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Review Article

Intraductal Papillary Neoplasms of the Bile Duct

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Intraductal papillary neoplasm of the bile duct (IPNB) is a rare variant of bile duct tumors characterized by papillary growth within the bile duct lumen and is regarded as a biliary counterpart of intraductal papillary mucinous neoplasm of the pancreas. IPNBs display a spectrum of premalignant lesion towards invasive cholangiocarcinoma. The most common radiologic findings for IPNB are bile duct dilatation and intraductal masses. The major treatment of IPNB is surgical resection. Ultrasonography, computed tomography, magnetic resonance image, and cholangiography are usually performed to assess tumor location and extension. Cholangioscopy can confirm the histology and assess the extent of the tumor including superficial spreading along the biliary epithelium. However, pathologic diagnosis by preoperative biopsy cannot always reflect the maximum degree of atypia, because IPNBs are often composed of varying degrees of cytoarchitectural atypia. IPNBs are microscopically classified into four epithelial subtypes, such as pancreatobiliary, intestinal, gastric, and oncocytic types. Most cases of IPNB are IPN with high-grade intraepithelial neoplasia or with an associated invasive carcinoma. The histologic types of invasive lesions are either tubular adenocarcinoma or mucinous carcinoma. Although several authors have investigated molecular genetic changes during the development and progression of IPNB, these are still poorly characterized and controversial.

1. Introduction

Intraductal papillary neoplasm of the bile duct (IPNB) is a rare variant of bile duct tumors, which is characterized by papillary or villous growth within the bile duct lumen.

Formerly, attention has been drawn to biliary tumors with macroscopically visible mucin secretion, which show predominantly papillary growth within the dilated bile duct lumen and secrete a large amount of mucin. These tumors were called by various names, such as mucin-producing cholangiocarcinoma [1–4], mucin-hypersecreting bile duct tumor [5], and intraductal papillary mucinous tumor of the bile duct [6, 7], and were identified as a biliary counterpart of intraductal papillary mucinous neoplasm (IPMN) of the pancreas. On the other hand, biliary intraductal tumors without macroscopically visible mucin secretion are also known, which have a macroscopically recognizable papillary or granular structure but no clinically visible mucin secretion. Since certain morphological features of these tumors, especially intraductal papillary growth pattern, are also similar to those of IPMN of the pancreas, Zen et al. [8] proposed that they, together with tumors with macroscopically visible mucin secretion, may belong to a single tumor entity named IPNB. Now, IPNB was adopted in the 2010 World Health Organization (WHO) classification [9] as a distinct clinical and pathologic entity. In this review, we describe the concept, clinical and pathologic features, and pathogenesis of IPNB.

2. Concept of IPNB

2.1. Definition of IPNB. IPNB is defined as a biliary epithelial tumor with exophytic nature exhibiting papillary mass within the bile duct lumen and with prominent intraductal growth pattern. IPNB can develop anywhere along the biliary tree,

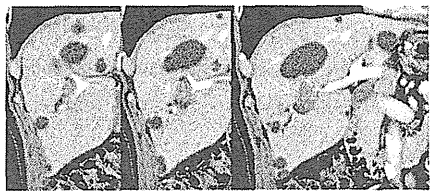


FIGURE 1: Representative images of intraductal papillary neoplasm of the bile duct on computed tomography. Localized bile duct dilatation and an intraductal mass are shown (arrows).

including both intrahepatic and extrahepatic bile ducts. Mucin hypersecretion and dilatation of the bile duct are sometimes encountered. Microscopically, IPNB is composed of papillary fronds with fine vascular cores. Neoplastic epithelial cells display a spectrum of cytoarchitectural atypia ranging from none to borderline to marked and also can be associated with invasive carcinoma. Due to these features, IPNB is regarded as a premalignant lesion towards invasive cholangiocarcinoma. In the WHO classification [9], IPNB is classified into IPN with low- or intermediate-grade intraepithelial neoplasia, IPN with high-grade intraepithelial neoplasia, and IPN with an associated invasive carcinoma. This classification is similar to that of IPMN of the pancreas, and an analogous multistep progression model is assumed in IPNB.

2.2. Diseases Included in IPNB. Before inclusion of IPNB in the WHO classification, many different terms have been used for the spectrum of this entity. These include biliary papilloma/papillomatosis, some of the intraductal growth type of cholangiocarcinoma and papillary carcinoma of the extrahepatic bile duct, and some of the biliary cystadenoma/cystadenocarcinoma. Among the intraductal growth type of intrahepatic cholangiocarcinoma and papillary carcinoma of the extrahepatic bile duct, cases with intraductal component composed of papillary fronds with fine vascular cores are exclusively included in IPNB. In the previous categories of biliary cystadenoma/cystadenocarcinoma, cystic tumors with bile duct communication and absence of ovarian-like stroma are considered as a cystic variant of IPNB [10].

3. Clinical Features

3.1. Clinical Characteristics. The prevalence of IPNB shows wide geographic variation. The highest incidence is reported in Far Eastern countries, probably because hepatolithiasis and clonorchiasis that are believed to be major risk factors of IPNB are endemic. IPNB is relatively rare and comprises 9–38% of all bile duct carcinomas [11–15]. Most patients are between 50 and 70 years of age [11–18] and show a slight male predominance in most reported series [12–14, 16–18]. Intermittent abdominal pain and acute cholangitis or jaundice are the most common clinical manifestations [11–13, 16, 18, 19], but certain frequency (5–29%) of patients have no symptoms [12, 13, 16, 18, 19]. Around 30% of patients have a previous history or concomitant existence of biliary stones, as shown in the reports from Far Eastern countries [12, 16, 20], but not from Western countries [13].

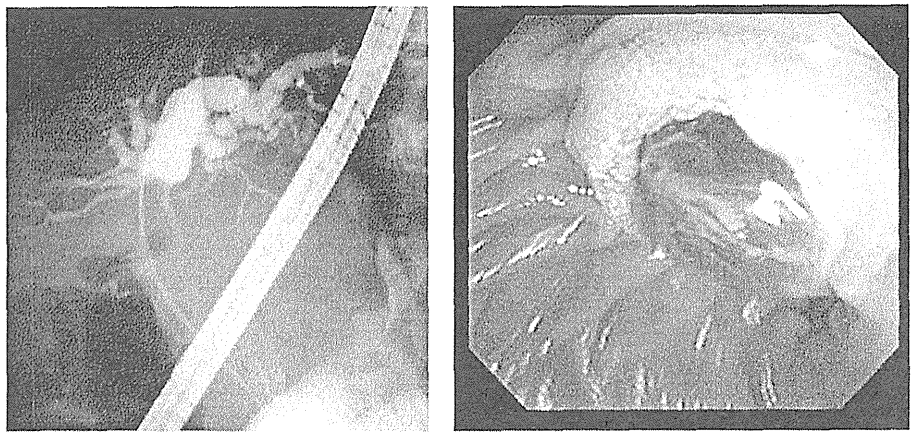
Tumor location varies by a report. Some reports showed that the majority of IPNB was located at the intrahepatic bile duct [16, 17], whereas the other showed that the most common location of IPNB was the hepatic hilum [13]. Despite these variable locations, IPNB tends to be found in the left-sided biliary ductal system, when IPNB exists in the intrahepatic bile duct, due to unknown reasons [13, 20, 21].

3.2. Radiologic Findings. The most common radiologic findings for IPNB are bile duct dilatation and intraductal masses (Figure 1). The patterns of bile duct dilatation are diffuse duct ectasia, localized duct dilatation, and cystic dilatation, which can be recognized by ultrasonography (US), computed tomography (CT), and magnetic resonance image (MRI). These modalities can also detect intraductal masses, although its sensitivity is reported to be in the range of 41.2–97% [22–24]. MRI images reveal IPNB as iso- to hypointense masses on T1-weighted image and hyperintense masses on T2-weighted image [24]. The enhancement pattern on CT scan is isodense or hyperdense during the late arterial phase and not hyperdense during the portal-venous and delayed phase, as compared with normal hepatic parenchyma [23]. Mucin, even if it exists, cannot be detected on US, CT, and MRI.

Direct cholangiography such as endoscopic retrograde cholangiography (ERC) is useful for the detection of mucobilia (Figure 2(a)) that is seen in nearly one-third of patients with IPNB, evidenced by diffuse dilatation of the bile duct with amorphous filling defect [6], and duodenoscopy shows a dilated papillary orifice with mucin (Figure 2(b)). However, the thick mucin that filled the dilated biliary tree often prevents the visualization of intraductal tumors [6, 25, 26]. In cases with IPNB without excessive mucin production, cholangiography can define the tumors as irregular filling defects.

