Table 3 Risk factors for postoperative hyperbilirubinemia in patients with biliary tract malignancies

Parameter	No postoperative hyperbilirubinemia (n = 94)	Postoperative hyperbilirubinemia (n = 17)	*P* value
Patient background and preoperative parameters			
Gender (M/F)	58/36	10/7	.82
Age (y)	66.2 ± 8.7	65.9 ± 8.6	.89
Chronic viral hepatitis (+)	7	1	.81
Obstructive jaundice (+)	56	12	.75
Serum total bilirubin level at operation (mg/dL)	1.5 ± 1.1	2.0 ± 1.4	.10
b value (<−.05/>−.05)	41/16	7/6	.24
ICG-R15 (%)	12.4 ± 8.1	16.6 ± 9.8	.07
GaTT-T/2 (min)	21.2 ± 7.4	22.7 ± 8.8	.47
Portal vein embolization (+)	31	5	.75
Cholangitis (+) (mild/ severe)	18/7	5/1	.59
Intraoperative parameters			
Type of hepatic resection (ELH/ERH/TS)	38/49/7	3/11/3	.15
Vascular resection and reconstruction (+)	27	7	.30
Bilioenteric anastomosis (+)	91	17	.46
Blood loss during operation (mL)	1,769 ± 1,959	4,438 ± 5,266	.01
Operative time (min)	489 ± 96	562 ± 142	.01
Total duration of intermittent Pringle maneuver (min)	36.2 ± 9.7	38.3 ± 17.6	.54
Volumetric parameter			
RLV/ELV (%)	55.1 ± 16.9	42.4 ± 15.7	.009

ELH = extended left hepatectomy; ERH = extended right hepatectomy; TS = trisegmentectomy; RLV = remnant liver volume; ELV = entire liver volume.

Intraoperative parameters and postoperative outcome

The amount of blood loss during surgery and the operative time were significantly greater among patients who developed postoperative hyperbilirubinemia and who subsequently died than among those without postoperative liver dysfunction. Factors related to surgical procedures were not significantly associated with postoperative liver dysfunction (Tables 3 and 4).

Table 4 Risk factors for postoperative mortality due to liver failure in patients with biliary tract malignancies

Parameter	No postoperative fatal outcome (n = 102)	Postoperative fatal outcome (n = 9)	*P* value
Patient background and preoperative parameters			
Gender (M/F)	64/38	4/5	.28
Age (y)	65.8 ± 8.8	69.0 ± 6.0	.29
Chronic viral hepatitis (+)	7	1	.64
Obstructive jaundice (+)	62	6	.81
Serum total bilirubin level at operation (mg/dL)	1.6 ± 1.2	1.8 ± 1.3	.60
b value (<−.05/>−.05)	44/19	4/3	.58
ICG-R15 (%)	12.4 ± 8.0	19.6 ± 11.2	.02
GaTT-T/2 (min)	21.4 ± 4.2	21.9 ± 9.8	.98
Portal vein embolization (+)	33	3	.81
Cholangitis (+) (mild/ severe)	19/7	4/1	.16
Intraoperative parameters			
Type of hepatic resection (ELH/ ERH/ TS)	41/53/8	0/7/2	.92
Vascular resection and reconstruction (+)	30	4	.35
Bilioenteric anastomosis (+)	99	9	.60
Blood loss during operation (mL)	1,942 ± 2,126	4,848 ± 6,862	.03
Operative time (min)	494 ± 100	573 ± 160	.04
Total duration of intermittent Pringle maneuver (min)	36.2 ± 14.1	4.3 ± 2.4	.76
Volumetric parameter			
RLV/ELV (%)	54.8 ± 16.9	35.1 ± 1.7	.004

ELH = extended left hepatectomy; ERH = extended right hepatectomy; TS = trisegmentectomy; RLV = remnant liver volume; ELV = entire liver volume.

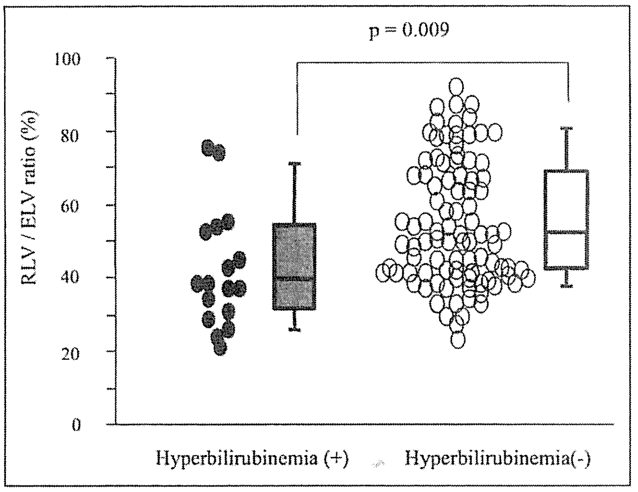

Figure 1 A comparison of the RLV/ELV ratios of patients with and without postoperative hyperbilirubinemia. Mean RLV/ELV ratio in patients with hyperbilirubinemia was 42.4% ± 15%, while that in patients without hyperbilirubinemia was 55.1% ± 17%. The RLV/ELV ratio in patients with postoperative hyperbilirubinemia was significantly lower than in patients without hyperbilirubinemia (p = 0.009).

Volumetric analysis and postoperative outcome

The RLV/ELV ratio was significantly lower in patients with postoperative liver dysfunction than in patients without postoperative liver dysfunction ($P < .01$). Mean RLV/ELV ratio in patients with postoperative hyperbilirubinemia was 42.4% ± 15 %, while that in patients without postoperative hyperbilirubinemia was 55.1% ± 17 % (Figure 1). Patients who ultimately died of liver failure had the lowest RLV/ELV ratios, with a mean of 35.1% ± 11%. Peak postoperative serum total bilirubin levels were negatively correlated with RLV/ELV ratio (Figure 2) (Tables 3 and 4).

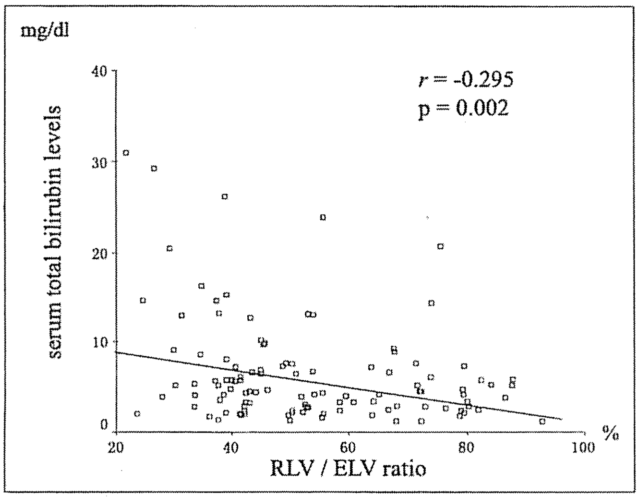

Figure 2 Relationship between RLV/ELV ratio and peak postoperative total bilirubin levels within 2 weeks after surgery. A significant negative correlation was observed (P = 0.002, r = −0.295).

Table 5 Multivariate analysis of liver dysfunction

	P value	Odds ratio (95% confidence interval)
Hyerbilirubinemia		
RLV/ELV ratio	.006	.938 (.896–.981)
Blood loss	.17	1.000 (1.000–1.000)
Operative time	.09	1.006 (.999–1.012)
Fatal outcome		
ICG-R15	.041	1.105 (1.004–1.215)
RLV/ELV ratio	.005	0.864 (.780–.957)
Blood loss	.73	1.000 (1.000–1.000)
Operative time	.17	1.008 (0.997–1.018)

Logistic regression analysis

Multivariate analysis indicated that only RLV/ELV ratio was an independent risk factor that influenced hyperbilirubinemia after extended hepatic resection, as shown in Table 5. When logistic regression was used, in order to distinguish which patients had died of liver failure, ICG-R15 and, again, RLV/ELV ratio were selected as independent risk factors.

Determination of the RLV/ELV ratio cut off value affecting postoperative hyperbilirubinemia

According to receiver operating characteristic curve, the best RLV/ELV cutoff value was 40%, with sensitivity 59% and specificity 81%, to distinguish patients with from those without postoperative hyperbilirubinemia. When RLV/ELV ratio was used in the logistic regression model as a categorical variable, instead of a continuous variable, with a cutoff of 40%, it was an independent risk factor that influenced hyperbilirubinemia after extended hepatic resection (odds ratio 7.6; 95% confidence interval, 2.1–27; $P < .002$).

RLV/ELV ratio and ICG-R15 in patients with fatal outcome

All patients who died of liver failure had a RLV/ELV ratio of less than 40% and/or higher than 25% of ICG-R15 (Figure 3). Conversely, all patients who had RLV/ELV greater than 40% and less than 25% of ICG-R15 tolerated extended hepatic resection.

Comments

Since extended hepatic resection was first performed to achieve curative resection, which is reported to be a major prognostic factor,[2–5,7] patient survival in cases of biliary tract malignancies has improved greatly. However, the mortality rate after extended hepatic resection is still high, ranging from 0% to 25%.[2,3,16–18] The high mortality rate is

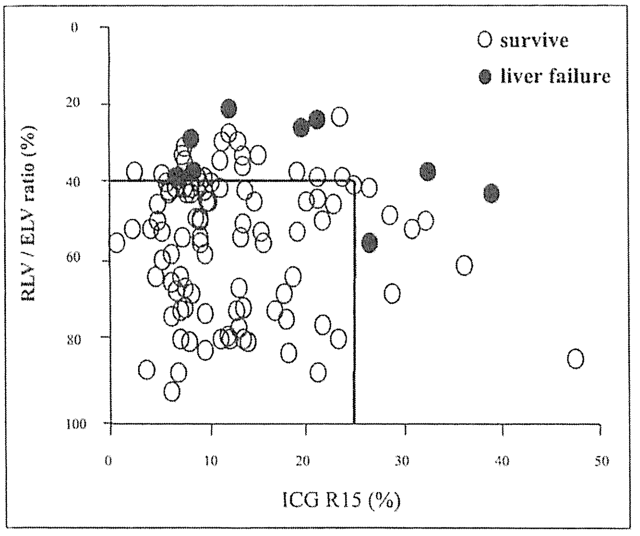

Figure 3 RLV/ELV ratio and ICG-R15 in patients with fatal outcomes. Open circles: patients who tolerated extended hepatic resection. Filled circles: patients who died of liver failure after extended hepatic resection. All patients tolerated surgery when their RLV/ELV ratio was >40% and ICG-R15 was <25%.

mainly attributable to postoperative hyperbilirubinemia, followed by hepatic failure. Therefore, investigation of factors that influence postoperative liver dysfunction is of great interest for surgeons hoping to improve perioperative outcome in patients with biliary tract malignancies.

Since the majority of patients with biliary tract malignancies have obstructive jaundice, it has been suggested that preoperative cholestasis is associated with postoperative liver dysfunction. Many retrospective clinical reports and experimental data suggest that preoperative obstructive jaundice is related to postoperative morbidity and mortality.[19–21] Based on these facts, routine preoperative biliary decompression, to a serum bilirubin level of 2–3 mg/dL, has been advocated to reduce postoperative complications.[18,20] In the present study, all patients with obstructive jaundice received preoperative biliary drainage, but 13 (19%) of these patients still had jaundice with serum total bilirubin levels greater than 3 mg/dL at the time of extended hepatic resection. However, serum total bilirubin levels at the time of surgery and the rate of decrease in the level of serum bilirubin were not found to be significant risk factors for postoperative liver dysfunction. These results raise the question of whether or not preoperative biliary decompression should be routinely performed before extended hepatic resection, although it is possible that patients in this study who had jaundice at the time of surgery had already received effective relief of cholestasis in spite of their bilirubin levels. There have been few reports on this issue, especially in regard to patients with extended hepatic resections, but Cherqui et al[22] have recently shown that major liver resections without preoperative biliary drainage are safe for most patients with obstructive jaundice.

