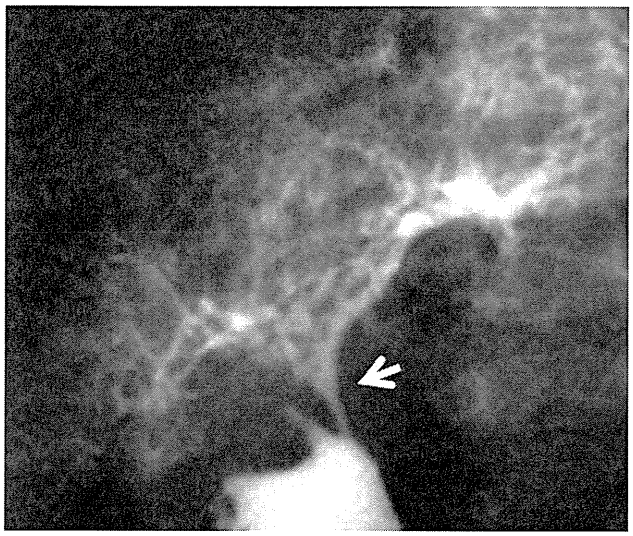

Fig. 3 Cholangiography of subtype α. The cholangiography demonstrated a patent hepatic duct (*arrow*)

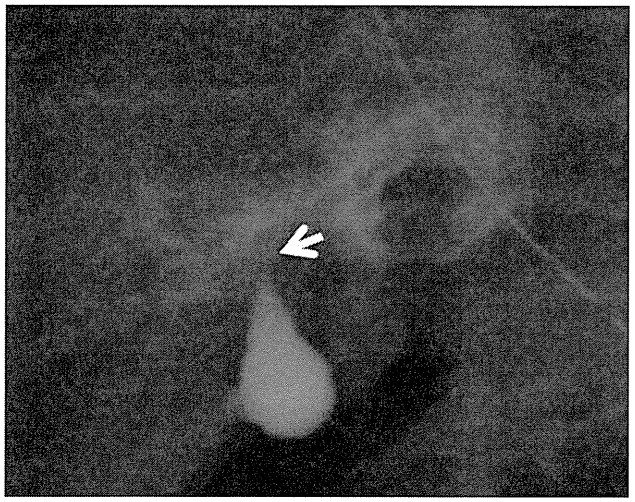

Fig. 4 Cholangiography of subtype β. The hepatic ducts (*arrow*) are shown as small ductules forming a fine network

hepaticojejunostomy, 3 underwent revision Kasai portojejunostomy. Of the 22 patients in subtype β, all underwent Kasai portojejunostomy ($p < 0.001$).

Jaundice clearance

Jaundice clearance was achieved in 16 (89 %) and 19 (86 %) patients in subtypes α and β, respectively. There was no significant difference ($p = 0.81$).

Cholangitis

Five (28 %) and 16 (73 %) patients in subtypes α and β, respectively, developed early cholangitis within 1 year after surgery. The difference in the incidence of cholangitis was statistically significant ($p = 0.0046$).

Table 2 Patient characteristics and outcomes

	α ($n = 18$)	β ($n = 22$)	p
Sex (M/F)	5/13	7/15	0.78
Age at initial surgery			
Mean (SD) (days)	61.2 (24.9)	59.6 (24.3)	0.77
Type of obstruction (I or I cyst)			
I	2	8	0.067
I cyst	16	14	
Procedure			
H-J	14	0	<0.001
HP-J	4	22	
Jaundice clearance	89 %	86 %	0.81
Cholangitis	28 %	73 %	0.0046
Portal hypertension	11 %	23 %	0.34
Treatment of portal hypertension			
EIS	0	1	
PSE	1	2	
EIS + PSE	0	1	
Splenectomy	0	1	
Splenectomy + SR-shunt	1	0	
Current status			
Alive with native liver	13	12	0.18
Alive following LTx	3	2	
Dead	2	8	
Current age of survivors with native liver			
Mean (SD) (years)	23.3 (11.6)	25.5 (12.3)	0.42

H-J hepaticojejunostomy, *HP-J* hepatic portojejunostomy, *EIS* endoscopic injection sclerotherapy, *PSE* partial splenic embolization, *SR-Shunt* splenorenal shunt, *LTx* liver transplantation

Portal hypertension

Two (11 %) and 5 (23 %) patients in subtypes α and β, respectively, developed clinical bleeding or impending rupture of esophageal varices was suspected, which was endoscopically confirmed; they underwent treatment of portal hypertension during the postoperative course ($p = 0.34$). Treatment included partial splenic embolization (PSE) and splenectomy with splenorenal shunt placement in one patient each in subtype α; in subtype β, endoscopic injection sclerotherapy (EIS), EIS followed by PSE, and splenectomy were performed in one patient each and PSE was performed in two patients.