Cholangioscopy including percutaneous transhepatic cholangioscopy (PTCS) and peroral cholangioscopy (POCS) can approach the bile duct directly, and it can confirm the histology and assess the extent of the tumor including superficial spreading along the biliary epithelium (Figure 3), which provides information to choose appropriate treatment [22], although an accurate diagnosis of the maximum degree of cytoarchitectural atypia cannot be always made by biopsy because of the existence of mixed pathologic findings in the same lesion. POCS is advantageous in the fact that it can be performed without serious complications, such as catheter dislodgement, hemobilia, and tumor seeding of the sinus tract caused by PTCS [25, 27]. In cases with IPNB with abundant mucin, however, PTCS seems to be more useful than POCS, because discrimination of the location and extent of a tumor may be difficult by POCS in some cases [27].

Intraductal ultrasonography (IDUS) is a simple method for diagnosing the location of IPNB and assessing the depth of invasion, even in the presence of thick mucin. However, IDUS image is sometimes difficult to interpret, since coexisting



(a) (b)

FIGURE 2: A representative case of intraductal papillary neoplasm of the bile duct with mucin hypersecretion. (a) Endoscopic retrograde cholangiogram. Diffuse dilatation of the common bile duct with amorphous filling defect is shown. (b) Duodenoscopy shows a dilated papillary orifice with mucin.

biliary sludge may have an appearance like that of elevated tumors. Furthermore, it is difficult to distinguish between inflammatory wall thickness and the superficial spreading of a tumor [25].

3.3. Treatment. Unlike patients with IPMNs of the pancreas, all patients with IPNB should be considered to treat, because papillary tumors and associated mucin often cause recurrent cholangitis and obstructive jaundice, even if these tumors are not malignant. Patients without distant metastasis are considered for surgical resection. In order to choose appropriate surgical procedure, exact preoperative assessment of tumor location and extension is important. In particular, for evaluating of the extent of superficial spreading, cholangioscopic observation and biopsy might be essential. The depth of invasion and the presence of lymph node involvement are also assessed preoperatively by CT, cholangiography, and IDUS.

In principle, IPNBs should be resected in a manner similar to that employed for other types of intrahepatic cholangiocarcinomas and extrahepatic bile duct carcinomas. That is, major hepatectomy with or without extrahepatic bile duct resection or pancreaticoduodenectomy should be chosen as surgical procedure. Even though it is suspected that the tumor is premalignant, a similar strategy should be considered, because pathologic diagnosis by preoperative biopsy cannot always reflect the maximum degree of cytoarchitectural atypia. Intraoperative frozen section at the stumps of the bile duct is essential to confirm cancer-free surgical margin. Regional lymphadenectomy should also be performed.

On the other hand, in cases of IPNB with low- to high-grade intraepithelial neoplasia and limited superficial spreading and precise diagnosis which is completed preoperatively, limited resections preserving organ functions, for example, extensive hilar bile duct resection using a transhepatic approach [28, 29], can be considered as a choice among surgical procedures, although these should always be contingent on a careful intraoperative final assessment. In contrast, in cases of IPNB with extensive superficial spreading that may have positive margins or IPNB with multifocal involvement, tumor recurrence may occur with a high risk after surgical resection. In such cases, resection for the whole biliary tree by liver transplantation and pancreaticoduodenectomy can be theoretically regarded as the only curative treatment [30]. However, liver transplantation should not be performed in patients with advanced tumor invasion or with positive lymph nodes. Since accurate preoperative assessment of IPNB is usually difficult, indication of liver transplantation for patients with IPNB is very limited.

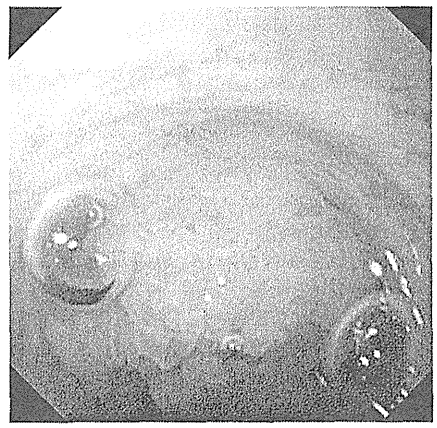


FIGURE 3: Peroral cholangioscopy reveals a papillary tumor within the lumen of the bile duct, but no obvious superficial spreading along the biliary epithelium is observed.

4. Pathologic Features

4.1. Macroscopic Findings. The most common macroscopic findings of IPNB are singular, or occasionally multiple, polypoid masses elevating into the lumen of the dilated bile duct and/or clinically visible granular or small papillary mucosa (Figure 4(a)). Polypoid masses occasionally extend longitudinally and fill the lumen of the bile duct, showing cast-like appearance. Multilocular, rarely unilocular, well-defined cystic mass, which contains mucinous fluid, is another manifestation of IPNB (Figure 4(b)). The internal surfaces of cystic masses are generally smooth or finely granular, and papillary mural nodules are commonly observed. Anatomic communication with the bile duct is sometimes difficult to confirm.

4.2. Microscopic Findings

4.2.1. Conventional Histology. Prominent papillary proliferation with delicate fibrovascular cores is a characteristic finding (Figure 5). Coexistence of tubulopapillary architecture can be found in IPNB, especially without mucin hypersecretion [12]. Similar to IPMNs of the pancreas, IPNBs are classified into four epithelial subtypes (Figure 5), such as pancreatobiliary, intestinal, gastric, and oncocytic types, of the intraductal component [12–14, 16, 31]. The most frequent subtype is pancreatobiliary, followed by intestinal in all IPNBs, whereas IPNBs with mucin hypersecretion are more prevalent in the intestinal subtype than those without mucin hypersecretion [12]. The pancreatobiliary or the intestinal type is commonly associated with histologic grade of more than high-grade intraepithelial neoplasia, and, therefore, most cases of IPNB are IPN with high-grade intraepithelial neoplasia or IPN with an associated invasive carcinoma. The histologic types of invasive lesions are either tubular adenocarcinoma or mucinous (colloid) carcinoma [8]. Mucinous carcinoma usually arises in association with the intestinal type of IPNB.

IPNBs, however, often exhibited marked variation in histologic grade between different regions of individual tumors, making an accurate preoperative diagnosis difficult. This feature is significantly more common in IPNBs with mucin hypersecretion than those without [12].

IPNBs manifesting cystic mass have similar morphological features to biliary mucinous cystic neoplasms. These two entities are histologically distinct. Biliary mucinous cystic neoplasms have densely cellular connective tissue resembling ovarian stroma (ovarian-like stroma) in their wall, whereas this is never seen in IPNBs [10, 32].

4.2.2. Immunohistochemical Phenotypes (Table 1). Immunohistochemical mucin core proteins are reported to be associated with epithelial subtypes in IPMN of the pancreas. Similarly, MUC1 is often detected in the pancreatobiliary type of IPNBs, but very few are expressed in the intestinal or gastric type. MUC2 is primarily expressed in the intestinal type of IPNBs compared to the pancreatobiliary or the gastric type. MUC5AC expression is common in all epithelial subtypes, including the oncocytic type. In the oncocytic type of IPNBs, MUC1 expression is focally seen [16].

Some cytokeratin is also associated with epithelial subtypes. Cytokeratin 20 is expressed in the intestinal type of IPNBs with high frequency but not in the gastric type. High expression of cytokeratin 7 is observed in the gastric type of IPNBs [33].

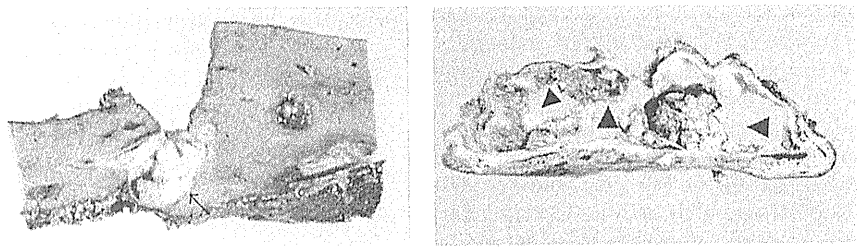
5. Pathogenesis

5.1. Molecular Events during Development and Progression of IPNB (Tables 2 and 3). IPNBs derive from normal epithelium of the bile duct and progress through low-, intermediate-, and high-grade intraepithelial neoplasia to invasive carcinoma. During this process, cumulative aberrations in gene expression may be associated. However, these aberrations are still poorly characterized, and it is also not well known whether progression pathways of biliary intraepithelial neoplasia (BilIN), a precursor associated with the development of nonpapillary invasive cholangiocarcinoma, and IPNB are regulated differently. Several authors have investigated molecular genetic changes during the development and progression of the IPNB lineage and compared them with those of the BilIN lineage. According to the results in these studies mentioned below, IPNB and BilIN lineages were suggested to display a lot of similarities, but some differences, in the molecular genetic changes, although there were some inconsistent data among the reports.