Our logistic regression model has shown that the RLV/ELV ratio was the strongest risk factor for liver dysfunction after extended hepatic resection in patients, the majority of whom had preoperative jaundice. Recently, with an increase of the number of cases with major hepatic resection and living-related liver transplantation, the importance of volumetric analysis by computed tomography images has been emphasized to avoid postoperative liver dysfunction.[23] Several reports have shown the minimum extent of remnant liver volume compatible with a safe postoperative outcome, with RLV/ELV ratios ranging from 25% to 30%.[8,24,25] A significant correlation between remnant liver volume and postoperative peak bilirubin level has also been reported.[8,25] These results were similar to our current results, although the extent of remnant liver volume in patients who developed postoperative hyperbilirubinemia (mean 42% of RLV/ELV ratio) and subsequent fatal outcome (mean 35% of RLV/ELV ratio) was a bit large in our study. The reason for this might be that, in previous reports, the patients who were assessed mostly had normal liver parenchyma, while in our study, the majority of patients had cholestatic liver. Takahashi et al[26] have also shown that resection of up to 48.7% of the liver was safe and hepatectomy of up to 71.6% was the maximum permissible resection, calculated on the basis of postoperative bilirubin levels, in patients with obstructive jaundice, even after relief of it. Their results and ours suggest that the extent of liver that can be safely resected is limited in the case of cholestatic liver, even after this condition is relieved, and, when the estimated RLV/ELV ratio is ≤40%, which is the critical point for postoperative liver dysfunction as shown in this study, portal vein embolization should be performed before extended hepatic resection to increase the RLV/ELV ratio.

Another significant factor for mortality due to hepatic failure, but not for postoperative hyperbilirubinemia, was ICG-R15. Use of ICG-R15 has been proposed by many institutions as one of the best ways to evaluate the safe limits for hepatic resection.[11,27] However, since such assessment is directly influenced by the severity of jaundice, due to excretory competition with bilirubin, its result must be carefully interpreted in cases of patients with obstructive jaundice. In the present study, this evaluation was conducted principally after the total bilirubin level had declined below 3 mg/dL, even in 8 of 9 patients who died after extended hepatic resection, although 13 patients who had jaundice at the time of surgery had total serum bilirubin levels greater than 3 mg/dL but not beyond 6 mg/dL at the time of ICG-R15 evaluation. Therefore, the results of ICG-R15 in patients with fatal outcomes were relatively reliable, and these results suggested that special attention should be paid to the occurrence of liver failure after extended hepatic resection in patients with high ICG-R15 even after relief of obstructive jaundice, as mentioned by Lee and Hwang[28] (wherein the livers of patients with an ICG-R15 >15% after relief of obstructive jaundice often showed diffuse parenchymal shrinkage, without evidence of liver cirrhosis). This may be an irreversible phenomenon, and hence related to cases of death due to liver failure after extended hepatic resection. In our study, no patients with ICG-R15 less than 25% died of liver failure after extended hepatic resection when their RLV/ELV ratio was greater than 40%.

In addition to preoperative volumetric parameters, intraoperative parameters may also influence postsurgical course. However, our logistic regression model failed to identify any intraoperative parameters associated with postoperative hyperbilirubinemia and also with mortality, although, in univariate analysis, the amount of blood loss during surgery and the operative time were found to be significant factors for postoperative hyperbilirubinemia. These results were similar to those in previous reports by Nagino et al[14] and Fujii et al.[29]

In conclusion, we identified RLV/ELV ratio as having the strongest impact on postoperative liver dysfunction and found that ICG-R15, evaluated after relief of jaundice, had the next strongest relationship to mortality after extended hepatic resection in patients with biliary tract malignancies. To prevent postoperative liver dysfunction, volumetric analysis should be performed in a prospective fashion; based on the results, preoperative portal vein embolization or, if possible, limited hepatic resection after precise estimation of cancer extent[30] should be considered.

References

1. Baer HU, Stain SC, Blumgart LH, et al. Improvements in survival by aggressive resections of hilar cholangiocarcinoma. Ann Surg 1993; 217:20–7.
2. Kawasaki S, Imamura H, Miyagawa S, et al. Results of surgical resection for patients with hilar bile duct cancer: application of extended hepatectomy after biliary drainage and hemihepatic portal vein embolization. Ann Surg 2003;238:84–92.
3. Miyazaki M, Ito H, Suwa T, et al. Aggressive surgical approaches to hilar cholangiocarcinoma: hepatic or local resection? Surgery 1998; 123:131–6.
4. Washburn WK, Lewis WD, Jenkins RL. Aggressive surgical resection for cholangiocarcinoma. Arch Surg 1995;130:270–6.
5. Ohtsuka M, Ito H, Miyazaki M, et al. Results of surgical treatment for intrahepatic cholangiocarcinoma and clinicopathological factors influencing survival. Br J Surg 2002;89:1525–31.
6. Miyazaki M, Itoh H, Suwa T, et al. Radical surgery for advanced gallbladder carcinoma. Br J Surg 1996;83:478–81.
7. Dixon E, Vollmer CM Jr, Gallinger S, et al. An aggressive surgical approach leads to improved survival in patients with gallbladder cancer. Ann Surg 2005;241:385–94.
8. Shoup M, Gonen M, Fong Y, et al. Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. J Gastrointest Surg 2003;7:325–30.
9. Shirabe K, Shimada M, Sugimachi K, et al. Postoperative liver failure after major hepatic resection for hepatocellular carcinoma in the modern era with special reference to remnant liver volume. J Am Coll Surg 1999;188:304–7.
10. Okamoto E, Kyo A, Kuwata K, et al. Prediction of the safe limits of hepatectomy by combined volumetric and functional measurements in patients with impaired hepatic function. Surgery 1984;95:586–92.
11. Nonami T, Nakao A, Takagi H, et al. Blood loss and ICG clearance as best prognostic markers of post-hepatectomy liver failure. Hepatogastroenterology 1999;46:1669–72.
12. Suc B, Panis Y, Fekete F, et al. 'Natural history' of hepatectomy. Br J Surg 1992;79:39–42.
13. Bolder U, Brune A, Lohlein D, et al. Preoperative assessment of mortality risk in hepatic resection by clinical variables: a multivariate analysis. Liver Transplant Surg 1999;5:227–37.
14. Nagino M, Nimura Y, Hamajima N, et al. Logistic regression and discriminant analyses of hepatic failure after liver resection for carcinoma of the biliary tract. World J Surg 1993;17:250–5.
15. Shimizu T, Sano O, Tsukada K. Reestimation of the bilirubin decrease rate "b" (b value) in patients with obstructive jaundice. J Hepatobiliary Pancreat Surg 1996;3:12–6.
16. Kondo S, Hirano S, Katoh H, et al. Forty consecutive resections of hilar cholangiocarcinoma with no postoperative mortality and no positive ductal margins: results of a prospective study. Ann Surg 2004; 240:95–101.
17. Gerhards MF, van Gulik TM, Gouma DJ, et al. Evaluation of morbidity and mortality after resection for hilar cholangiocarcinoma—a single center experience. Surgery 2000;127:395–404.
18. Nagino M, Kamiya J, Nimura Y, et al. Complications of hepatectomy for hilar cholangiocarcinoma. World J Surg 2001;25:1277–83.
19. Denning DA, Ellison EC, Carey LC. Preoperative percutaneous transhepatic biliary decompression lowers operative morbidity in patients with obstructive jaundice. Am J Surg 1981;141:61–5.
20. Kawarada Y, Higashiguchi T, Mizumoto R, et al. Preoperative biliary drainage in obstructive jaundice. Hepatogastroenterology 1995;42: 300–7.
21. Ohtsuka M, Miyazaki M, Nakajima N, et al. Neutrophil-mediated sinusoidal endothelial cell injury after extensive hepatectomy in cholestatic rats. Hepatology 1997;25:636–41.
22. Cherqui D, Benoist S, Fagniez PL, et al. Major liver resection for carcinoma in jaundiced patients without preoperative biliary drainage. Arch Surg 2000;135:302–8.
23. Kubota K, Makuuchi M, Takayama T, et al. Measurement of liver volume and hepatic functional reserve as to a guide to decision-making in resectional surgery for hepatic tumors. Hepatology 1997;26:1176–81.
24. Vauthey JN, Chaoui A, Caridi J, et al. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. Surgery 2000;127:512–9.
25. Yigitler C, Farges O, Belghiti J, et al. The small remnant liver after major liver resection: how common and how relevant? Liver Transplant 2003;9:S18–25.
26. Takahashi T, Togo S, Shimada H, et al. Safe and permissible limits of hepatectomy in obstructive jaundice patients. World J Surg 2004;28: 475–481.
27. Zoedler T, Ebener C, Roeher HD, et al. Evaluation of liver function tests to predict operative risk in liver surgery. HPB Surg 1995;9:13–18.
28. Lee S, Hwang S. How I do it: assessment of hepatic functional reserve for indication of hepatic resection. J Hepatobiliary Pancreat Surg 2005;12:38–43.
29. Fujii Y, Shimada H, Togo S, et al. Risk factors of posthepatectomy liver failure after portal vein embolization. J Hepatobiliary Pancreat Surg 2003;10:226–232.
30. Miyazaki M, Ito H, Nakagawa K, et al. Segment I and IV resection as a new approach for hepatic hilar cholangiocarcinoma. Am J Surg 1998;175:229–231.

Similarities and Differences Between Intraductal Papillary Tumors of the Bile Duct With and Without Macroscopically Visible Mucin Secretion

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Abstract: Intraductal papillary neoplasms of the bile duct (IPNB) have been recently proposed as the biliary counterpart of intraductal papillary mucinous neoplasms of the pancreas (IPMN-P). However, in contrast to IPMN-P, IPNB include a considerable number of the tumors without macroscopically visible mucin secretion. Here we report the similarities and differences between IPNB with and without macroscopically visible mucin secretion (IPNB-M and IPNB-NM). Surgically resected 27 consecutive cases with IPNB were divided into IPNB-M (n = 10) and IPNB-NM (n = 17), and their clinicopathologic features were examined. Clinically, both tumors were similar. Pathologically, the most frequent histopathologic types were pancreatobiliary in IPNB-NM and intestinal in IPNB-M. Various degrees of cytoarchitectural atypia within the same tumor were exhibited in 8 IPNB-M, but only 3 in IPNB-NM. Although the tumor size was similar, 9 IPNB-NM were invasive carcinoma, whereas all but 1 IPNB-M with carcinoma were in situ or minimally invasive. Immunohistochemically, positive MUC2 expression was significantly more frequent in IPNB-M than in IPNB-NM, whereas MUC1 tended to be more frequently expressed in IPNB-NM compared with IPNB-M. Among IPNB-NM with positive MUC1 expression, 3 had negative MUC2 and MUC5AC expressions. These tumors showed a tubulopapillary growth with uniform degree of cytoarchitectural atypia. All IPNB-M were negative for p53, and the frequency of positive p53 protein in IPNB-NM was at the middle level of that in IPNB-M and nonpapillary cholangiocarcinoma. In conclusion, IPNB-M showed striking similarities to IPMN-P, but IPNB-NM contained heterogeneous disease groups.

