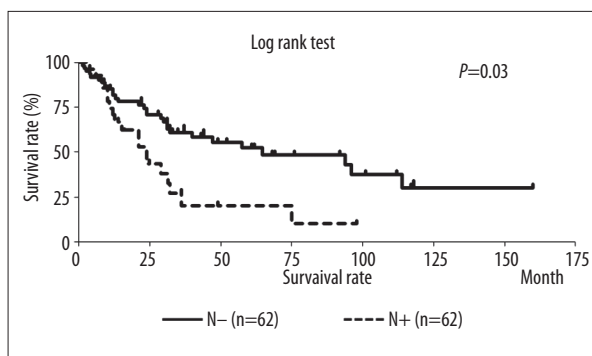


**Figure 2.** Survival rates according to tumor stage. The 5-year survival rates for patients at stages I, II, III, and IV were 75.0%, 67.2%, 39.7%, and 18.5%, respectively ( $P=0.01$ ).

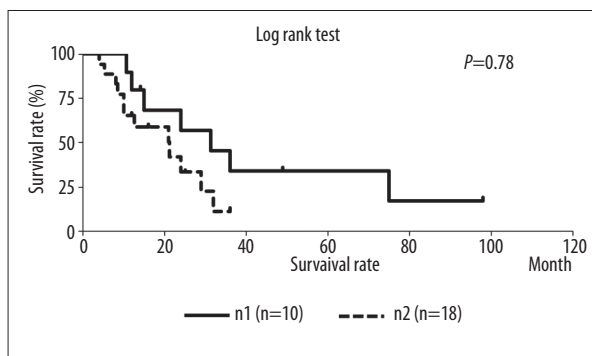
There were 28 patients with lymph node positivity (N+; 31.1%), including 18 who were N1+ only and 10 who were N2+; 62 patients were negative for lymph node metastasis (N-) [3]. The 5-year survival rate was 20.0% for N+ patients and, 52.4% for N- patients, which was significantly higher ( $P=0.03$ , Figure 3). The 3-year survival rate was 37.5% for patients who had N1+ lymph node metastasis and 12.7% for those who had N2+ lymph node metastasis. There were no significant differences between the 2 groups ( $P=0.78$ , Figure 4). Twelve patients had 1 lymph node metastasis, 17 had 2 to 3 lymph node metastases, and 20 patients had more than 3. The 5-year survival rate was 42.9% for patients with 1 lymph node metastasis ( $P=0.78$ , Figure 5A), 25.0% for those with 2 to 3 lymph node metastases ( $P=0.91$ , Figure 5B), and 23.5% for those with more than 3 lymph node metastases. There was no significant difference between the 2 groups ( $P=0.59$ , Figure 5C).

Nine cases (10.0%) showed hepatic-side ductal margin (HM) positivity for carcinoma. The 5-year survival rate was 18.7% for HM-positive patients and 48.3% for HM-negative patients, which was significantly higher ( $P=0.005$ , Figure 6).

In multivariate analysis, N+ was the strongest adverse prognostic factor (Table 2).



**Figure 3.** Survival rates according to lymph node metastasis. The 5-year survival rate was 20.0% for N+ patients and 52.4% for N- patients, which is significantly higher ( $P=0.03$ ).