Cyclins D1 and p21, which are the regulators of cell cycle progression, seem to play an important role in the development and progression in both BilIN and IPNB lineages, since expressions of these molecules have been reported to increase with histologic progression from low-grade to invasive carcinoma in both IPNBs and BilINs. Itatsu et al. [34] found that the positive rate of cyclin D1 expression in the IPNB lineage (65%) was significantly higher than that in the BilIN lineage (20%), suggesting that cyclin D1 is more important to the IPNB lineage, whereas Nakanishi et al. [35] have not shown such differences. Aberrant expression of p16, another regulator of cell cycle progression, was also seen from an early phase in the development of both BilIN and IPNB lineages, although the frequency of positive cases was relatively low, and the expression reached a plateau despite histologic progression [36, 37].

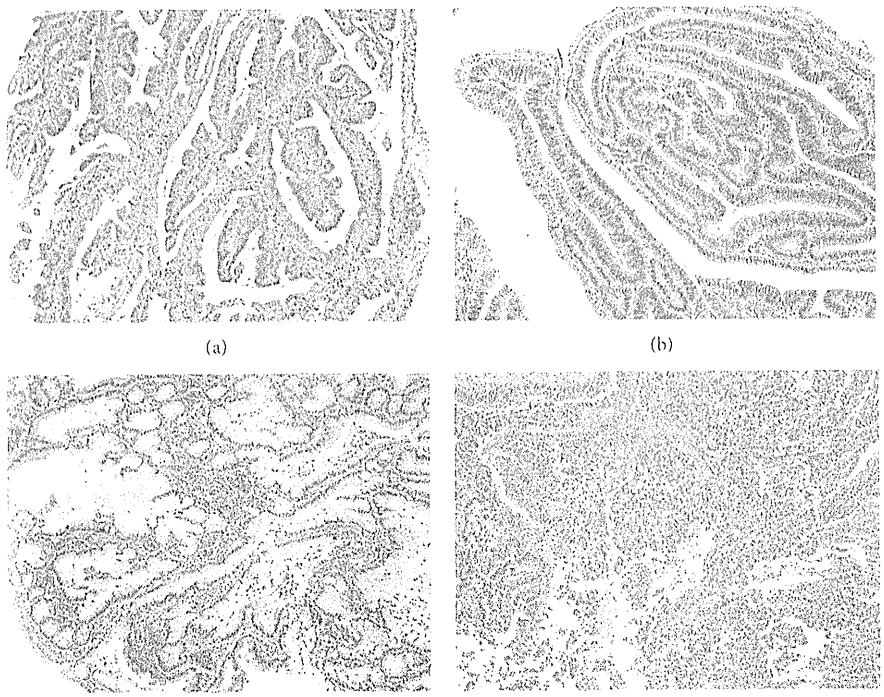
C-myc, which is a transcriptional factor for modulating regulators of cell cycle progression and a target molecule of Wnt signaling pathway, is suggested to be more important in the progression of the IPNB lineage than in that of the BilIN lineage. The expression of c-myc was demonstrated to be in more than half of IPNBs [34]. Similarly, nuclear accumulation of β-catenin protein, indicating genetic alteration of Wnt signaling pathway, was found only in approximately 25% of IPNBs [34, 38], concluding that this is significantly involved in the progression of IPNBs but not BilINs. However, a recent report has shown an inconsistent conclusion, in which β-catenin protein accumulation in the nucleus is less important for the progression of IPNBs due to its infrequency (9%) [36].

v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations are indicated to be an early event in IPNBs,



(a) (b)

FIGURE 4: Macroscopic findings of intraductal papillary neoplasm of the bile duct. (a) A polypoid mass (arrow) is elevated into the lumen of the bile duct. (b) Polypoid mural nodules (arrowheads) are observed in the well-defined cystic lesion. This lesion was communicated with the bile duct.



(a) (b) (c) (d)

FIGURE 5: Microscopic findings of intraductal papillary neoplasm of the bile duct. Prominent papillary proliferation with delicate fibrovascular cores is a characteristic feature. Epithelial subtypes are classified as pancreatobiliary (a), intestinal (b), gastric (c), and oncocytic (d).

TABLE 1: Immunohistochemical phenotypes in intraductal papillary neoplasms of the bile duct (IPNB) and intraductal papillary mucinous neoplasms of the pancreas (IPMN) [16, 33].

Epithelial subtypes	Mucin core proteins			Cytokeratin (CK)			
				CK20		CK7	
	MUC1	MUC2	MUC5AC	IPNB	IPMN	IPNB	IPMN
Gastric	−	−	+	0 (0/5)*	0 (0/10)	100 (5/5)	80 (8/10)
Intestinal	−	+	+	75 (3/4)	71 (12/17)	50 (2/4)	82 (14/17)
Pancreatobiliary	+	−	+	22 (2/9)	0 (0/2)	78 (7/9)	100 (2/2)
Oncocytic	− ~ +	− ~ +	+	0 (0/2)	N.D.	50 (1/2)	N.D.

*% of positive cases (positive cases/total cases examined); N.D.: not determined.

Table 2: Molecular events in the intraductal papillary neoplasms of the bile duct lineage and the biliary intraepithelial neoplasia lineage.

Authors	Cyclin D1		p16		c-myc		β-catenin		SMAD4/DPC4		p53			
	IPNB	BilIN	IPNB	BilIN	IPNB	BilIN	IPNB	BilIN	IPNB	BilIN	IPNB non-inv.	IPNB inv.	BilIN non-inv.	BilIN inv.
Itatsu et al. [34]	65 (17)*	20 (45)	N.D.		54 (13)	13 (45)	22 (18)	0 (45)	N.D.			N.D.		
Nakanishi et al. [35]	53 (10)	43 (11)	N.D.		N.D.		N.D.		21 (36)	27 (49)	38 (16)	36 (10)	8 (38)	82 (11)
Schlitter et al. [36]	N.D.		24 (42)	36 (22)	N.D.		9 (45)	0 (22)	7 (45)	14 (22)	60 (52)	85 (13)	N.D.	64 (22)
Sasaki et al. [37]	N.D.		29 (34)	N.D.	N.D.		N.D.		N.D.		0 (15)	30 (19)	N.D.	
Abraham et al. [38]	N.D.		N.D.		N.D.		25 (12)	N.D.	0 (12)	N.D.	0 (12)		N.D.	

*% of cases with positive staining or mutations (total cases examined); N.D.: not determined; inv.: invasive.

Table 3: KRAS and GNAS mutations in the intraductal papillary neoplasms of the bile duct lineage, the biliary intraepithelial neoplasia lineage, the intraductal papillary mucinous neoplasms of the pancreas lineage, and pancreatic ductal adenocarcinoma.

Authors	KRAS mutation				GNAS mutation			
	IPNB	BilIN	IPMN	PDAC	IPNB	BilIN	IPMN	PDAC
Furukawa et al. [39]	N.D.		47 (118)*	22 (32)	N.D.		41 (118)	0 (32)
Schlitter et al. [36]	36 (45)	14 (22)	N.D.		2 (44)	0 (22)	N.D.	
Abraham et al. [38]	29 (12)	N.D.	N.D.		N.D.	N.D.	N.D.	
Matthaei et al. [40]	18 (34)	N.D.	N.D.		4 (23)	N.D.	N.D.	
Sasaki et al. [41]	46 (26)	33 (76)	N.D.		50 (30)	0 (76)	N.D.	
Tsai et al. [42]	32 (41)	N.D.	N.D.		29 (41)	N.D.	N.D.	

*% of cases with mutations (total cases examined); N.D.: not determined.

as shown by several reports [36, 38, 40–42]. The occurrence of these mutations was more common in IPNBs (17.6 to 46.2% of cases) than in BilINs. In contrast, with regard to guanine nucleotide-binding protein, α-stimulating activity polypeptide (GNAS) codon 201 mutations, which have been exclusively detected in approximately two-thirds of IPMNs of the pancreas but not pancreatic ductal adenocarcinoma [39], there are some conflicting data among the studies. Sasaki et al. [41] showed that GNAS mutation was detected in 15 of 30 IPNBs, whereas Schlitter et al. [36] and Matthaei et al. [40] found GNAS mutation only in one of 44 IPNBs and one of 23 IPNBs, respectively. Although reasons for this discrepancy are unknown, one possible reason may be difference of phenotypes of IPNBs studied. Tsai et al. [42] recently reported that 12 of 41 IPNBs showed GNAS mutation, which was correlated with a distinct subgroup of IPNB characterized by the intestinal subtype, villous configuration, and mucin hypersecretion. These features were extremely similar to those of IPMN of the pancreas. Similarly, all IPNBs with GNAS mutation only showed high-mucin production in the study by Sasaki et al. [41], whereas GNAS mutation was detected in the intestinal subtype in both studies by Schlitter et al. [36] and Matthaei et al. [40]. Furthermore, only one IPNB with mucin hypersecretion was included in the study by Schlitter et al. [36] and only two tumors with the intestinal subtype in the study by Matthaei et al. [40].