Outcomes and current status

Of the patients in subtype α, two with persistent jaundice, who underwent initial surgery at the age of 66 and 92 days,

Table 3 Patients who died or underwent liver transplantation

Case	Pattern of obstruction	Sex	Age at initial surgery (days)	Procedure	Age at death (m, months/years)	Age at LTx (years)	Current age (years)
1	Icyst-α	M	91	H-J	–	27	42
2	Icyst-α	F	59	H-J*	–	25	39
3	Icyst-α	M	66	H-J	3 m	–	–
4	Icyst-α	F	92	H-J*	5 m	–	–
5	Icyst-α	F	79	HP-J		4	21
6	Icyst-β	F	72	HP-J	7 m	–	–
7	I-β	F	41	HP-J	–	25	36
8	Icyst-β	F	88	HP-J	11 m	–	–
9	Icyst-β	M	73	HP-J	5	–	–
10	Icyst-β	M	82	HP-J	14	–	–
11	I-β	M	47	HP-J	11**	10	–
12	I-β	F	50	HP-J	29	–	–
13	Icyst-β	F	140	HP-J	8 m	–	–
14	Icyst-β	F	49	HP-J	5	–	–
15	I-β	F	55	HP-J	–	6	25

H-J hepaticojejunostomy, *HP-J* hepatic portojejunostomy, *LTx* liver transplantation

* Two patients underwent revision by HP-J following H-J

** A patient died of complications following LTx

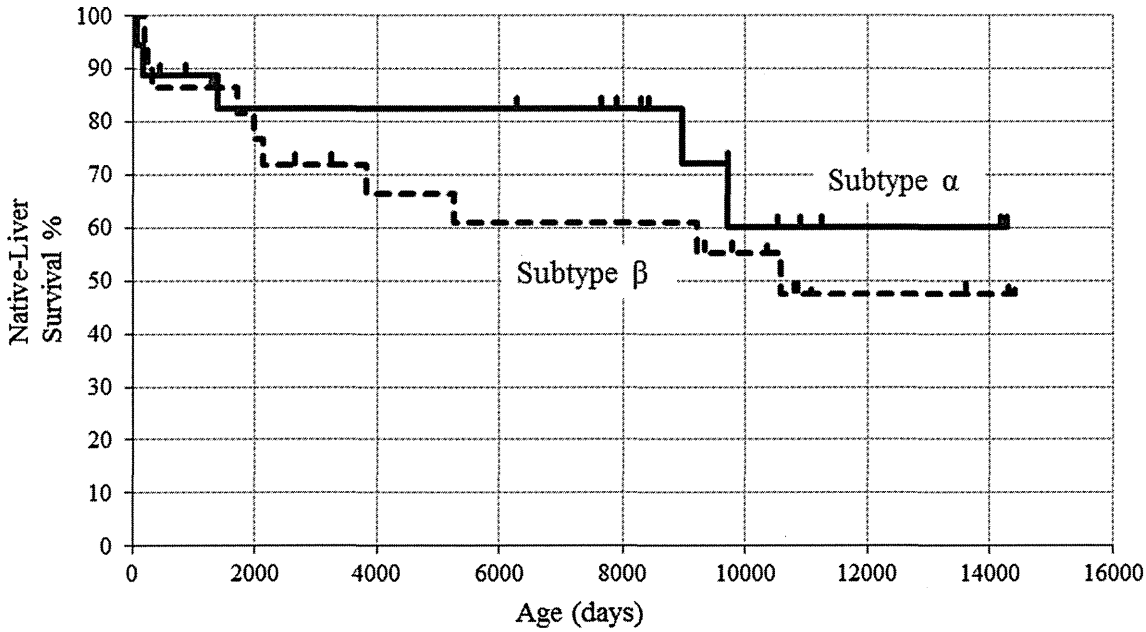

Fig. 5 Kaplan–Meier native liver survival *curves*. There was no significant difference in cumulative native liver survival rates between subtypes α and β ($p = 0.43$, log-rank test)

respectively, died of pulmonary complications 12 days and 2 months after surgery, respectively. Of the patients in subtype β, three with persistent jaundice, whose operative ages were 72, 82, and 140 days, respectively, died of liver failure at the age of 3 months, 14 years, and 3 months, respectively. In total, two patients died and three underwent liver transplantation in subtype α, and seven patients died and three underwent liver transplantation in subtype β.