Key Words: bile duct neoplasm, pathology, mucins, p53, cholangiocarcinoma

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Bile duct tumors with macroscopically visible mucin secretion are a rare form among bile duct neoplasms. These tumors show predominantly papillary or, rarely, flat growth within the dilated bile duct lumen, and secrete a large amount of mucin, which is often seen draining from a patulous orifice of the duodenal papilla. As these features are similar to those in intraductal papillary mucinous neoplasms of the pancreas (IPMN-P), it is speculated that this type of tumor is a biliary counterpart of IPMN-P.[11,17,19] Microscopically, both types of tumor are composed of papillary fronds with fine vascular cores. Neoplastic epithelial cells of both tumors can be of the pancreatobiliary type or can show gastric or intestinal differentiation, and show a spectrum of cytoarchitectural atypia ranging from none to borderline to marked and can be associated with invasive carcinoma as well. On the basis of these results, the nomenclature, "intraductal papillary mucinous tumor of the bile ducts" has been used for such tumors.[12]

In contrast, biliary intraductal tumors without macroscopically visible mucin secretion are also encountered more frequently than tumors with mucin secretion. Similar to tumors with macroscopically visible mucin secretion, these tumors have a macroscopically recognizable papillary or granular structure, but no clinically visible mucin secretion. As certain morphologic features of these tumors, especially intraductal papillary growth patterns, are also similar to those of IPMN-P, Zen et al[24] recently proposed that they, together with tumors with macroscopically visible mucin secretion, may belong to a single tumor entity, "intraductal papillary neoplasms of the bile duct" (IPNB). Not only tumors with mucin secretion, but also those without macroscopically visible mucin secretion, may be the biliary counterpart of IPMN-P. However, this hypothesis is still speculative, as one tumor produces and secretes a large amount of mucin and the other tumor does not. Among IPNB, there are a considerable number of the tumors without macroscopically visible mucin secretion, whereas among IPMN-P, tumors with little mucin secretion are rare. Furthermore, in the pancreas, intraductal tubulopapillary neoplasms (ITPNs) have been recently reported as new intraductal pancreatic neoplasms.[22] These neoplasms were characterized by the appearance of a solid nodular tumor obstructing dilated ducts without visibly secreted mucin on macroscopic examination and predominant tubulopapillary growth with uniform high-grade atypia throughout the neoplasm on microscopic examination.

The aim of this study was to clarify the similarities and differences between intraductal tumors of the bile duct with and without macroscopically visible mucin secretion, with regard to their clinical course and pathologic findings, including mucin immunophenotype and p53 protein accumulation.

MATERIALS AND METHODS

From January 1990 until March 2008, 274 patients with intrahepatic or extrahepatic bile duct tumors were treated surgically at the Chiba University Hospital. Among them, 27 patients (9.9%) were diagnosed as having intraductal papillary neoplasms of the intrahepatic or extrahepatic bile duct. IPNB are defined as tumors that are characterized by macroscopically recognizable papillary and/or granular growth within the bile duct lumen, according to earlier studies.[10,24] Biliary cystadenoma and cystadenocarcinoma, and any papillary lesions of Vater ampulla or gallbladder as well, were excluded from this study. IPNB were divided into 2 groups, that is tumors with and without macroscopically visible mucin secretion, which was judged by not only pathologic but also preoperative clinical examinations. Ten patients were diagnosed with the former (IPNB-M) and 17 patients with the latter (IPNB-NM). Clinical and pathologic information on these patients were retrospectively reviewed.

The following clinical variables were examined: age, sex, symptoms, history of biliary diseases, preoperative serum levels of carbohydrate antigen 19-9 (CA19-9), location of the main tumor, surgical procedures, and outcome. The follow-up periods ranged from 12 to 134 months, with a median of 61 months. The surgically resected specimens were investigated, and macroscopic tumor size and morphology were recorded. After fixation in 10% buffered formalin, multiple sections transverse to the longitudinal axis of the bile duct were made at approximately 5-mm intervals. Histologic sections, stained with hematoxylin and eosin, were examined for histopathologic types, cytoarchitectural atypia, and mode of spreading. As there are no established criteria as to histopathologic types and cytoarchitectural atypias among IPNB, we identified them in accordance with the consensus criteria for IPMN-P.[6,9] Histopathologic types were classified as gastric, intestinal, pancreatobiliary, and oncocytic types, which were also applied for some earlier studies regarding IPNB.[10,19,21,24] Degrees of cytoarchitectural atypia were characterized as adenoma, borderline, and carcinoma.

In addition to conventional staining, immunohistochemical studies were carried out using an Envision^{+}-Horseradish Peroxidase system (DakoCytomation, Glostrup, Denmark). Eight consecutive cases with IPNB-M and 16 consecutive cases with IPNB-NM in the last 10 years were used in this study. As disease controls, 10 cases of nonpapillary cholangiocarcinoma randomly obtained from the disease files of our department were also provided for this assessment. All nonpapillary cholangiocarcinoma were located in the extrahepatic bile duct (6 cases) or intrahepatic large bile ducts (4 cases), appearing as the nodular or sclerosing type, and histologically, as invasive tubular adenocarcinoma. From each case, 1 or 2 paraffin blocks with tumor tissue were selected. The following monoclonal antibodies were used as primary antibodies: MUC1 glycoprotein (clone Ma695; 1:100, Novocastra Laboratories Ltd, Newcastle upon Tyne, UK), MUC2 (clone Ccp58; 1:100, Santa Cruz Biotechnology, Inc., Santa Cruz, CA), MUC5AC (clone CLH2; 1:100, Novocastra Laboratories Ltd), human gastric mucin (clone 45M1; 1: 100, Novocastra Laboratories Ltd), MUC6 (clone CLH5; 1: 100, Novocastra Laboratories Ltd), and p53 (clone DO-7; 1:100, DakoCytomation). In addition, Ki-67 (clone MIB-1; 1:50, DakoCytomation) was assessed in cases with IPNB-M and IPNB-NM to compare proliferative activity. Antigen was retrieved from deparaffinized and rehydrated tissues by autoclave treatment (121°C, 15 min) in a Target Retrieval Solution, pH 6.0 (DakoCytomation), for mucins, and in a Target Retrieval Solution, pH 9.0 (DakoCytomation), for p53 and Ki-67. Diaminobenzidine was used as the chromogen and the sections were counterstained with hematoxylin. As a negative control, nonimmunized mouse immunoglobulin was substituted for the primary antibody. The criteria for determining positive staining of mucin antigens was labeling of any intensity in > 10% of the cells. An accumulation of p53 was considered to be present if > 10% of tumor cells showed nuclear staining. For Ki-67, nuclear labeling index was manually counted among 1000 cells in each tumor. These criteria are based on several earlier studies.[1,2,14]

All anonymous histologic specimens were reviewed by 1 author (M.O., with > 5 y of experience in pathology), under the supervision of 1 expert pathologist (Y.K.).

Statistical analysis was carried out using the χ^2 test, Fisher exact test, and the Mann-Whitney U test. $P < 0.05$ was considered to be statistically significant. Patient survival was calculated by the Kaplan-Meier method.

RESULTS

Clinical Features and Pathologic Findings

Age and sex distributions were not significantly different between patients with IPNB-NM (mean age, 65.4 y; 8 men/9 women) and IPMN-M (mean age, 64.3 y; 8 men/2 women) on the basis of statistical analyses ($P = 0.51$ and $P = 0.12$, respectively). Intermittent

TABLE 1. Comparison of Pathologic Features Between IPNB-M and IPNB-NM, and Comparable Data on IPMN-P Derived From the Literature

	IPNB			
	IPNB-NM (n = 17)	IPNB-M (n = 10)	*P*	IPMN-P*
Size (average; cm)	2.7	3.4	0.60	3.7-4.3
Gross appearance				
Polypoid	9 (53%)	7 (70%)	0.08	Not classified
Polypoid-granular	6 (35%)	0 (0%)		
Granular	2 (12%)	3 (30%)		
Histopathologic type				
Gastric	1 (6%)	1 (10%)	0.003	31%
Intestinal	3 (18%)	8 (80%)		35%
Pancreatobiliary	13 (76%)	1 (10%)		22%
Maximum degree of cytoarchitectural atypia				
Adenoma or borderline	1 (6%)	1 (10%)	> 0.99	24%-38%
Carcinoma	16 (94%)	9 (90%)		62%-76%
Well: moderately: poorly differentiated	13: 3: 0	9: 0: 0	0.28	
Existence of various degrees of cytoarchitectural atypia	3 (18%)	8 (80%)	0.003	Usually
Depth of invasion				
Within ductal wall	8 (47%)	9 (90%)	0.04	55%-73%
Beyond ductal wall	9 (53%)	1 (10%)		27%-45%
Invasive pattern†				
Pushing growth margin	2 (22%)	1 (100%)	0.30	Not assessed
Infiltrating growth margin	7 (78%)	0 (0%)		
Existence of lymphovascular invasion	6 (35%)	0 (0%)	0.06	47% of invasive cases
Ki-67 labeling index‡	32 ± 15%	27 ± 11%	0.40	24%-40%
Existence of superficial spread	9 (53%)	3 (30%)	0.42	Often
Existence of multiple lesions	3 (18%)	1 (10%)	> 0.99	Sometimes
Existence of lymph node metastasis	2 (12%)	0 (0%)	0.52	0%-20%

*Data derived from the literature.[1,7,10,16,18–20,24]
†Data obtained from cases with invasive carcinoma.
‡Mean ± standard deviation.

abdominal pain and fever related to cholangitis or jaundice were the most common complaints among patients with and without mucin. Eight of 17 IPNB-NM (47%) were located in the intrahepatic bile duct, whereas 5 of 10 IPNB-M (50%) were located in the intrahepatic bile duct. A total of 9 patients with IPNB (33%) had histories of bile duct stones or bile duct stones detected perioperatively; 1 patient with IPNB-NM had common bile duct stones and 3 patients had intrahepatic bile duct stones, detected perioperatively, and 1 had a history of common bile duct stones. In patients with IPNB-M, 2 had histories of common bile duct stones, 1 had a history of common and intrahepatic bile duct stones, and 1 had intrahepatic bile duct stones detected perioperatively. One patient with IPNB-NM was diagnosed with sclerosing cholangitis during the diagnostic workup. Although a positive level (> 40 U/mL) of serum CA19-9 was more commonly observed in patients with IPNB-NM (11 cases) than in patients with IPNB-M (3 cases), this was not statistically significant ($P = 0.12$).

Eight patients with IPNB-NM underwent surgery more than hemihepatectomy with extrahepatic bile duct resection (BDR), 1 underwent hemihepatectomy with pancreatoduodenectomy, 1 hemihepatectomy, 2 hepatic segmentectomy with BDR, 2 hepatic segmentectomy, 1 BDR alone, and 2 pancreatoduodenectomy. Six patients with IPNB-M underwent surgery more than hemihepatectomy with BDR, 2 underwent hemihepatectomy, 1 hepatic caudate lobectomy with BDR, and 1 hilar BDR. Pathologic features are summarized in Tables 1 and 2.

Macroscopic Findings

In IPNB-NM, the average tumor size was 2.7 cm (range, 1.3 to 4.6 cm), whereas in IPNB-M, the average size was 3.4 cm (range, 1.5 to 5.0 cm). In 15 of 17 IPNB-NM, the tumors appeared as polypoid masses elevating into the lumen of the bile duct (polypoid type) (Fig. 1A). Among these tumors, 6 had clinically visible granular or small papillary mucosa in which the maximum height of mucosal protrusion was < 5 mm in the vicinity of the main polypoid mass (polypoid-granular type) (Fig. 1B). The other 2 IPNB-NM were composed of only granular mucosa (granular type) (Fig. 1C). Similarly, 7 IPNB-M were classified as polypoid type and 3 as granular type, in all of which intraductal mucin accumulation was noted.