Involvement of SMAD4/DPC4, which acts as a tumor suppressor that functions in the regulation of the TGF-β signal transduction pathway, and p53, which acts also as a tumor suppressor, during the development and progression of IPNB is still controversial. Nakanishi et al. [35] showed that loss of SMAD4/DPC4 expression was seen in both IPNB (21.4%) and BilIN (27.3%) lineages with gradually increasing frequency with progression. Schlitter et al. [36] revealed similar results despite less frequency (IPNBs, 7%; BilINs, 14%). In contrast, Abraham et al. [38] reported that immunohistochemical labeling for SMAD4/DPC4 showed intact protein expression in all the IPNBs examined. One report [35] showed that aberrant immunohistochemical expression of p53 was early on in low-grade IPNB and reached a plateau, whereas that remained low in the early phase of BilIN lineage and its expression was significantly upregulated in the cases with invasive carcinoma. However, there were reports in which aberrant expression of p53 was never seen in all IPNBs examined [38], or p53 was not aberrantly expressed in IPNBs without invasion but extensively expressed in IPNBs with invasion [37]. Another report revealed that frequency of p53 aberrant expression progressively increased from low-grade intraepithelial neoplasia to invasive carcinoma [36].

There were few studies on DNA mismatch repair functionality in IPNBs. Abraham et al. [43] showed that impaired DNA mismatch repair evidenced by microsatellite instability was seen in 8 of 17 IPNBs (high-level in 2, low-level in 1). This frequency was higher than that previously reported for extrahepatic [44] and intrahepatic cholangiocarcinoma [45], indicating that impaired DNA mismatch repair might play a role in the pathogenesis of a subset of IPNBs. However, the mechanism that causes impaired DNA mismatch repair was not clarified, and no methylation of the human Mut L homologue gene promoter was detected in IPNBs.

Mucin core proteins such as MUC1 and MUC2 are involved in the progression of both IPNB and BilIN lineages. Zen et al. [46] reported that MUC1 expression was more common in BilINs, especially in invasive lesions, than in IPNB with an associated invasive carcinoma. They supposed two progression pathways of IPNB to tubular adenocarcinoma and mucinous carcinoma, featuring the phenotypes of MUC1+/MUC2+ and MUC1−/MUC2+, respectively, which are analogous to that of IPMN of the pancreas. However, Onoe et al. [14] revealed that most IPNB with ≤50% invasive component showed MUC1+/MUC2− carcinogenetic pathway progressing to papillary/tubular adenocarcinoma, whereas a few IPNBs with ≤50% invasive progressed to mucinous carcinoma characterized by a MUC1+/MUC2+ pathway. Sasaki et al. [37] showed that the polycomb group protein enhancer of zeste homolog 2 may play a role in the regulation of MUC1 and MUC6 in IPNBs.

5.2. IPNB Originated from Peribiliary Glands. IPNB normally arises from the biliary epithelium in the extra- or intrahepatic large bile duct. However, recently, IPNBs that involved significantly the peribiliary glands and grossly showed cystic dilatation particularly aneurysmal or diverticular dilatation were reported [47–49], suggesting that some type of IPNB may arise from the peribiliary glands located within the wall or scattered in the surrounding connective tissue of the intrahepatic large bile ducts and extrahepatic bile ducts. These lesions are proposed to be IPNBs corresponding to pancreatic IPMN of the branch duct type [49, 50]. Sato et

al. [51] showed that cystic and micropapillary changes of the epithelial cells of intrahepatic peribiliary glands, which were found in 9 (1%) of 938 autopsy livers, had abundant apical mucin and increased expression of MUC5AC, cyclin D1, and Ki-67. Since these characteristics were similar to those of pancreatic IPMN of the branch duct type, they insisted that cystic and micropapillary lesions of peribiliary glands may have neoplastic features and might represent a precursor of biliary epithelial neoplasms, including IPNB of "the branch duct type." Cardinale et al. [52] suggested that biliary stem/progenitor cells located in the peribiliary glands might be implicated in the carcinogenesis of mucin-producing cholangiocarcinomas. However, these are still speculative.

6. Conclusion

Originally, IPNB was proposed as a new disease entity because of striking similarities to IPMN of the pancreas, of which the disease entity and clinicopathological features are well established. Both neoplasms share intraductal papillary growth pattern, microscopic features such as papillary proliferation with delicate fibrovascular core and 4 types of epithelial subtypes, rarely occurrence of multiple lesions, and possible progression to tubular adenocarcinoma and mucinous carcinoma. However, several important differences exist between IPNB and IPMN of the pancreas. In IPNB, pancreatobiliary type is the most common and gastric type is rare. Most cases of IPNB are IPNBs with high-grade intraepithelial neoplasia or IPNBs with an associated invasive carcinoma, and IPNBs with low- or intermediate grade intraepithelial neoplasia are infrequent. Furthermore, mucin hypersecretion is usually observed in most cases with IPMN of the pancreas, whereas only one-third of IPNB cases involve mucin hypersecretion. These differences raise a question whether all IPNBs can be included in a single disease entity. In fact, our previous study [12] revealed that IPNB without mucin hypersecretion contained heterogeneous disease groups, and the majority of IPNB without mucin hypersecretion had the characteristics close to those of nonpapillary cholangiocarcinoma. Onoe et al. [14] showed that papillary cholangiocarcinoma with >50% invasive component was clinicopathologically similar to nonpapillary cholangiocarcinoma. A lot of inconsistent data with regard to the molecular events during development and progression of IPNB mentioned above may also reflect heterogeneous disease groups in the currently defined IPNB. The concept of IPNB as a biliary counterpart of IPMN of the pancreas is attractive, but the definition of this disease entity is still somewhat confused. Further study with a large number of cases is required to elucidate the essential differences between IPNBs and BilINs.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Surgical Strategy for Hilar Cholangiocarcinoma of the Left-Side Predominance

Current Role of Left Trisectionectomy

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Objectives: To evaluate recent surgical strategy for hilar cholangiocarcinoma (HC) of the left-side predominance.

Background: When employing left hemihepatectomy (LH) for HC, vasculobiliary anatomy of the right liver often makes it difficult to achieve a tumor-free margin of the right posterior sectional bile duct (RPSBD). Because left trisectionectomy (LTS) can produce a longer resection margin for the RPSBD, we have expanded the indications for LTS over the last 5 years.

Methods: Sixty-one consecutive patients underwent left-sided hepatectomy for HC, divided into 2 groups according to the operative periods: period 1 (2001–2007; n = 29) and period 2 (2008–2012; n = 32). Clinicopathological outcomes of the groups were compared. The difference in the length of the resectable RPSBD between LH and LTS was radiologically investigated using multidetector-row computed tomography.

Results: The proportion of LTS increased from 10.3% (3/29) in period 1 to 46.9% (15/32) in period 2. R0 resection rates were also improved in period 2. The most common margin positive site in period 1 was the stump of the proximal bile duct; high rates of positive RPSBD stump were noted after LH. The positive proximal ductal margin ratio decreased significantly in period 2. The difference in the length of resectable RPSBD between LH and LTS was 9.0 ± 1.3 mm. There was no mortality in period 2, even after LTS.

Conclusions: LTS for HC of the left-side predominance improved R0 resection rates without affecting postoperative mortality. LTS should be aggressively performed in patients with appropriate hepatic function, even if tumors are possibly resectable by LH.