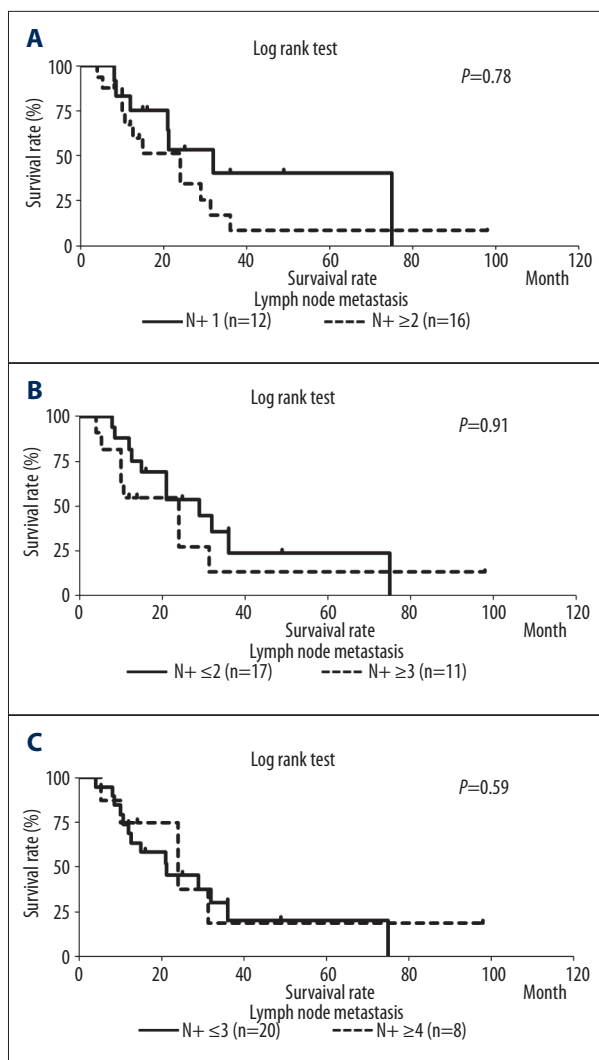
**Figure 4.** Survival rates according to location of lymph node metastasis. The 3-year survival rate was 37.5% for patients who had N1+ lymph node metastasis and 12.7% for patients who had N2+ lymph node metastasis. There were no significant differences between the 2 groups ( $P=0.78$ ).

Subclass analysis of 62 cases (excluding 28 N+ cases) revealed 7 patients with positive HMs (11.3%) and 55 patients with negative HMs (88.7%). The 5-year survival rate was 47.6% for HM-positive patients and 49.8% for HM-negative patients ( $P=0.73$ , Figure 7).

Thirty-five cases (38.9%) recurred; there were 19 cases of local recurrence (21.1%), 11 cases of the liver metastasis (12.2%), 4 cases of distant recurrence (4.4%), and 1 case of the para-aortic lymph node metastasis (1.1%).

## Discussion

The prognosis of EDBDC is poor, even when curative resection is performed [6]. The reported 5-year survival of patients with EDBDC ranges from 18% to 47% [7–10]. These low survival rates are due mainly to invasion of veins, lymph nodes, or nerve tissue at the time of resection [11]. According to the classification of biliary tract carcinoma [3], any case showing

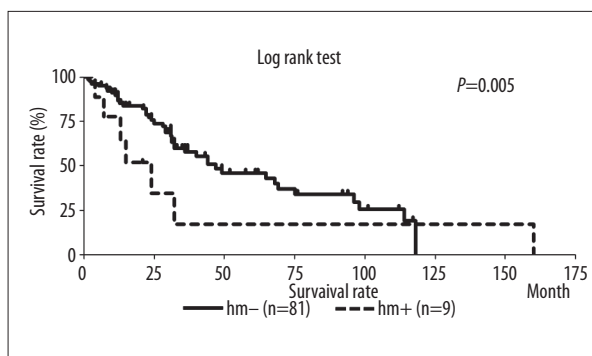


**Figure 5.** Survival rates according to number of lymph node metastasis. (A) Twelve patients had one lymph node metastasis, 17 patients had 2 more lymph node metastases, and 20 patients had more than 3. The 5-year survival rate of patients with 1 lymph node metastasis was 42.9% ( $P=0.78$ ). (B) Survival rate of patients with 2 to 3 lymph node metastases was 25.0% ( $P=0.91$ ). (C) Survival rate of patients with more than 3 lymph node metastases was 23.5%. There was no significant difference between the 2 groups ( $P=0.59$ ).

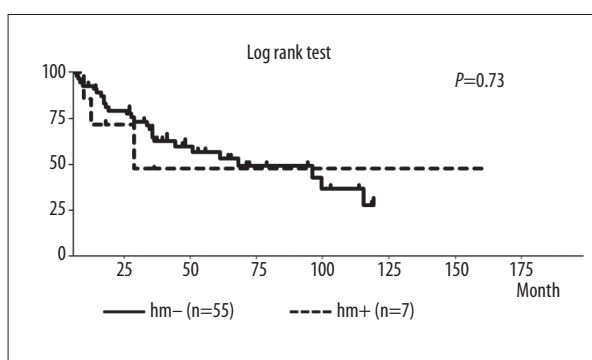
**Table 2.** Multivariate logistic regression analysis in relation to mortality.