Microscopic Findings

All neoplasms included a portion of papillary fronds with fine vascular cores. Coexistence of tubulopapillary growth was exhibited more commonly in IPNB-NM (12 cases) than in IPNB-M (2 cases).

On the basis of dominant morphologic features, 1 IPNB-NM was classified as the gastric type (Fig. 2A), 3 as

TABLE 2. Immunohistochemical Mucin Expression and p53 Nuclear Accumulation in IPNB-M and IPNB-NM and Nonpapillary Cholangiocarcinoma, and Comparable Data on IPMN-P Derived From the Literature

Tumor Type	MUC1	MUC2	MUC5AC	HGM	MUC6	p53
IPNB-M (n = 8)	3 (38%)	7 (88%)	7 (88%)	7 (88%)	1 (13%)	0 (0%)
IPNB-NM (n = 16)	13 (81%)	4 (25%)	12 (75%)	10 (63%)	9 (56%)	8 (50%)
Nonpapillary cholangiocarcinoma (n = 10)	10 (100%)	1 (10%)	7 (70%)	9 (90%)	3 (30%)	7 (70%)
IPMN-P*	11%-39%	42%-92%	97%-100%	NA	29%	0%

*Data derived from the literature.[4,8,14,16,24]
NA indicates not assessed.

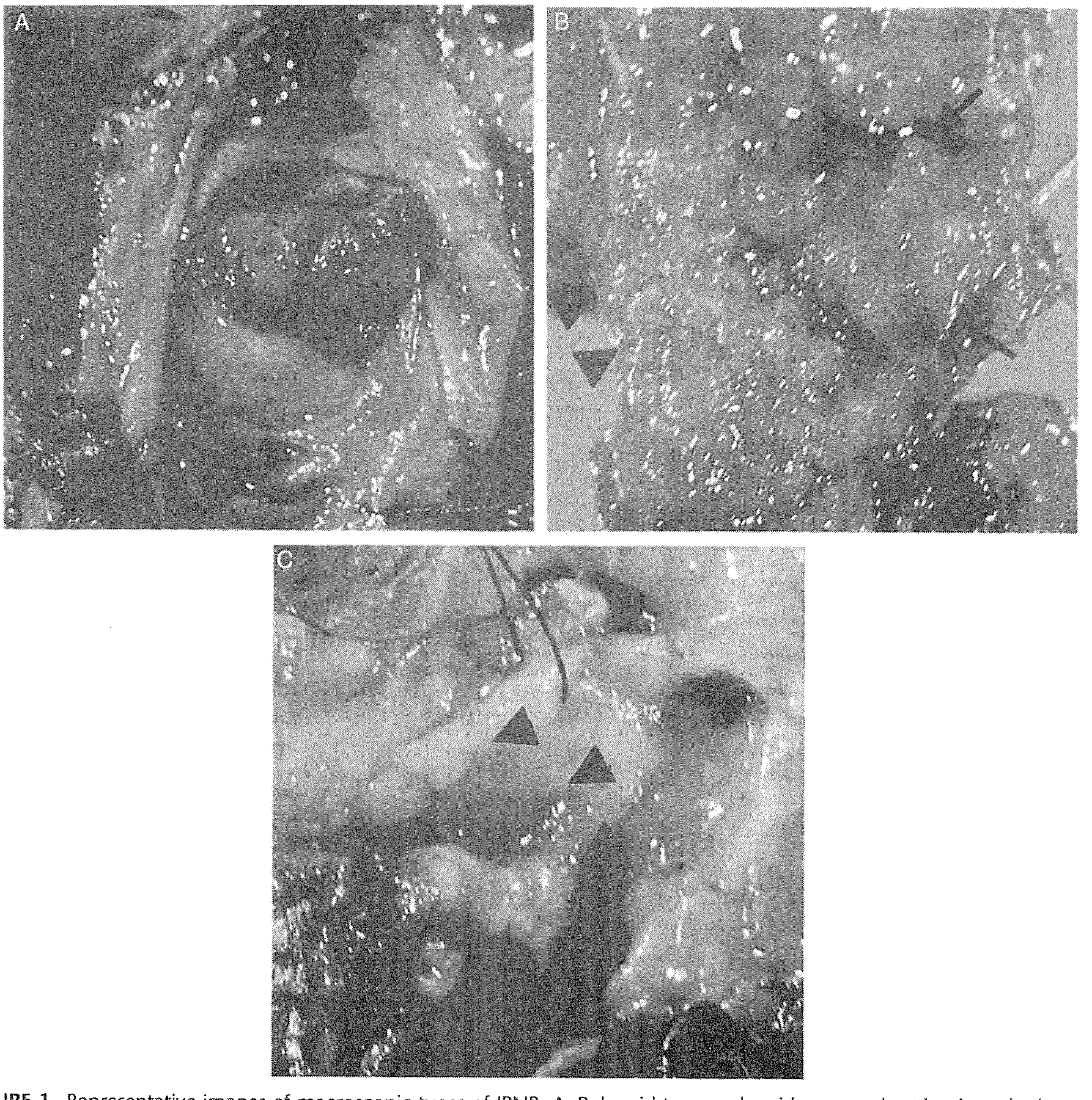

FIGURE 1. Representative images of macroscopic types of IPNB. A, Polypoid type: polypoid masses elevating into the lumen of the bile duct. B, Polypoid-granular type: main polypoid mass (arrows) with clinically visible granular or small papillary mucosa (arrowheads). C, Granular type: clinically visible granular or small papillary mucosa only (arrowheads).

the intestinal type (Fig. 2B), and 13 as the pancreatobiliary type (Fig. 2C). In 4 tumors with pancreatobiliary type, other morphologic components were concomitantly present: 2 with the intestinal component, 1 with the gastric component, and 1 with the oncocytic component (Fig. 2D). In IPNB-M, tumors of the intestinal type were significantly more common (8 of 10 tumors). Only 1 tumor seemed to be of the pancreatobiliary type and 1 was classified as the gastric type. These morphologic features were not size dependent: the average size of IPNB with gastric, intestinal, and pancreatobiliary types were 1.9, 3.2, and 2.7 cm, respectively, and these were not statistically significant.

The maximum degree of cytoarchitectural atypia of 16 IPNB-NM was characterized as carcinoma: 13 carcinomas were well differentiated and 3 were moderately differentiated. In IPNB-M, 9 tumors were diagnosed as well-differentiated papillary carcinoma. Only 1 IPNB-NM and 1 IPNB-M were characterized as papillary adenoma, which is the same disease entity as biliary papilloma. However, it was recognized that IPNB often exhibited marked variation in cytoarchitectural atypia between different regions of individual tumors. This feature was significantly more common in IPNB-M than in IPNB-NM, and 3 IPNB-NM (18%) and 8 IPNB-M (80%) showed various degrees (carcinoma, borderline, and adenoma) of cytoarchitectural atypia (Fig. 3). With regard to the relationship between cytoarchitectural atypia and histopathologic types, 10 of 11 tumors with various degrees of cytoarchitectural atypia were characterized as the intestinal type. In contrast, all but 1 tumor of the pancreatobiliary type that corresponded to carcinoma were not concomitant with any other degree of cytoarchitectural atypia ($P < 0.0001$). In a tumor of the pancreatobiliary type accompanied with another degree of cytoarchitectural atypia, a gastric component coexisted. A tumor of the intestinal type without any other degree of cytoarchitectural atypia was nonmucin producing.

Nine of 17 IPNB-NM (53%) were invasive carcinomas that extended beyond the ductal wall, whereas all but 1 IPNB-M were in situ carcinomas or minimally invasive carcinomas confined to the ductal wall. All

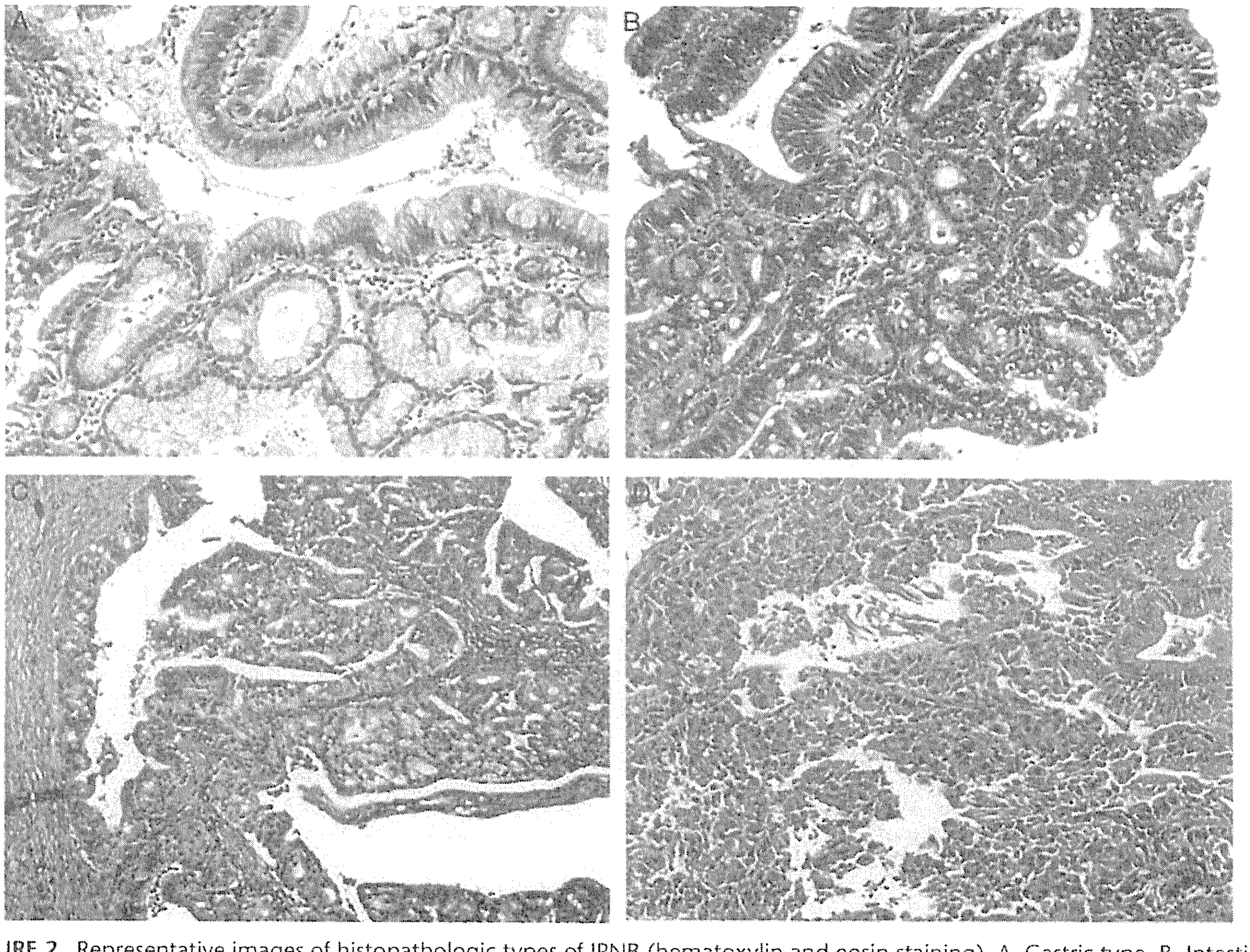

FIGURE 2. Representative images of histopathologic types of IPNB (hematoxylin and eosin staining). A, Gastric type. B, Intestinal type. C, Pancreatobiliary type. D, Oncocytic type. full color online