Keywords: hilar cholangiocarcinoma, left hemihepatectomy, left hepatic trisectionectomy, R0 resection

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Left-sided hepatectomy extending to segment I with extrahepatic bile duct resection has been recognized as a standard surgical procedure for hilar cholangiocarcinoma (HC) of the left-side predominance.[1–3] However, achieving histologically negative margin (R0) resection remains often difficult, although this may offer the only chance for cure and long-term survival.[4–13] Longitudinally, tumor spreading along the bile duct at the proximal side may be a crucial factor for achieving R0 resection.[3,14–16] Recent advances in diagnostics, particularly multidetector-row computed tomography (MDCT) allows detailed evaluation of tumor extension to the bile duct.[17–20] Bile duct wall thickening with contrast enhancement on MDCT can provide direct information about the tumor involvement. However, the accuracy of the tumor extension along the bile duct, especially at the proximal side, is suboptimal. According to previous reports, the accuracy rate for proximal bile duct involvement is in the range of 77% to 92%.[17–21] Generally, MDCT tends to underestimate the proximal spread of tumors with respect to the pathological findings, probably due to the presence of a minimally invasive cancer and/or superficial invasion along the bile duct without recognizable enhanced wall thickening on MDCT. Ebata et al[22] previously demonstrated that the mean length of proximal superficial and intramural microscopic tumor spread from the macroscopic tumor margin was 14 mm and 4.6 mm, respectively. Furthermore, if biliary drainage catheters have been placed before MDCT imaging, it is not easy to evaluate the extent of bile duct involvement, mainly because of artifacts from the drainage catheters and the disappearance of dilated intrahepatic bile ducts. Therefore, in our institution, the longitudinally tumor extension along the bile duct has been routinely diagnosed by MDCT combined with direct cholangiography using either endoscopic nasobiliary or percutaneous transhepatic biliary drainage tubes for more accurate diagnosis.

We previously reported[23] that the right posterior sectional bile duct (RPSBD) runs cranially around the right portal vein (RPV) to form a confluence with the right anterior sectional bile duct (RASBD) at the cranial side of the RPV (supraportal type) in 84% of cases (Fig. 1A). Therefore, in cases with the supraportal type of RPSBD, the resection line for RPSBD is anatomically restricted at the craniodorsal border of the RPV (Figs. 2A, B), when left hemihepatectomy (LH) is performed for Bismuth-Corlette (B-C) type IIIb tumors[24] or B-C type IV tumors with the left-sided predominance. In contrast, RASBD can be resected at the most peripheral site where it is detached from the corresponding portal vein (PV) and hepatic artery (HA). Therefore, the resectable length of the RPSBD may be shorter than that of the RASBD, when conducting LH (Figs. 2A, B). However, in patients with the infraportal type of the RPSBD (Fig. 1B), a longer resection margin of the RPSBD can be obtained even when employing LH, as we previously reported.[23] Therefore, left trisectionectomy (LTS) may not be needed to achieve a negative proximal ductal margin in most cases with an infraportal type of the RPSBD, unless the RASBD is deeply infiltrated. On the contrary, when LTS is applied in patients with the supraportal type of the RPSBD, the RPSBD can be resected much longer (Fig. 2C, D) when compared with that in LH, thereby resulting in a longer RPSBD resection margin. In this study, differences in the length of the resectable RPSBD between LH and LTS were radiologically investigated using preoperative MDCT in patients with the supraportal type of RPSBD.

For determination of resectability and the optimal surgical procedure for patients with HC of the left-side predominance, it is critical to evaluate the positional relationship between the most peripherally infiltrated RPSBD and RPV, rather than whether the tumor invades into the right secondary biliary confluence or not. We previously performed LTS in patients with HC of the left-side predominance

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when right biliary involvement extended apparently beyond the craniodorsal border of the RPV. However, over the last 5 years, we have expanded the indications for LTS to achieve negative proximal ductal margin and therefore have performed LTS more frequently (Fig 3). However, this expected benefit must be balanced against an increased operative risk in regard to postoperative liver failure.

To evaluate our recent surgical strategy for HC of the left-side predominance, we analyzed R0 resection rates, postoperative morbidity and mortality, and postoperative survival for the last 5 years (2008–March 2012) and compared these results with those of a previous time period (2001–2007).

PATIENTS AND METHODS

Patients

From 1991 to March 2012, a total of 289 patients (185 men, 104 women) with HC underwent surgical resection with curative intent at our institution. In this study, 61 consecutive patients who underwent left-sided hepatectomy from 2001 to March 2012 for HC, excluding intrahepatic cholangiocarcinoma involving the hepatic confluence, were included. These patients were divided into 2 groups according to the operative periods: period 1 (2001–2007; n = 29), period 2 (2008–2012; n = 32). Patient background and preoperative parameters, including age, gender, indocyanine green retention rate at 15 minutes (ICG-R15), obstructive jaundice (presence/absence), and serum total bilirubin at the time of surgery were investigated in both groups.

Preoperative Assessment

For preoperative clinical assessment, laboratory and imaging workups including ultrasonography, MDCT, magnetic resonance cholangiopancreatography, and cholangiography using either endoscopic nasobiliary or percutaneous transhepatic biliary drainage catheters, were performed. Proximal and distal tumor extension to the bile duct was evaluated mainly by multiphase contrast-enhanced MDCT, particularly before biliary drainage in patients with obstructive jaundice. The bile duct was considered to be involved by the tumor when the bile duct had irregularly thickening with contrast

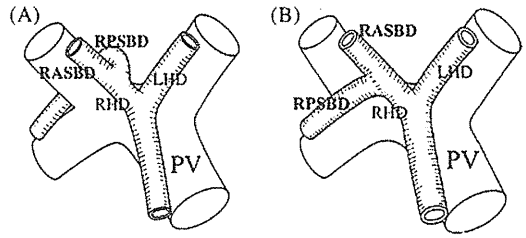

FIGURE 1. Confluence patterns of the RPSBD.[23] (A) Supraportal type: the RPSBD runs cranially around the RPV to form a confluence with the RASBD duct at cranial side of the RPV. (B) Infraportal type: the RPSBD runs caudal to the RPV and joins to the RASBD at caudal side of the RPV.

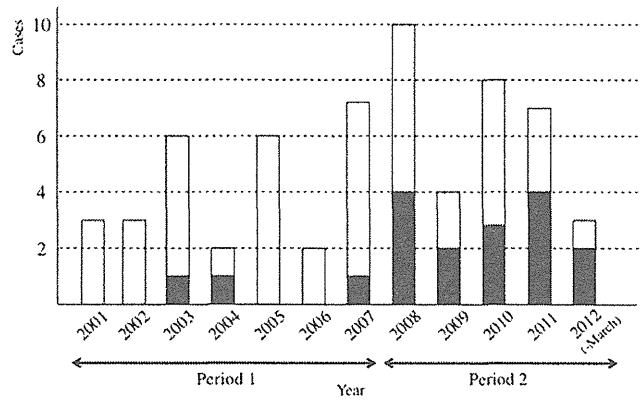

FIGURE 3. Surgical procedures for hilar cholangiocarcinoma of left-side predominance from 2001 to March 2012. Left hemihepatectomy (open bars) and left trisectionectomy (closed bars).

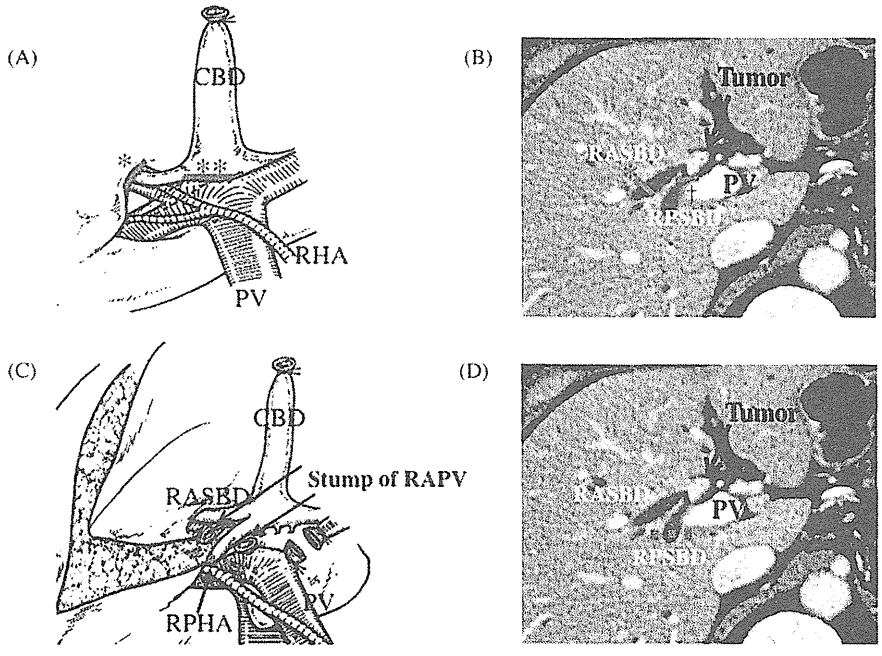

FIGURE 2. Schema (A), (C) and MDCT (B), (D) of proximal bile duct resection line in patients with the supraportal type of the RPSBD when employing left-sided hepatectomy for hilar cholangiocarcinoma. (A), (B) Solid lines indicate the resection lines of the RASBD* and the RPSBD† in left hemihepatectomy, respectively. (C), (D) Dotted line indicates the resection line of RPSBD in left trisectionectomy.

enhancement, obliterated a lumen with upstream dilatation of the intrahepatic ducts, or had an intraductal soft-tissue mass.[25] Furthermore, confluence patterns of the RPSBD in relation to the RPV (Fig. 1) were determined by preoperative contrast-enhanced MDCT, when employing left-sided hepatectomy for HC.