	P	Odds ratio	95% CI
N+	0.043*	4.532	1.049–19.582
HM	0.969	763.3	612.8–765.2

\* Significant difference.



**Figure 6.** Survival rates according to HM status. Nine cases (10.0%) showed HM positivity for carcinoma. The 5-year survival rate was 18.7% for HM-positive patients and 48.3% for HM-negative patients, which is significantly higher ( $P=0.005$ ).



**Figure 7.** Subclass analysis of 62 cases (excluding 28 N+ cases) revealed 7 patients with positive HMs (11.3%) and 55 patients with negative HMs (88.7%). The 5-year survival rates for HM positive and negative patients were 47.6%, and 49.8%, respectively ( $P=0.73$ ).

invasion at the excisional margin, HM, or distal ductal margin is defined as non-curative resection, and is thought to have a poor prognosis. However, previous reports have indicated no significant difference in prognosis between curative and non-curative resection [12], which is consistent with our present results. Here, we focused especially on carcinoma with HM positivity and N+, and investigated the significance of these factors.

In EDBDC, which is characterized by local progression rather than distant metastasis, curative resection is the most important prognostic factor. However, HM positivity is the most frequently observed non-curative factor after resection [13–15]. In cases in which rapid intraoperative histopathological diagnosis reveals HM positivity, we perform additional resection of the first branch of the intrahepatic bile duct. Some previous reports have concluded that HM positivity affects prognosis [16,17], while others have concluded otherwise [18–20], and the reasons for this difference is not well understood.

Several studies have reported that N+ is a strong adverse prognostic factor [21–24]. Our multivariate analysis also found that N+ was the strongest adverse prognostic factor, and our series included only 1 N+ patient who survived longer than 5 years. However, the 62 N- cases in the present study did not reveal HM positivity as a significant adverse prognostic factor. Given the strong influence of N+, HM positivity alone did not influence the outcome of any of the 90 resected cases.

In cases that are HM-positive, recent studies have reported significantly better prognoses for HM-m positivity than for HM-f positivity. In addition, the prognosis of HM-m-positive patients is similar to that for N- patients. Many reports have suggested that HM-m positivity should be differentiated from HM-f positivity [17,19,25–27].