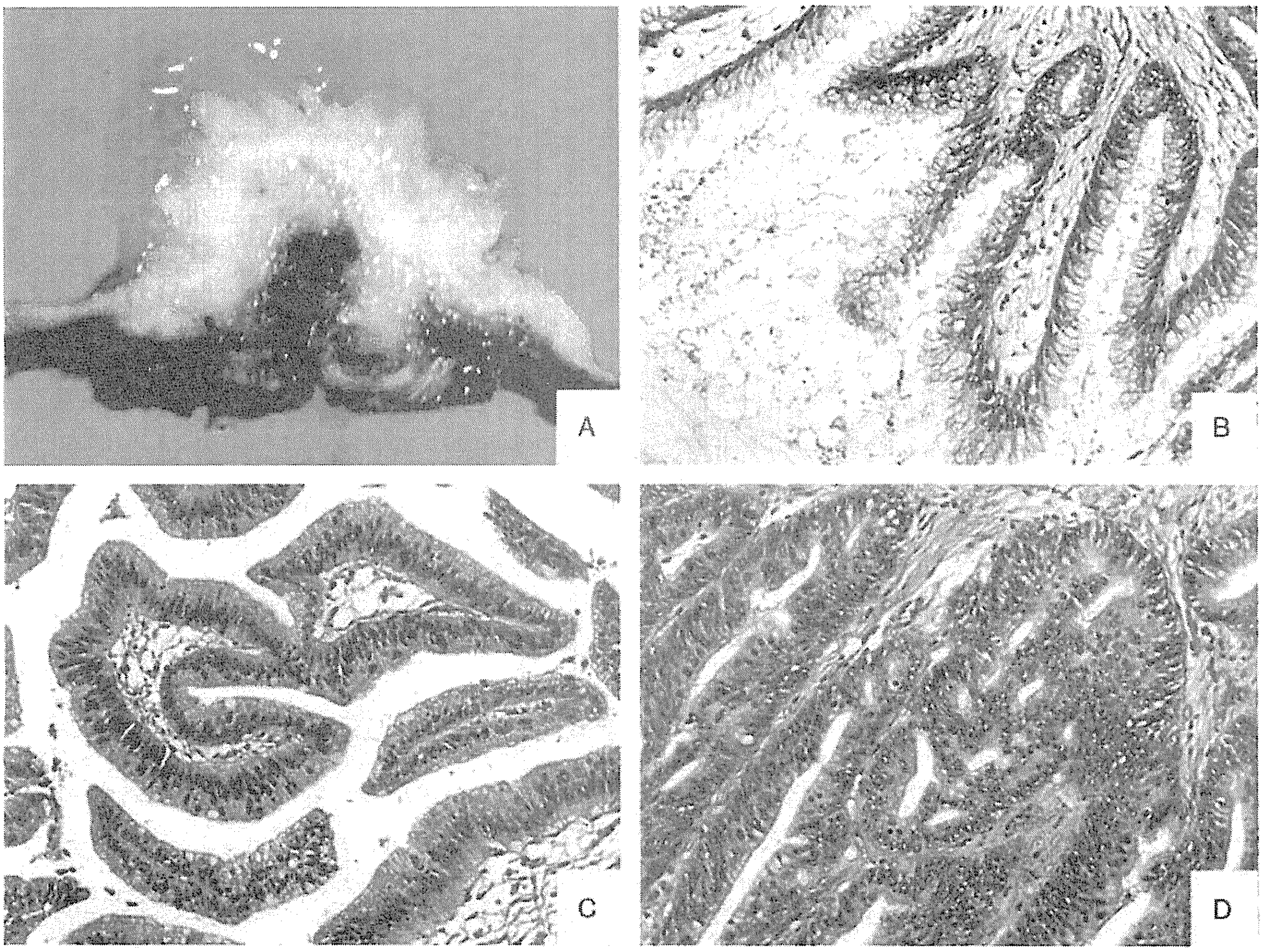

FIGURE 3. A representative case of IPNB with macroscopically visible mucin secretion. Within a single tumor (A), coexistence of adenoma (B), borderline lesion (C), or adenocarcinoma (D) was found (hematoxylin and eosin staining). full color online

IPNB-NM with invasive carcinoma exhibited tubular-type adenocarcinomas, 7 of which had infiltrating growth margin, whereas IPNB-M with invasive carcinoma showed colloid carcinoma with a pushing growth margin (Fig. 4). Lymphovascular invasion was seen within the invasion site in 6 IPNB-NM. Proliferative activity assessed by the Ki-67 labeling index was almost identical between IPNB-M and IPNB-NM. Nine of 10 IPNB with invasive carcinomas were of the pancreatobiliary type, and in IPNB of the intestinal type, only 1 tumor with mucin production showed invasion beyond the bile duct wall ($P < 0.01$).

Superficial spread along the epithelium or glands of the bile duct beyond the macroscopically detectable tumor was also observed in 3 IPNB-M and 9 IPNB-NM. This spreading pattern was generally seen in association with granular mucosa; all tumors of the polypoid-granular and granular types had this spreading pattern, whereas only 1 tumor of the polypoid type extended superficially along the bile duct. Three IPNB-NM and 1 IPNB-M showed another focus of carcinoma separated from the main mass, and were therefore considered to be multicentric. Lymph node metastasis was observed in 2 tumors without macroscopically visible mucin secretion. These pathologic features were not statistically significant between IPNB-M and IPNB-NM.

In 14 patients with IPNB-NM, ductal resected margins were free from cancer invasion, whereas no patients with IPNB-M had cancer-positive ductal resected margins.

Immunohistochemical Findings

MUC1 was expressed mainly in the apical membrane and occasionally in the cytoplasm of tumor cells. MUC2 was expressed in the cytoplasm of tumor cells. Although positive MUC2 expression was observed in only 1 case, all 10 of 10 cases with nonpapillary cholangiocarcinomas were positive for MUC1. In contrast, all but 1 IPNB-M were positive for MUC2, but positive MUC1 expression was observed in only 3 IPNB-M, including 2 with coexpression of MUC2 (Fig. 5). In cases with IPNB-NM, the frequency of positive MUC2 expression was significantly lower than in those with IPNB-M ($P < 0.01$), whereas MUC1 tended to be more

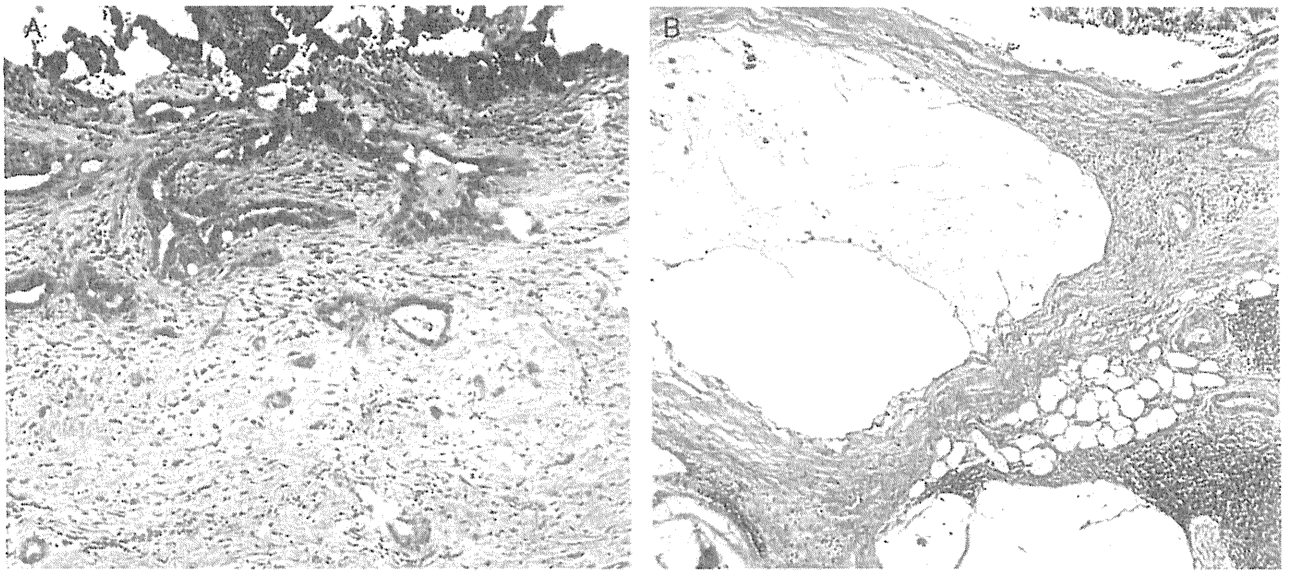

FIGURE 4. Different types of invasive carcinoma (hematoxylin and eosin staining). A, Tubular-type adenocarcinoma that developed from IPNB without macroscopically visible mucin secretion. B, Colloid carcinoma that developed from IPNB with macroscopically visible mucin secretion. full color online

frequently expressed compared with cases with IPNB-M (Fig. 6), and was expressed with similar frequency to cases with nonpapillary cholangiocarcinoma. Even 5 of 7 IPNB-NM with in situ carcinoma or minimally invasive carcinoma confined to the ductal wall showed positive MUC1 expression. Among IPNB-NM with positive MUC1 expression, 2 IPNB-NM coexpressed MUC2. Only 2 IPNB-NM showed positive MUC2 expression and negative MUC1 expression.

MUC5AC and MUC6 were expressed in the cytoplasm, and human gastric mucin was expressed in the luminal content of tumor cells. There were no statistically significant differences among IPNB-NM, IPNB-M, and nonpapillary cholangiocarcinoma as to the positive frequency of these mucin immunophenotypes. Among 4 IPNB-NM without MUC5AC expression, 3 had positive MUC1 and negative MUC2 expressions. These 3 tumors had a tubulopapillary growth pattern (Fig. 7), with a uniform degree of cytoarchitectural atypia.

All IPNB-M were negative for p53. The positivity of p53 in nonpapillary cholangiocarcinoma was significantly higher than that in IPNB-M ($P < 0.01$). The frequency of positive p53 nuclear protein in IPNB-NM was the middle level of that in IPNB-M and nonpapillary cholangiocarcinoma. Even 3 of 7 IPNB-NM with in situ carcinoma or

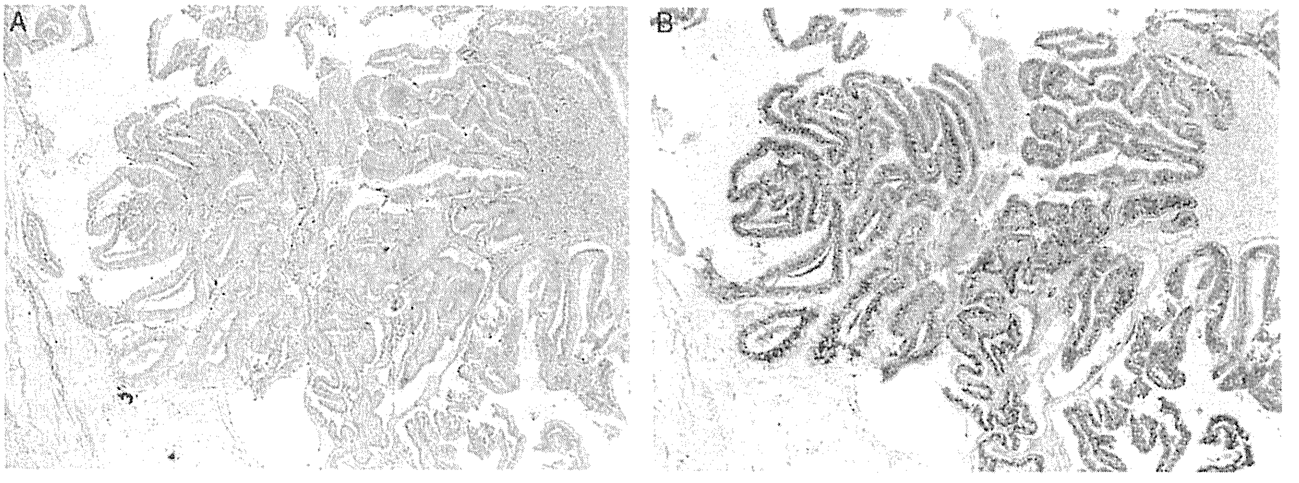

FIGURE 5. A representative pattern of the mucin immunophenotype of IPNB with macroscopically visible mucin secretion. Expression of MUC1 was negative (A) and strongly positive expression of MUC2 was observed (B). full color online