Our criteria of irresectability defined by local tumor-related factors were as follows: (1) tumor extension to bilateral secondary PV branches; (2) tumor extension to bilateral secondary hepatic artery branches; and (3) expected remnant liver volume (RLV) less than 30% of the total liver volume (TLV), even after portal vein embolization (PVE). At our institution, preoperative PVE has been performed since 1994, when RLV was expected to be less than 40% of TLV. In this series, preoperative PVE was performed 15 to 24 days before surgery in 14 of 18 cases in LTS (77.8%), and in one of 43 cases in LH (2.3%).

Indication for Surgical Procedures

In period 1, LH was applied in patients with HC of the left-side predominance when right-sided biliary invasion, especially tumor extension to the RPSBD, was within the craniodorsal border of the RPV according to preoperative MDCT. LTS was indicated when RPSBD invasion apparently extended beyond the craniodorsal border of the RPV (maximal resection line of the RPSBD in LH) or when RASBD invasion extended deeply into the segmental ducts. Meanwhile, in period 2, LTS was performed more aggressively in patients with good hepatic functional reserve (<15% in ICG-R15) when right-sided biliary invasion was suspected to be near the left side of the RPV according to MDCT, even if the tumor was possibly resectable by LH. In principle, LH was applied only to cases in which a negative proximal ductal margin is clearly demonstrated. That is, LH was performed only when tumor extension to the right biliary system was very limited and mostly within bifurcation of the left and right hepatic ducts. In our institution, the most appropriate type of hepatectomy was determined preoperatively according to the extent of the tumor along the bile duct and hepatic functional reserve. We did not change the type of hepatectomy intraoperatively (eg, from LH to LTS), even if the proximal ductal margin was positive according to the intraoperative frozen section examination.

Surgical Procedures

Left-sided hepatectomies included caudate lobectomy, hilar resection, and lymph node dissection in the hepatoduodenal ligament and around the pancreas head. Parenchymal transection was performed using Cavitron ultrasonic surgical aspirator under Pringle maneuver (inflow occlusion time, 15 minutes; reperfusion time, 7 minutes). In the case of LH with the supraportal type of RPSBD, liver resection was performed with preservation of the middle hepatic vein on the transaction plane of the right anterior section. After completion of liver transection, RASBDs were first divided at the ventral side of the RPV, and then the RPSBD was divided along the craniodorsal side of the RPV (maximal resection line of the RPSBD in LH) (Figs. 2A, B). Meanwhile, in the case of LTS, the right hepatic vein was preserved on the transection plane of the right posterior section. After completion of liver transection, the RPSBD was divided more distal to the Louviere fissure (Figs. 2C, D). Bile duct orifices to be reconstructed in the vicinity of the resected liver surface were routinely grouped as much as possible to reduce the number of anastomoses required. Bilioenteric anastomosis was established by Roux-en-Y hepaticojejunostomy with a stent tube (RTBD tube, Sumitomo Bakelite, Tokyo, Japan).

Intraoperative Parameters

Intraoperative parameters were assessed, included operative time, operative blood loss, number of bilioenteric anastomoses, combined pancreatoduodenectomy, and PV resection and/or HA resection and reconstruction. Postoperative complications were also examined. Furthermore, pathological findings in resected specimens were evaluated using the TNM Classification of Malignant Tumors by the *International Union Against Cancer Classification* (7th edition, 2009). R0 resection was defined as histologically negative ductal (proximal and distal ducts) and radial margins. The radial margin was the vertical margin between the tumor edge and dissected periductal structures (eg, liver, blood vessels) and was assessed with permanent section only.

Difference in Length of the Resectable RPSBD Between LH and LTS.

The length of the RPSBD running behind the RPV was assumed to be the difference in the resected RPSBD between LH and LTS (Fig. 4A). This distance was measured using preoperative MDCT in 56 patients with the supraportal type of RPSBD, as shown in Fig. 4B.

Statistics

Results are expressed as the mean ± SD. Statistical analyses were performed using the χ^2 test and the Fisher exact probability test, where appropriate. Statistical analysis of patient survival was performed using the Kaplan-Meier method. Comparison of patient survival between groups was performed using the log-rank test. Multivariate regression analysis of factors related to survival was performed using the Cox proportional hazard model. $P < 0.05$ was considered statistically significant. Statistical calculations were performed using SPSS software (SPSS Inc, Chicago, IL).

RESULTS

Patient Characteristics

Patient characteristics and clinicopathological features in the 2 different operative periods are shown in Table 1. No significant differences were found between the 2 groups in terms of age, gender, ICG-R15, B-C type,[24] obstructive jaundice (presence/absence), or total bilirubin levels at the time of operation.

Operative Procedures and Intraoperative Parameters

In period 1, left-sided hepatectomy for B-C type IIIb tumors or B-C type IV tumors with left-side predominance was performed in 29 patients, including LH in 26 patients (89.7%), and LTS in 3 patients (10.3%). In period 2, left-sided hepatectomy was performed

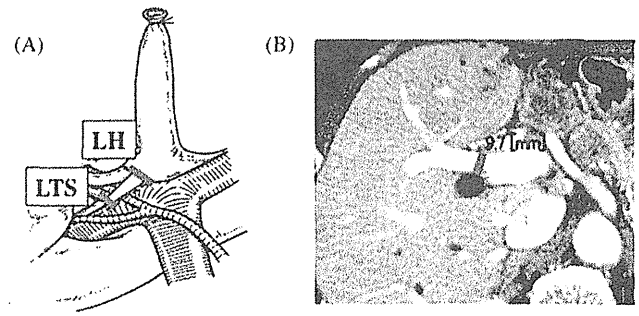

FIGURE 4. (A) Solid lines indicate the resection line of RPSBD in LH or LTS. The length of RPSBD running behind the RPV was assumed to be the difference in the resected RPSBD between LH and LTS. (B) The distance of RPSBD running behind RPV (solid line) was measured using MDCT imaging in 56 patients with the supraportal type of RPSBD.

TABLE 1. Patient Characteristics

	Period 1 (2001–2007, n = 29)	Period 2 (2008–2012, n = 32)
Age, mean ± SD (yrs)	63.8 ± 10.2	66.0 ± 8.6
Gender (M:F)	20:9	24:8
Bismuth-Corlette type (II/IIIb/IV)	4/8/17	1/14/17
ICG-R15 (%)	13.1 ± 7.3	12.4 ± 8.5
Obstructive jaundice (−/+)	8/21	8/24
Total bilirubin at operation (mg/dL)	1.8 ± 1.1	1.2 ± 0.6

TABLE 2. Perioperative Parameters

	Period 1 (2001–2007, n = 29)		Period 2 (2008–2012, n = 32)	
	LH (n = 26)	LTS (n = 3)	LH (n = 17)	LTS (n = 15)
Portal vein embolization (+/−)	0/26	2/1	1/16	12/3
Remnant liver volume at operation (%)	66.6 ± 9.6	39.3 ± 10.1	70.9 ± 7.1	41.9 ± 4.5
Operative time (min)	529 ± 125	439 ± 37	460 ± 68	452 ± 47
Operative blood loss (mL)	3018 ± 6977	1700 ± 71	1269 ± 638	1496 ± 643
Blood transfusion (+/−)	6/20	1/2	3/14	3/12
No. bilioenteric anastomosis	2.3 ± 0.5	1.0	2.3 ± 0.7	1.1 ± 0.3
Pancreatoduodenectomy (+/−)	1/25	0/3	0/17	0/15
Portal vein resection (+/−)	9/17	0/3	4/13	2/13
Hepatic artery resection (+/−)	2/24	0/3	0/17	0/15

TABLE 3. Surgical Curability by the Operative Period

	Period 1 (2001–2007, n = 29)		Period 2 (2008–2012, n = 32)	
	LH (n = 26)	LTS (n = 3)	LH (n = 17)	LTS (n = 15)
Curability	18/29 (62.1%)		26/32 (81.3%)	
R0 resection	16 (61.5%)	2 (66.7%)	13 (76.4%)	13 (86.7%)
Surgical margin positive cases	10	1	4	2
Margin positive sites				
Stump of proximal ducts*	9	1	2	2
Stump of distal ducts	3	1	1	1
Dissected margin at periductal structures	5	1	3	2

*The positive proximal ductal margin ratio decreased significantly in period 2 (4/32,12.5%), as compared with that in period 1 (10/29, 34.5%) ($P < 0.05$).

in 32 patients, including LH in 17 (53.1%) patients and LTS in 15 (46.9%) patients.