## References:

1. Kondo S, Hirano S, Ambo Y et al: Forty consecutive resections of hilar cholangiocarcinoma with no postoperative mortality and no positive ductal margins: result of a prospective study. *Ann Surg*, 2004; 240: 95–101
2. Allen PJ, Reiner AS, Gonen M et al: Extrahepatic cholangiocarcinoma: a comparison of patients with resected proximal and distal lesions. *HPB*, 2008; 10: 341–46
3. General rules for surgical and pathological studies on cancer of the biliary tract. September 2003 (the 5<sup>th</sup> ed.): Japanese Society of Biliary Surgery (JSBS)
4. Kubota K, Makuuchi M, Takayama T et al: Appraisal of two-staged pancreatoduodenectomy: its technical aspects and outcome. *Heptogastroenterology*, 2000; 47(31): 269–74
5. International Union Against Cancer (UICC); Sobin L, Gospodarowicz M, Wittekind C (eds.), TNM Classification of malignant tumours. 7<sup>th</sup> ed. New York: Wiley-Liss, 2009
6. Yoshida T, Matsumoto T, Sasaki A et al: Prognostic factors after pancreatoduodenectomy with extended lymphadenectomy for distal bile duct cancer. *Arch Surg*, 2002; 137: 69–73
7. Hong SM, Pawlik TM, Cho H et al: Depth of tumor invasion better predicts prognosis than the current American Joint Committee on Cancer T classification for distal bile duct carcinoma. *Surgery*, 2009; 146: 250–57
8. Ebata T, Nagino M, Nishio H et al: Pancreatic and duodenal invasion in distal bile duct cancer: paradox in the tumor classification of the American Joint Committee on Cancer. *World J Surg*, 2007; 31: 2008–15
9. DeOliveria ML, Cunningham SC, Cameron JL et al: Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg*, 2007; 245: 755–62
10. Park SW, Park YS, Chung JB et al: Patterns and relevant factors of tumor recurrence for extrahepatic bile duct carcinoma after radical resection. *Hepato-gastroenterology*, 2004; 51: 1612–18
11. Cheng Q, Luo X, Zhang B et al: Distal bile duct carcinoma: prognostic factors after curative surgery. A series of 112 cases. *Ann Surg Oncol*, 2007; 14: 1212–19
12. Todoroki T, Kawamoto T, Koike N et al: Treatment strategy for patients with middle and lower third bile duct cancer. *Br J Surg*, 2001; 88: 364–70
13. Miyazaki M, Kato A, Ito H et al: Combined vascular resection in operative resection for hilar cholangiocarcinoma: does it work or not? *Surgery*, 2007; 141: 581–88
14. Sano T, Shimada K, Sakamoto Y et al: Progression of perihilar cholangiocarcinoma: hilar bile duct cancer versus intrahepatic cholangiocarcinoma involving the hepatic hilus. *Ann Surg Oncol*, 2008; 15: 590–99
15. Nakajima M, Otsuka M, Kimura H et al: Frozen section diagnosis of the bile duct margin in bile duct cancer. *Tan to Sui*, 2010; 31: 837–41 [in Japanese]
16. Murakami Y, Uemura K, Hayashidani Y et al: Prognostic significance of lymph node metastasis and surgical margin status for distal cholangiocarcinoma. *J Surg Oncol*, 2007; 95: 207–12
17. Sasaki R, Takeda Y, Funato O et al: Significance of ductal margin status in patients undergoing surgical resection for extrahepatic cholangiocarcinoma. *World J Surg*, 2007; 31: 1788–96
18. Hernandez J, Cowgill SM, Al-Saadi S et al: An aggressive approach to extrahepatic cholangiocarcinomas is warranted: margin status does not impact survival after resection. *Ann Surg Oncol*, 2008; 15: 807–14
19. Wakai T, Shirai Y, Moroda T et al: Impact of ductal resection margin status on long-term survival in patients undergoing resection for extrahepatic cholangiocarcinoma. *Cancer*, 2005; 103: 1210–16
20. Sakamoto Y, Kosuge T, Shimada K et al: Prognostic factors of surgical resection in middle and distal bile duct cancer. An analysis of 55 patients concerning the significance of ductal and radial margins. *Surgery*, 2005; 137: 396–402
21. Otani K, Chijiwa K, Kai M et al: Outcome of surgical treatment of hilar cholangiocarcinoma. *J Gastrointest Surg*, 2008; 12: 1033–40
22. Pichlmayr R, Weimann A, Klempnauer J et al: Surgical treatment in proximal bile duct cancer. A single-center experience. *Ann Surg*, 1996; 224: 628–38
23. Nagakawa T, Kayahara M, Ikeda S et al: Biliary tract cancer treatment: results from the biliary tract cancer statistics registry in Japan. *J Hepatobiliary Pancreat Surg*, 2002; 9: 569–75
24. Otani K, Chijiwa K, Kai M et al: Significance of ductal margin status as a prognostic factor in patients undergoing surgical resection for extrahepatic cholangiocarcinoma. *Journal of Japan Biliary Association*, 2009; 23: 749–55 [in Japanese with English abstract]
25. Igami T, Nagino M, Oda K et al: Clinicopathologic study of cholangiocarcinoma with superficial spread. *Ann Surg*, 2009; 249: 296–302
26. Nakanishi Y, Kondo S, Zen Y et al: Impact of residual *in situ* carcinoma on postoperative survival in 125 patients with extrahepatic bile duct carcinoma. *J Hepatobiliary Pancreat Sci*, 2010; 17: 166–73
27. Higuchi R, Ota T, Araida T et al: Prognostic relevance of ductal margins in operative resection of bile duct cancer. *Surgery*, 2010; 148: 7–14
28. Sakamoto E, Nimura Y, Hayakawa N et al: The pattern of infiltration at the proximal boarder of hilar bile duct carcinoma: a histologic analysis of 62 resected cases. *Ann Surg*, 1998; 227: 405–11