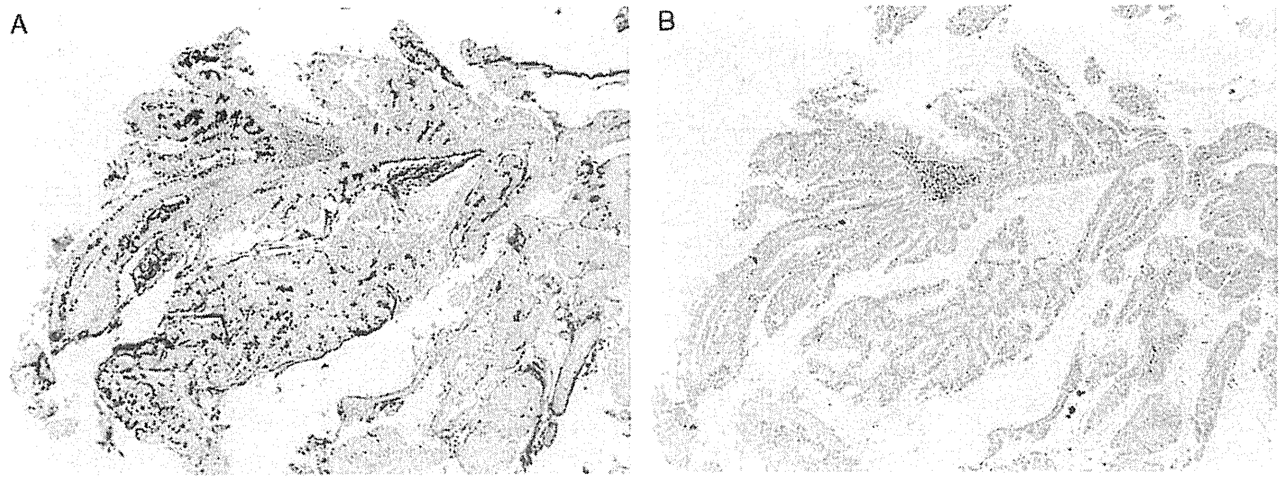

FIGURE 6. A representative pattern of the mucin immunophenotype of IPNB without macroscopically visible mucin secretion. Expression of MUC1 was observed (A) but expression of MUC2 was negative (B). full color online

minimally invasive carcinoma confined to the ductal wall showed positive p53 protein expression. Furthermore, positive p53 protein expression was observed in 2 of 3 IPNB-NM of the intestinal type.

Surgical Outcome

None of the patients with IPNB-M showed evidence of recurrent disease after a median follow-up period of 52 months (range, 12 to 80 mo). In patients with IPNB-NM, overall median survival was 31 months (range, 3 to 134 mo), and the cumulative 5-year survival rate was 49%. Six of 17 patients had died of disease 3, 11, 14, 25, 56, and 59 months after surgical resection. Among these 6 patients, 2 had invasive carcinoma with lymph node metastasis, 1 had invasive carcinoma and positive surgical margin, and 2 had invasive carcinoma. The remaining 1 patient had in situ carcinoma, but surgical margin was positive. Among the 9 patients with invasive carcinoma, overall median survival was 56 months (range, 3 to 134 mo), and the cumulative 1-year, 3-year, and 5-year survival rates were 67%, 53%, and 40%, respectively.

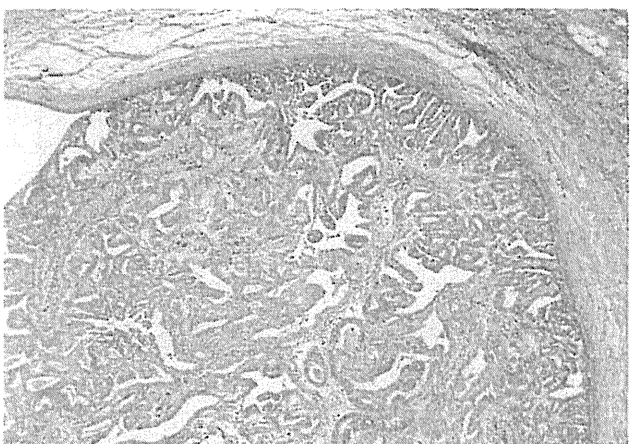

FIGURE 7. A representative image of IPNB without macroscopically visible mucin secretion that had similar characteristics to ITPNs of the pancreas (hematoxylin and eosin staining). A tubulopapillary growth pattern was indicated. full color online

DISCUSSION

Several studies have indicated radiologic and histologic similarities between IPNB-M and IPMN-P.[11,13,17,19] In our series, IPNB-M appeared as polypoid masses or granular mucosa growing into the lumen of the bile duct, with hypersecretion of mucin. Microscopically, the majority of IPNB-M was of the intestinal phenotype and showed various degrees of cytoarchitectural atypia in different regions of the individual tumors. Nine of 10 IPNB-M were less-invasive tumors confined to the ductal wall. The remaining tumor was invasive carcinoma of the colloid type. Furthermore, all but 1 IPNB-M were immunohistochemically positive for MUC2. Consistent with earlier studies, these features were very similar to those in IPMN-P reported earlier (Tables 1, 2).[2,3,6,9,14]

In contrast, pathologic findings of IPNB-NM were somewhat different from those of IPNB-M in this study, although patients with IPNB-NM resembled patients with IPNB-M in terms of clinical features. In IPNB-NM, the major histopathologic type was pancreatobiliary with a few variations in cytoarchitectural atypia. Although tumor size was almost similar between IPNB-M and IPNB-NM, the frequency of invasive carcinoma extending beyond the ductal wall was higher in IPNB-NM than in IPNB-M, suggesting that IPNB-NM was more invasive than IPNB-M, even when it is small. Furthermore, all invasive components exhibited tubular-type carcinoma. With regard to the mucin immunophenotype, the frequency of positive MUC2 expression was significantly lower in IPNB-NM than that in IPNB-M, and MUC1 was more frequently expressed. As this phenotypic pattern was also seen in IPNB-NM with noninvasive carcinoma or minimally invasive carcinoma, it was not dependent on tumor progression. These features were rather similar to those of conventional nonpapillary cholangiocarcinoma, although IPNB-NM that had similar clinical and pathologic features to those of IPNB-M were certainly encountered, as mentioned above. Alternatively, IPNB-NM with similar characteristics (tubulopapillary growth pattern and uniform degree of cytoarchitectural atypia throughout the neoplasm) to recently proposed ITPN of the pancreas[22] were also observed. These tumors had positive MUC1 expression and negative MUC2 and MUC5AC expressions, which was the same phenotypic pattern as ITPN of the pancreas.[22]

These results were somewhat inconsistent with those provided by Zen et al,[24] in which the pathologic characteristics of biliary papillary tumors, which are in the same disease category as IPNB in this study, were compared with those of nonpapillary cholangiocarcinoma and IPMN-P. Zen et al[24] concluded that the pathologic characteristics of biliary papillary tumors were different from those of nonpapillary cholangiocarcinoma, and rather closely resembled those of IPMN-P. However, in their study, biliary papillary tumors included both IPNB-M and IPNB-NM, and the 2 types of tumor were not distinguished, possibly confusing the results. In our study, pathologic characteristics of IPNB-M resembled those of IPMN-P, whereas IPNB-NM had complex pathologic characteristics.

In terms of carcinogenesis, pancreatic carcinoma and cholangiocarcinoma develop in a stepwise progression. In the pancreas, there are 2 putative intraductal precursor lesions preceding invasive carcinoma: IPMN-P and pancreatic intraepithelial neoplasia (PanIN).[9] Although some features in both types of lesion overlap, IPMN-P commonly reach a relatively large size while remaining confined to the ducts, whereas PanIN usually progress to invasive carcinoma before they reach a significant size. At the molecular level, the *p53* gene is less frequently inactivated in IPMN-P than in PanIN.[5,8] Nuclear p53 immunohistochemical expression is reported as being more frequently observed in PanIN-3 than in carcinoma in situ in IPMN-P.[1,16] Similarly, IPNB and biliary intraepithelial neoplasia (BilIN) have recently been proposed as 2 major intraductal precursor lesions that are related to the development of invasive cholangiocarcinoma.[23,25] These lesions are probably analogous to IPMN-P and PanIN, respectively. In our study, IPNB-M did not invade beyond the bile duct wall, even when they reached a considerable size, and all IPNB-M showed negative immunohistochemical expression of p53. These findings were similar to those in IPMN-P, suggesting that IPNB-M may follow a similar carcinogenic pathway to that of IPMN-P lineage in the pancreas, and can probably develop through the IPNB carcinogenic pathway. In contrast, some IPNB-NM invaded beyond the bile duct wall while remaining smaller than IPNB-M, as mentioned above, and some IPNB-NM, even with in situ carcinoma or minimally invasive carcinoma confined to the ductal wall, showed positive p53 protein expression, which were similar findings to those in PanIN. These results suggested that some IPNB-NM, but not all, in this study might develop through a similar progressive pathway from BilIN to conventional nonpapillary cholangiocarcinoma. In the pancreas, IPMN usually arises from the main pancreatic duct or branch ducts, whereas PanIN typically involves smaller ducts. However, because in the biliary tract, both IPNB and BilIN could usually involve the same large ducts,[23,25] there may be grossly visible papillary carcinomas derived from BilIN, which is regarded as a papillary variant of conventional cholangiocarcinoma and not a subtype of IPNB.

Several studies have shown that survival rate after surgical resection in patients with IPNB were better than in patients with conventional nonpapillary cholangiocarcinoma.[10,24] This is 1 rationale for distinguishing IPNB from other types of cholangiocarcinoma. However, tumors with different backgrounds, for example, those with and without macroscopically visible mucin secretion and those with and without invasion, were combined and analyzed together in most series. In fact, survival of patients with IPNB-M was relatively favorable in this study, but invasive carcinoma that extended beyond the ductal wall was presented in only 1 case. In contrast, although only a small sample was evaluated, the survival of patients with invasive IPNB-NM was similar to that of patients with bile duct cancer in an analysis based on a large number of patients.[15]

In conclusion, IPNB-M showed striking similarities to IPMN-P in its clinical, morphologic, immunophenotypical, and biological findings. In contrast, IPNB-NM contained heterogeneous disease groups; some tumors had similar characteristics to IPNB-M and IPMN-P, some had the characteristics resembled in those of ITPN of the pancreas, and the majority of IPNB-NM had the characteristics close to those of nonpapillary cholangiocarcinoma. The concept of IPNB as a biliary counterpart of IPMN-P is attractive, but these findings suggest that it may be difficult to assume that all IPNB-NM are included in this disease entity with IPNB-M. Further study with a large number of cases, especially on the basis of a molecular analysis, is required to assess which tumors among IPNB-NM could be categorized to the tumors of the IPNB lineage.