According to the CT volumetry, RLV/TLV ratio was 66.6% ± 9.6% in LH and 39.3% ± 10.1% in LTS for period 1 and 70.9% ± 7.1% in LH and 41.9% ± 4.5% in LTS for period 2 (Table 2). For both LH and LTS, no significant differences were seen in terms of operative time, operative blood loss, blood transfusion, combined pancreatoduodenectomy, combined vascular resection, and number of bilioenteric anastomosis when comparing periods 1 and period 2 (Table 2).

Operative Curability and Histopathological Features

In period 1, R0 resection was obtained in 18 (62.1%) of 29 patients who underwent left-sided hepatectomy, including 16 (61.5%) of 26 patients who underwent LH and 2 (66.7%) of 3 patients who underwent LTS. The most common margin positive site in period 1 was the stump of the proximal bile duct, as shown in Table 3. In particular, high rates of positive RPSBD stump were observed in patients undergoing LH (Table 4). On the contrary, in period 2,

TABLE 4. Proximal Ductal Margin-Positive Sites After Left Hemihepatectomy in Period 1

Proximal ductal margin-positive sites	
Both RASBD and RPSBD	3
RPSBD alone	5
RASBD alone	1
Total	9

R0 resection was obtained in 26 (81.3%) of 32 patients who underwent left-sided hepatectomy, including 13 (76.4%) of 17 patients who underwent LH, and 13 (86.7%) of 15 patients who underwent LTS (Table 3). The positive proximal ductal margin ratio (4/32, 12.5%) decreased significantly in period 2 ($P < 0.05$), when compared with that in period 1 (10/29, 34.5%). Furthermore, patients with the negative ductal margins were divided into 2 subgroups, according to the length of the ductal margins based on the final histopathology: wide ductal margin (tumor free-margin ≥ 5 mm) group and narrow ductal

TABLE 5. Length of Tumor Free-Margin for Bile Ducts

	Period 1 (2001–2007, n = 29)		Period 2 (2008–2012, n = 32)	
	LH (n = 26)	LTS (n = 3)	LH (n = 17)	LTS (n = 15)
Proximal side				
Negative ductal margin	17	2	15	13
Wide ductal margin (≥5 mm)*	4	1	10	11
Narrow ductal margin (<5 mm)	13	1	5	2
Distal side				
Negative ductal margin	23	2	16	14
Wide ductal margin (≥5 mm)	20	2	14	14
Narrow ductal margin (<5 mm)	3	0	2	0

*The wide proximal ductal margin ratio was significantly higher in period 2 (21/28, 75.0%), as compared with that in period 1 (5/19, 26.3%) ($P < 0.05$).

TABLE 6. Histopathological Findings

	Period 1 (2001–2007, n = 29)		Period 2 (2008–2012, n = 32)	
	LH (n = 26)	LTS (n = 3)	LH (n = 17)	LTS (n = 15)
Histological differentiation (G1/G2/G3)*	7/12/7	3/0/0	10/4/3	8/5/2
Lymph node metastasis (−/+)	15/11	2/1	11/6	10/5
Lymphatic vessel invasion (−/+)	5/21	2/1	3/14	5/10
Venous invasion (−/+)	7/19	1/2	8/9	5/10
Perineural invasion (−/+)	3/23	1/2	2/15	2/13
T1/ T2/ T3/ T4*	6/12/4/4	0/2/0/1	6/6/3/2	4/7/3/1
Stage I/II/III/IV*	4/11/7/4	0/2/0/1	5/5/5/2	4/6/4/1

*According to The International Union Against Cancer Classification, 7th edition.

TABLE 7. Surgical Morbidity and Mortality

	Period 1 (2001–2007, n = 29)		Period 2 (2008–2012, n = 32)	
	LH (n = 26)	LTS (n = 3)	LH (n = 17)	LTS (n = 15)
Morbidity	13 (50.0%)	2 (66.7%)	8 (47.1%)	8 (53.3%)
Hyperbilirubinemia	2	0	0	1
Bile leak from liver stump	2	0	4	4
Intra-abdominal abscess	4	0	2	1
Bilioenteric anastomosis leakage	5	1	4	1
Wound infection	4	1	3	0
Pleural effusion	5	1	3	2
Sepsis	3	0	2	1
Pneumonia	3	0	1	0
Rupture of pseudoaneurysm	1	0	0	0
Mortality	2 (7.7%)	0 (0)	0 (0)	0 (0)

margin (tumor free-margin < 5 mm) group. The wide proximal ductal margin ratio was significantly higher in period 2 (21/28, 75.0%) than in period 1 (5/19, 26.3%) ($P < 0.05$), but the wide distal ductal margin ratio was almost similar, when comparing period 1 and period 2 (Table 5).

Histopathological findings in resected specimens, including differentiation of tumors, lymphatic vessel invasion, venous invasion, perineural invasion, lymph node involvement, primary tumor classification (T), and stage grouping based on the *International Union Against Cancer Classification* (7th edition), were not significantly different when comparing the 2 different time periods (Table 6).

Surgical Morbidity and Mortality

Surgical morbidity and mortality are shown in Table 7. The morbidity rate was similar when comparing period 1 and period 2. The morbidity rate tended to be higher in patients who underwent LTS than in patients who underwent LH, but this difference did not reach the statistical significance in either time period. However, bilioenteric anastomotic leakage tended to occur more often after LH than after LTS. Two patients died after LH in period 1, including 1 patient with hepatic failure due to rupture of HA pseudoaneurysm, and another with hepatic failure and pneumonia. There was no mortality in period 2, even after LTS.

Postoperative Survival and Recurrence

Overall 3- and 5-year survival rates, including hospital deaths, were 43.5% and 28.3% (median survival, 25.1 months), respectively, in period 1 (Fig. 5). In period 2, overall 3-year survival rates were 70.5% (median survival, 41.7 months), but statistically significant difference was not reached between period 1 and period 2, probably due to the small number of the patients.

Most of patients with ductal margin positive (R1) resection had locoregional recurrence with/without distant metastasis such as liver or peritoneum in both period 1 (10/11, 90.9%) and period 2 (5/6, 83.3%). In contrast, the incidence of locoregional recurrence after R0 resection was less frequent in period 2 (6/26, 23.0%) than in period 1 (6/18, 33.3%), but this difference was not statistically significant.

Difference in Length of the Resected RPSBD Between LH and LTS

The difference in length of the resected RPSBD between LH and LTS was 9.0 ± 1.3 mm according to MDCT evaluation in 56 patients with the supraportal type of RPSBD.

Univariate and Multivariate Analysis of Prognostic Factors

Univariate analysis of survival of patients who underwent left-sided hepatectomy in our institution identified curability ($P = 0.0001$), lymphatic invasion ($P = 0.049$), venous invasion ($P = 0.004$), PV resection alone ($P = 0.020$), and HA resection ($P = 0.0005$) as significant prognostic factors. The following 5 background factors were not found to be significant: age ($P = 0.85$), gender ($P = 0.37$), lymph node metastasis ($P = 0.157$), perineural invasion ($P = 0.13$), and tumor differentiation ($P = 0.75$). Furthermore, multivariate analysis revealed only 2 independent factors influencing survival: curability and HA resection (Table 8)

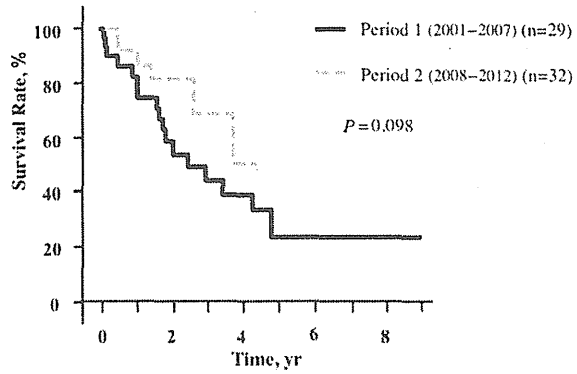

FIGURE 5. Survival after left-sided hepatectomy for hilar cholangiocarcinoma according to the operative period.