REFERENCES

1. Abe K, Suda K, Arakawa A, et al. Different patterns of p16INK4A and p53 protein expressions in intraductal papillary-mucinous neoplasms and pancreatic intraepithelial neoplasia. *Pancreas*. 2007;34:85–91.
2. Adsay NV, Merati K, Andea A, et al. The dichotomy in the preinvasive neoplasia to invasive carcinoma sequence in the pancreas: differential expression of MUC1 and MUC2 supports the existence of two separate pathways of carcinogenesis. *Mod Pathol*. 2002;15:1087–1095.
3. Adsay NV, Merati K, Basturk O, et al. Pathologically and biologically distinct types of epithelium in intraductal papillary mucinous neoplasms. Delineation of an "intestinal" pathway of carcinogenesis in the pancreas. *Am J Surg Pathol*. 2004;28:839–848.
4. Basturk O, Khayyata S, Klimstra DS, et al. Preferential expression of MUC6 in oncocytic and pancreatobiliary types of intraductal papillary neoplasms highlights a pyloropancreatic pathway, distinct from the intestinal pathway, in pancreatic carcinogenesis. *Am J Surg Pathol*. 2010;34:364–370.

5. Fujii H, Inagaki M, Kasai S, et al. Genetic progression and heterogeneity in intraductal papillary-mucinous neoplasms of the pancreas. *Am J Pathol.* 1997;151:1447–1454.
6. Furukawa T, Klöppel G, Adsay NV, et al. Classification of types of intraductal papillary-mucinous neoplasm of the pancreas: a consensus study. *Virchows Arch.* 2005;447:794–799.
7. Hara T, Yamaguchi T, Ishihara T, et al. Diagnosis and patient management of intraductal papillary-mucinous tumor of the pancreas by using peroral pancreatoscopy and intraductal ultrasonography. *Gastroenterology.* 2002;122:34–43.
8. Hoshi T, Imai M, Ogawa K. Frequent K-ras mutations and absence of p53 mutations in mucin-producing tumors of the pancreas. *J Surg Oncol.* 1994;55:84–91.
9. Hruban RH, Takaori K, Klimstra DS, et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *Am J Surg Pathol.* 2004;28:977–987.
10. Ji Y, Fan J, Zhou J, et al. Intraductal papillary neoplasms of bile duct: a distinct entity like its counterpart in pancreas. *Histol Histopathol.* 2008;23:41–50.
11. Kim HJ, Kim H, Lee SK, et al. Mucin-hypersecreting bile duct tumor characterized by a striking homology with an intraductal papillary mucinous tumor (IPMT) of the pancreas. *Endoscopy.* 2000;32:389–393.
12. Lim JH, Yi CA, Lim HK, et al. Radiological spectrum of intraductal papillary tumors of the bile ducts. *Korean J Radiol.* 2002;3:57–63.
13. Lim JH, Yoon KH, Kim SH, et al. Intraductal papillary mucinous tumor of the bile duct. *Radiographics.* 2004;24:53–67.
14. Lüttges J, Zamboni G, Longnecker D, et al. The immunohistochemical mucin expression pattern distinguishes different types of intraductal papillary mucinous neoplasms of the pancreas and determines their relationship to mucinous noncystic carcinoma and ductal adenocarcinoma. *Am J Surg Pathol.* 2001;25:942–948.
15. Miyakawa S, Ishihara S, Horiguchi A, et al. Biliary tract cancer treatment: 5,584 results from the Biliary Tract Cancer Statistics Registry from 1988 to 2004 in Japan. *J Hepatobiliary Pancreat Surg.* 2009;16:1–7.
16. Moriya T, Kimura W, Semba S, et al. Biological similarities and differences between pancreatic intraepithelial neoplasias and intraductal papillary mucinous neoplasms. *Int J Gastrointest Cancer.* 2005;35:111–119.
17. Oshikiri T, Kashimura N, Katanuma A, et al. Mucin-secreting bile duct adenoma: clinicopathological resemblance to intraductal papillary mucinous tumor of the pancreas. *Dig Surg.* 2002;19:324–327.
18. Sadakari Y, Ohuchida K, Nakata K, et al. Invasive carcinoma derived from the nonintestinal type intraductal papillary mucinous neoplasm of the pancreas has a poorer prognosis than that derived from the intestinal type. *Surgery.* 2010;147:812–817.
19. Shibahara H, Tamada S, Goto M, et al. Pathologic features of mucin-producing bile duct tumors: two histopathologic categories as counterparts of pancreatic intraductal papillary-mucinous neoplasms. *Am J Surg Pathol.* 2004;28:327–338.
20. Sohn TA, Yeo CJ, Cameron JL, et al. Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. *Ann Surg.* 2004;239:788–799.
21. Tanaka M, Fukushima N, Noda N, et al. Intraductal oncocytic papillary neoplasm of the bile duct: clinicopathologic and immunohistochemical characteristics of 6 cases. *Hum Pathol.* 2009;40:1543–1552.
22. Yamaguchi H, Shimizu M, Ban S, et al. Intraductal tubulopapillary neoplasms of the pancreas distinct from pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *Am J Surg Pathol.* 2009;33:1164–1172.
23. Zen Y, Aishima S, Ajioka Y, et al. Proposal of histological criteria for intraepithelial atypical/proliferative biliary epithelial lesions of the bile duct in hepatolithiasis with respect to cholangiocarcinoma: preliminary report based on interobserver agreement. *Pathol Int.* 2005;55:180–188.
24. Zen Y, Fujii T, Itatsu K, et al. Biliary papillary tumors share pathological features with intraductal papillary mucinous neoplasm of the pancreas. *Hepatology.* 2006;44:1333–1343.
25. Zen Y, Adsay NV, Bardadin K, et al. Biliary intraepithelial neoplasia: an international interobserver agreement study and proposal for diagnostic criteria. *Mod Pathol.* 2007;20:701–709.

広範囲肝切除において術前減黄術は必須なのか？

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索引用語：胆道癌，閉塞性黄疸，胆道ドレナージ，肝切除

1 はじめに

胆道癌診療ガイドライン[1]では，「胆管炎，広範囲肝切除予定例に術前減黄術が必要である.」というクリニカルクエスチョンに対して推奨度B，つまり，胆管ドレナージを行うよう勧めるという回答を示している．ガイドラインでは，胆管炎に関しての解説はなされてないものの，これまでに多くの論文で胆管炎は肝切除術後の肝不全発生のリスクファクターの一つであるとが報告されており[2]，欧米でも閉塞性胆管炎に対しての胆道ドレナージの施行は異論のないところであろう．その一方，胆管炎の合併を認めない閉塞性黄疸患者に対する術前胆管ドレナージの臨床的意義はいまだ明らかでないのが現状である．欧米においてはむしろ胆道ドレナージ，とくにPTBDの合併症による弊害がみられたとする報告さえもある[3-5]．さらに，最近の画像診断の進歩に伴い，とくにMultidetector-row CT（MDCT）の登場以来，Multiplanar reconstruction（MPR）をはじめとする再構成法（図1），さらには，MR cholangiographyの精度も飛躍的な進歩[6]をとげており，以前ほど直接胆管造影での長軸方向への癌の進展度診断の必要性がなくなってきたことも事実である．本邦でも，術前減黄に対する考え方も少しずつ変化してきており，肝切除を要さない中下部胆管閉塞では，術前胆道ドレナージは必須ではない[7]（肝機能不良例などを除けば）とのコンセンサスも得られつつある．しかしながらこれもRCTによるエビデンスレベルの高いstudyによって裏付けられているわけではない．その一方で，術後肝不全を中心とした合併症率の高い黄疸を伴う患者に対しての広範囲肝切除例では，本邦ではほぼ全例，

Hiroaki SHIMIZU et al: Significance of preoperative biliary drainage in patients with obstructive jaundice before extended hepatectomy
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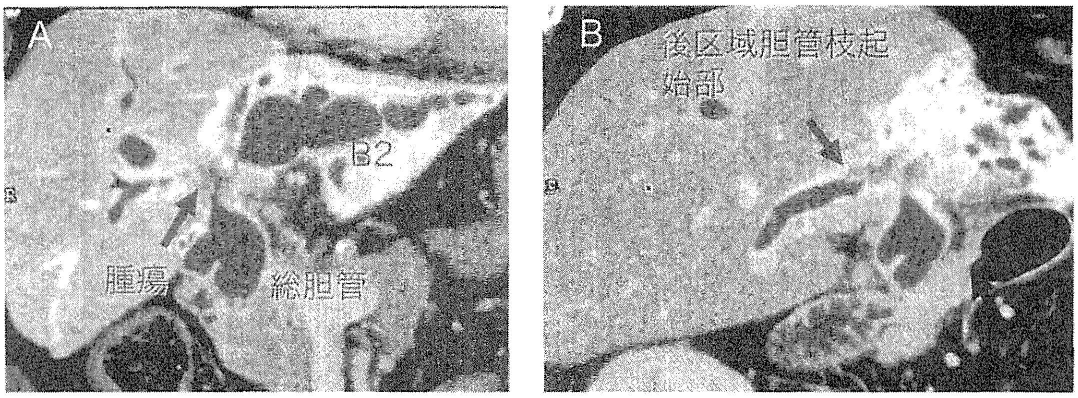

図1　肝門部胆管癌症例のMD-CT（MPR冠状断像）
肝実質に比し軽度低吸収域として肝門部に描出される腫瘍を認める.
(B)後区域胆管枝起始部まで腫瘍の浸潤を認める.

術前減黄術が行われているのが現状である[8〜10]. これは, 以下に示す基礎的研究, 後ろ向きの研究の結果をよりどころとして施行されており, その科学的意義を明らかにするための多数例を対象としたRCTの結果に基づいている訳ではない. したがって, 全国レベルでのRCTが今後, 期待されるところであるが, 実際には術後死亡率の高い疾患を対象としてのRCTの実現は極めて困難であろう.

この項では最近報告された論文, さらには基礎的研究より, 黄疸症例における術前減黄術の意義についてのエビデンスをまとめ, 広範囲肝切除が予定された際の術前減黄術の適応についての再考してみた.

2 基礎実験からみた肝切除前の減黄術の有用性について

閉塞性黄疸肝では正常肝と比較し, 細胞障害に結びつくさまざまな変化が生じていることが基礎的研究により示されてきた. すなわち, 黄疸期間の延長とともに肝組織血流量は低下し, 肝細胞膜障害も惹起される[11]. さらに肝ミトコンドリア機能の障害も認められ[12], 血漿中・肝組織中に高値となる胆汁酸はこのミトコンドリア機能障害を介して[13], あるいはFasを介して肝細胞のアポトーシスを誘導する[14]と報告されている. また, 免疫能からみてみると腸管内胆汁の欠如により, 腸管内のCD8陽性Tリンパ球とマクロファージ数は減少し[15], さらにKupffer細胞のサイトカイン産生性もTh2優位の状態となり[16], 門脈血中・肝へのbacterial translocationが容易に発生しやすい状況となっている. また, その一方で, 胆道ドレナージ(とくに内瘻化)を図ることによって, これらの閉塞性黄疸時に障害された機能がある程度改善し得ることも報告されている[17]. さらに, 閉塞性黄疸時には, 抱合型ビリルビンの胆汁への排泄に必要不可欠な輸送蛋白であるmultidrug resistance protein 2 (MPR2) の肝細胞毛細胆管膜での発現が低下し, 肝切除術後の高ビリルビン血症が発生しやすい病態であるとされる[18]. われわれもラット70%肝切除モデルを用いて, 閉塞性黄疸が肝切除後の肝再生に及ぼす影響を残肝組織中の増殖因子/抑制因子の発現の推移より検討してみたところ, 閉塞性黄疸によりIto細胞の数の増

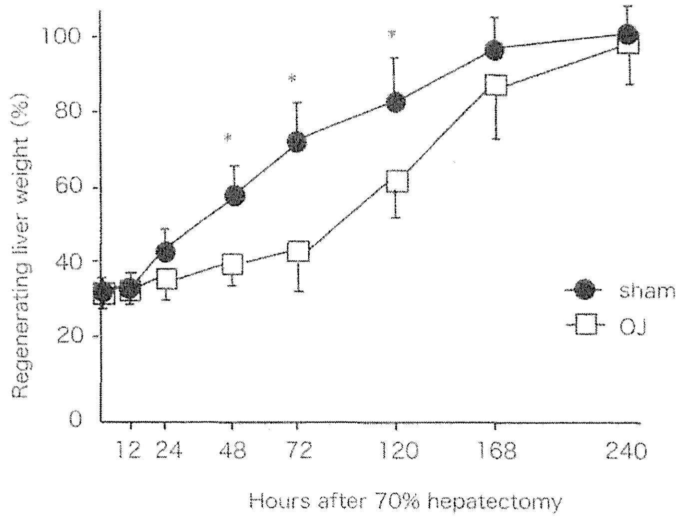

図2　閉塞性黄疸（OJ）群（ラット胆管結紮2週間）とsham群における70%肝切除施行後に再生肝重量の変化
OJ群の肝再生はsham群に比し，有意に遅延（*$p<0.05$）.

加と活性化が起こり，肝切除後にはその活性化したIto細胞からのTGF-β1産生亢進とHGFの産生低下により，有意に肝再生は抑制・遅延する（図2）結果を得ている[19].

このように閉塞性黄疸時の肝切除後には容易に肝障害，高ビリルビン血症，肝再生抑制さらには感染性合併症が引き起こされやすい状態となっているわけである．したがって，胆道ドレナージによってある程度その病態の改善が期待し得ることから，実際の臨床，とくに術後肝不全による死亡率の高い，胆道癌の広汎肝切除が予定される症例においては，術前減黄術を実施する意義があるだろうと考えられるわけである．

3　肝切除前の減黄術についての臨床的検討について

本邦でもMR cholangiography，MDCTなどの各種画像診断から，外科切除に際し，肝切除を要さない中下部胆管閉塞（中下部胆管癌，乳頭部癌，膵癌）は，術前胆管ドレナージによる減黄は必要としないとする報告[7]も多数みられており，この点では術前減黄に関しての考え方も変わりつつある．しかしながら，その一方で，手術関連死亡率が高いとされる広範肝切除術を選択することが多い肝門部胆管癌[8～10,20,21]，肝門浸潤を伴う胆嚢癌[22]ではその肝機能の面から，さらには挿入されたドレナージチューブからの胆管造影による進展度診断法としての意味合いから，術前に胆管ドレナージを挿入し，十分に減黄を待って根治手術を行うのが，本邦では一般的なstrategyとされる．

現在まで閉塞性黄疸を伴った症例での拡大肝切除術における検討はCherquiら[23]による報告（n = 20）が唯一あるのみである．この論文では術前胆道ドレナージなしで施行した拡大肝葉切除の成績は，手術関連死亡率5%，術後合併症率50%であり，閉塞性黄疸を伴わない症例とほぼ同様な手術関連死亡率であったとしている．これは本邦からの報告，すなわち術前胆道ドレナージを施行し，十分

減黄を図った後に肝切除を施行したときの成績[8〜10,25,26]と比べ大きな差異は認めていない．しかしながら，このCherquiら[23]の論文での留意すべき点は，閉塞性黄疸期間が1カ月以上と考えられる症例に対してはドレナージを施行している点である．さらに，この論文を詳細にみてみると，彼らは「栄養状態の悪い患者，低アルブミン血症，長期の黄疸例では術前胆管ドレナージは，必要であろう．」という見解も述べている．つまり，裏を返せば，「黄疸期間が短く，比較的状態の良い患者をすばやく手術することが可能であれば，術前ドレナージは必要ではない．」と理解できる．実際に彼らは胆道ドレナージを挿入しない症例は入院後できるだけ早く，1週間以内に根治手術を予定，施行したとしている．

ここで，本邦での黄疸を伴った肝門部胆管癌の治療計画について考えてみると，右からの肝切除，さらには，左三区域切除が予定される際には，残肝体積を考慮し，多くの施設で術前門脈塞栓を施行している．したがって，根治手術は少なくても門脈塞栓後2〜3週間後に予定されるわけであるから，門脈塞栓を要するような症例に対しては，胆管ドレナージを挿入せざる得ないことになるだろう．また，黄疸期間は患者からの問診によりなされることが多く，その評価はやはり難しいと考える．

4 胆道ドレナージに起因する合併症について

胆道ドレナージの有用性を検討するには，ドレナージ自体に起因する合併症についても考慮しなければならないのはいうまでもない．胆道ドレナージの最も重大な合併症はカテーテルに関連した感染であるといっても過言ではない．胆管炎を含めた感染症は肝切除術後の合併症発生率に影響を与える[2]．さらには経皮経肝ルートよりの胆管穿刺時における胆道出血，動脈損傷に起因する仮性動脈瘤[24]さらには，門脈血栓などその後の肝機能に悪影響を及ぼす重大な合併症も頻度は低いが報告されている[25]．また，胆道ドレナージ症例，とくにPTBD施行例における術後合併症発生率は欧米からの報告が，本邦の報告に比べ，明らかに高く[3,25]，これは，ドレナージの技術的因子もある程度関連している可能性も推測される．さらに，経皮経肝ルートよりのPTBDドレナージでは，瘻の瘻孔再発，腹膜播種（とくに胆汁細胞診にて癌細胞陽性であることの多い乳頭型胆管癌症例において）も起こる可能性もあり，注意すべき点と考える．

5 まとめ

閉塞性黄疸を伴った症例に対する肝切除術前の胆道ドレナージは，感染などのリスクはあるものの，障害された肝機能，免疫機能の回復などの面からも手術の安全性を高めるといった基礎実験データより裏付けされ，現状では少なくても門脈塞栓を併用した広汎肝切除術が予定される際には，胆道ドレナージは欠かすことができない術前処置と考えてよいと思われる．しかしながら，その一方で，区域切除など小範囲肝切除において術前減黄術の必要性については，なんら明確な結論はでていないといってよい．

文　献

1）胆道癌診療ガイドライン　第一版．高田忠敬編．医学図書出版，東京，2007
2）Nagino M, Nimura Y, Hayakawa N et al : Logistic regression and discriminant analyses of hepatic failure after liver resection for carcinoma of the biliary tract. World J Surg 17 : 250–255, 1993

3) Hatfield AR, Tobias R, Terblanche J et al : Preoperative external biliary drainage in obstructive jaundice. A prospective controlled clinical trial. Lancet 2 : 869–899, 1982
4) Pitt HA, Gomes AS, Lois JF et al : Does preoperative percutaneous biliary drainage reduce operative risk or increase hospital cost? Ann Surg 201 : 545–553, 1985
5) McPherson GAD, Benjamin IS, Hodgson HJF et al : Pre-operative percutaneous transhepatic biliary drainage: the results of a controlled trial. Br J Surg 71 : 371–375, 1984
6) 村上康二，那須克宏，黒木嘉典，他：MRIによる胆道癌の診断．胆と膵 22：1091–1096，2001
7) 福原稔之，小林展章，梶原建熙：膵頭十二指腸切除症例の術後合併症からみた術前減黄の意義に関する検討．臨外 53：21–25，1998
8) Kawasaki S, Imamura H, Kobayashi A et al : Results of surgical resection for patients with hilar bile duct cancer. Application of extended hepatectomy after biliary drainage and hemihepatic portal vein embolization. Ann Surg 238 : 84–92, 2003
9) Kondo S, Hirano S, Ambo Y et al : Forty consecutive resections of hilar cholangiocarcinoma with no postoperative mortality and no positive ductal margins: results of a prospective study. Ann Surg 240 : 95–101, 2004
10) Seyama Y, Kubota K, Sano K et al : Long-term outcome of extended hemihepatectomy for hilar bile duct cancer with no mortality and high survival rate. Ann Surg 238 : 73–83, 2003
11) 伊藤　博，宮崎　勝，宇田川郁夫，他：閉塞性黄疸肝における阻血・再灌流侵襲時の肝細胞障害に関する基礎的検討．日消病誌　88：1200–1207，1991
12) 鈴木克彦，小山研二，浅沼義博，他：閉塞性黄疸肝の分離肝細胞ミトコンドリア機能について．日外会誌 89：703–708，1988
13) Sokol RJ, Winklhofer-Roob BM, Devereaux MW et al : Generation of hydroperoxides in isolated rat hepatocytes and hepatic mitochondria exposed to hydrophobic bile acids. Gastroenterology 109 : 1249–1256, 1995
14) Miyoshi H, Rust C, Roberts PJ et al : Hepatocyte apoptosis after bile duct ligation in the mouse involves Fas. Gastroenterology 117 : 669–677, 1999
15) 味木徹夫，藤田恒憲，黒田嘉和：免疫能からみた閉塞性黄疸に対する内瘻術の意義．胆と膵 25：861–865，2004
16) 新井利幸，梛野正人，二村雄次：免疫能・胆汁排泄能からみた閉塞性黄疸に対する術前減黄術の意義—閉塞性黄疸に対する減黄術の基礎的意義—．胆と膵 25：871–874，2004
17) Parks RW, Clements WD, Smye MG et al : Intestinal barrier dysfunction in clinical and experimental obstructive jaundice and its reversal by internal biliary drainage. Br J Surg 83 : 1345–1349, 1996
18) Shoda J, Kano M, Oda K et al : The expression levels of plasma membrane transporters in the cholestatic liver of patients undergoing biliary drainage and their association with the impairment of biliary secretory function. Am J Gastroenterology 96 : 3368–3378, 2001
19) Makino H, Shimizu H, Ito H et al : Changes in growth factor and cytokine expression in biliary obstructed rat liver and their relationship with delayed liver regeneration after partial hepatectomy. World J Gastroentero 7 : 2053–2059, 2006
20) Ebata T, Nagino M, Kamiya J et al : Hepatectomy with portal vein resection for hilar cholangiocarcinoma: audit of 52 consecutive cases. Ann Surg 238 : 720–727, 2003
21) Miyazaki M, Kato A, Ito H et al : Combined vascular resection in operative resection for hilar cholangiocarcinoma: does it work or not? Surgery 141 : 581–588, 2007
22) Miyazaki M, Ito H, Ambiru S et al : Radical surgery for advanced gallbladder carcinoma. British J Surg 83 : 478–481, 1996
23) Cherqui D, Benoist S, Malassagne B et al : Major liver resection for carcinoma in jaundiced patients without preoperative biliary drainage. Arch Surg 135 : 302–308, 2000
24) Okuno A, Miyazaki M, Ito H et al : Nonsurgical management of ruptured pseudoaneurysm in patients with hepatobiliary pancreatic diseases. Am J Gastroenterol 96 : 1067–1071, 2001
25) Nimura Y, Kamiya J, Kondo S et al : Aggressive preoperative management and extended surgery for hilar cholangiocarcinoma: Nagoya experience. J Hepatobiliary Pancreat Surg 7 : 155–162, 2000

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特集：胆道癌診療ガイドラインを学ぶ — 最新のエビデンスとコンセンサス

I．総　論

1.「エビデンスに基づいた胆道癌診療ガイドライン」とその作成過程について

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