DISCUSSION

Advanced HC is a significant therapeutic challenge for biliary surgeons, as negative margin (R0) resection with minimizing postoperative mortality offers the only chance for long-term survival.[3,4–16] To determine the optimal surgical procedure for HC of left-side predominance, the positional relationship between the most peripheral infiltrated RPSBD and RPV is critical, because the RPSBD resection line in LH is anatomically restricted at the craniodorsal border of the RPV (supraportal type). Accordingly, when peripheral biliary invasion is localized within the craniodorsal border according to preoperative MDCT, LH may be generally indicated for HC of left-side predominance. On the contrary, LTS should be selected in patients when biliary invasion obviously extends beyond the craniodorsal border of the RPV and further extends upstream of the intrahepatic bile duct. However, precise diagnosis for tumor spreading along the proximal bile duct remains difficult, even with high-quality contrast-enhanced MDCT.[17–21] The most common reason for inaccuracy is underestimation of the extent of tumor, probably due to the presence of minimum invasive cancer without recognizable enhanced wall thickening on MDCT.

In period 1 of this study, R0 resection rate was 62.1% in patients who underwent left-sided hepatectomy. The most common margin positive site was the stump of the proximal bile ducts. In particular, high rates of positive RPSBD were noted after LH in period 1. Therefore, additional proximal bile duct resection seems well suited to achieve a negative ductal margin. If the initial proximal ductal margin was positive according to the intraoperative frozen section examination, we performed an additional ductal resection as far as was technically feasible. However, the additional resection length of the RPSBD was obviously less than 5 mm in all cases, because we usually performed the maximal or submaximal resection of the RPSBD. Furthermore, after additional resection of the RPSBD, anastomosis of the RPSBD with the jejunum may become technically difficult, because of more dorsal position of the RPV. Furthermore, Shingu et al[26] previously demonstrated that such limited resection of a margin positive proximal bile duct did not improve survival, even if negative margins were obtained, suggesting that cancer cell dispersion occurred during transection of margin positive bile duct. On the basis of these observations, LTS should be performed instead of LH, when the patient has good liver functional reserve to obtain negative ductal margin. According to radiological examination using preoperative MDCT, the RPSBD can be resected 9.0-mm longer in LTS than in LH in patients with the supraportal type of RPSBD. Thus, we have expanded the indication for LTS over the last 5 years. However, this expected benefit must be balanced against an increased operative risk, particularly, postoperative hepatic failure.

Our institution has practiced a policy of aggressive surgical resection of locally advanced HC, but postoperative liver failure remains a serious problem after extended hepatic resections. Previous studies clearly demonstrated that the rate of RLV/TLV significantly

TABLE 8. Multivariate Analysis of Survival in Patients Undergoing Left-Sided Hepatectomy

Factors	Relative Risk	95% confidence Intervals		P
		Lower	Upper	
Curability	2.560	1.317	4.975	0.006
Lymphatic vessel invasion	1.279	0.479	3.409	0.623
Venous invasion	1.833	0.717	4.690	0.206
PV resection alone	1.165	0.593	2.288	0.657
HA resection	3.063	1.289	7.282	0.011

correlated with postoperative mortality due to hepatic failure.[27–29] In the case of LTS, the RLV (right posterior sector) is generally about 30% to 35% of the TLV, and increases further after PVE. In our series, the RLV in the case of LTS was more than 40% of the TLV at the time of operation, which is almost similar to that after right hemihepatectomy (data not shown). With regard to the RLV, LTS is completely different from right trisectionectomy despite the fact that both are called "trisectionectomy," because the RLV in the case of right trisectionectomy is approximately 25% to 30% of TLV even after PVE.[30–32] However, LTS is generally considered to be a more complicated procedure, requiring greater skill.[33–35] Over the last 5 years, we have performed LTS more aggressively in patients with appropriate hepatic functional reserve, even if the tumor was possibly resectable by LH. As a result of this aggressive strategy, the proportion of LTS among left-sided hepatectomies increased from 10.3% (3/29) in period 1 to 46.9% (15/32) in period 2. R0 resection rates also improved in period 2 (62.1% vs 81.3%), mostly because of the decreased positive proximal ductal margin cases. In addition, PV resection and reconstruction is performed as necessary on the basis of both preoperative imaging findings and intraoperative macroscopic findings, even in cases with LTS. PV resection and reconstruction was performed to obtain negative radial margin in 2 of 15 LTS cases (13.3%) in period 2.

Furthermore, postoperative morbidity and mortality in period 2 was not significantly different from that in period 1, and there was no mortality in period 2, even after LTS. Overall survival after surgery in period 2 tended to be better than that in period 1, but this difference was not statistically significant, probably due to the small number of the patients. However, according to the multivariate analysis, R0 resection was the most powerful significant independent prognostic factor after left-sided hepatectomy for HC. Therefore, survival difference may be primarily related to the difference of the R0 resection rates between period 1 and period 2. Furthermore, although most of patients with ductal margin positive (R1) resection had locoregional recurrence with/without distant metastasis in both periods, the incidence of locoregional recurrence among patients who underwent R0 resection in period 2 was less frequent when compared with that in period 1, but the difference was not statistically significant. These results suggest that locoregional recurrence after R0 resection might be partly related to the length of ductal-free margin, but other factors such as the extent of vertical tumor spread, depth of tumor invasion, liver parenchyma invasion, and vascular invasion may be more important for locoregional recurrence in patients undergoing R0 resection.

Recently, DeOliveira et al[36] have proposed a new staging system for HC that aims at standardizing reports on this disease. A new online registry based on this classification has been started and is also available to all centers worldwide. Generally, a staging system for malignancy should provide the extent of severity of the tumor and have relevance in terms of resectability and prognosis. However, this newly proposed system does not satisfy all of these criteria, as Nagino[37] previously pointed out. Therefore, after careful validation of this system using accumulated online data, further revision might be necessary to increase its utility.

CONCLUSIONS

Our recent strategy for HC of left-side predominance improved proximal ductal margin status, without affecting postoperative mortality, probably leading to better survival after surgery. Therefore, LTS should be aggressively performed in patients with good hepatic functional reserve, even if the tumors are possibly resectable by LH.

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Intravenous Administration of High-Dose Paclitaxel Reduces Gut-Associated Lymphoid Tissue Cell Number and Respiratory Immunoglobulin A Concentrations in Mice

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Abstract

Background: Chemotherapy remains a mainstay of treatment for cancer patients. However, anti-cancer drugs frequently cause a wide range of side effects, including leukopenia and gastrointestinal toxicity. These adverse effects can lead to treatment delays or necessitate temporary dose reductions. Although chemotherapy-related changes in gut morphology have been demonstrated, the influences of chemotherapeutic regimens on gut immunity are understood poorly. This study aimed to examine whether the anti-cancer drug paclitaxel (PTX) impairs gut immunity in mice.

Methods: Male ICR mice were randomized into three groups: Control, low-dose PTX (low PTX; 2 mg/kg), or high-dose PTX (high PTX; 4 mg/kg). A single intravenous dose was given. On day seven after the injection, lymphocytes from Peyer patches (PP), intraepithelial (IE) spaces, and the lamina propria (LP) were counted and analyzed by flow cytometry ($CD4^+$, $CD8^+$, $\alpha\beta TCR^+$, $\gamma\delta TCR^+$, $B220^+$). Immunoglobulin A (IgA) concentrations were measured in small intestinal and respiratory tract washings.

Results: Total, $CD4^+$ and $\gamma\delta TCR^+$ lymphocyte numbers in PPs were significantly lower in the high PTX than in the control group. The $CD4^+$ lymphocyte numbers in the IE spaces were significantly lower in both PTX groups than in the control group. Respiratory tract IgA concentrations were lower in the high PTX than in the control group.

Conclusion: The present data suggest high-dose PTX impairs mucosal immunity, possibly rendering patients more vulnerable to infection. Careful dose selection and new therapies may be important for maintaining mucosal immunity during PTX chemotherapy.

Paclitaxel (PTX), isolated from the bark of mature yew trees, is one of the most useful antineoplastic drugs, exhibiting a broad spectrum of anti-tumor activities, which makes it an attractive choice for patients with a variety of advanced cancers. In many clinical situations, the drug has been successful for the treatment of human cancers, including breast, ovarian, lung, and gastrointestinal (GI) tumors. The drug kills tumor cells by inhibiting cell division via its action on microtubule assembly and apoptosis induction [1,2], thereby improving the survival of cancer patients [3,4].

However, PTX frequently causes severe side effects, which may include a low white blood cell count, weakness, infections, and muscle pain, as well as numbness, tingling, and burning sensations of the extremities; i.e., neuropathy. Gastrointestinal toxicities reported in patients treated with PTX include neutropenic enterocolitis, bowel obstructions/perforations, pseudomembranous colitis, mucositis, and ischemic colitis [5–8]. These side effects limit the dose of PTX that can be given safely. Although changes in gut morphology induced by PTX-based chemotherapy have been demonstrated [9–11], the influences of chemotherapeutic regimens on gut immunity are poorly understood. If GI injury induced by PTX impairs gut immunity, PTX may allow bacterial infection and thereby predispose patients to serious infection. Elucidation

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