One patient in subtype β, who underwent liver transplantation at the age of 10 years, died of postoperative complications at 11 years of age. Six patients (two of subtype α and four of subtype β) died or required liver transplantation after surviving 10 years or more (Table 3).

Currently, 13 (72 %) and 12 (55 %) patients are alive with native liver in subtypes α and β, respectively. No significant difference was found in the cumulative survival rate between the two subtypes (Fig. 5, $p = 0.43$). The mean age of native liver survivors in subtype α and β is 23.3 and 25.5 years, respectively ($p = 0.42$).

Discussion

The clinical courses of patients with type I biliary atresia are generally better than those of type III biliary atresia [3]. Among them, some patients have an exceptionally better prognosis than others. Caponcelli et al. [4] reported that cystic biliary atresia was a clinically distinct variant associated with a better prognosis. However, we found no difference between type I atresia and type I cysts with respect to jaundice clearance rates or native liver survival rates in our series (data not shown). Thus, we focused on the proximal subtype as a potential predictor of short- and long-term outcome.

In type III biliary atresia, the size of small bile ducts at the porta hepatis has been studied, and the existence of larger bile ducts has been associated with better outcomes [5, 6]. On the other hand, some researchers failed to identify a relationship between the size of bile ducts at the porta hepatis and clinical outcomes [7, 8].

No study has evaluated the relationship between the morphology at porta hepatis and the clinical outcome in type I cases. In JBAR [2], 2630 cases were registered between 1989 and 2011. Of 214 cases in which patent hepatic ducts were confirmed from intraoperative findings, 81 and 133 were subtypes α and β, respectively. The difference in jaundice clearance rates in subtypes α and β was statistically significant (93 vs. 77 %; $p = 0.002$). In contrast, the current study showed that the difference in the jaundice clearance rate between subtypes α and β was not significant (86 vs. 89 %, $p = 0.81$). Of the 22 patients experienced during the past 30 years in our hospital, 21 (95 %) became jaundice-free (data not shown). The remaining patients underwent hepaticoenterostomy at the age of 92 days and died of pneumonia 2 months after surgery. Overall, our results were comparable to those of JBAR. How can we explain the difference between the clinical outcomes of our study and those of JBAR, particularly in subtype β cases? In JBAR, a total of 150 patients underwent hepaticoenterostomy. Thus, at least 62 patients with subtype β (150 reduced by 88 of subtype α) underwent hepaticoenterostomy. Considering that some patients with subtype α may have undergone Kasai portoenterostomy, more than 62 patients, approximately one-half of patients with subtype β possibly, underwent hepaticoenterostomy [2].

Lilly et al. [9] recommended Kasai portoenterostomy instead of hepaticoenterostomy for patients with the correctable type of biliary atresia. On the other hand, Takahashi et al. [10] reported good results following hepaticoenterostomy for the cystic type of biliary atresia. We have employed many modifications in the surgery for biliary atresia. Since 1972, most of our surgical approaches have been standardized, and Kasai portoenterostomy has been a standard procedure even for type I biliary atresia if stenosis of the bile drainage route is revealed between patent hepatic ducts and intrahepatic biliary tree, including all subtype β cases. We employ hepaticoenterostomy only in patients with subtype α without stenotic segments in the extrahepatic ducts.

We speculated that the lower jaundice clearance rate in patients with subtype β than in patients with subtype α in JBAR may be attributable to the higher incidence of employment of hepaticoenterostomy in subtype β. In terms of short-term results, there may have been no conspicuous difference between subtypes α and β if Kasai portoenterostomy had been universally employed in patients with subtype β.

Masumoto et al. [11] reported a case of cystic biliary atresia and suggested that correctable biliary atresia may change into uncorrectable biliary atresia. Suzuki et al. [12] reported a case of the correctable type of biliary atresia in which the morphology of the extrahepatic bile ducts extensively changed during the early postoperative course. We also experienced a case in which a type I cyst changed into type III-d (atresia at the porta hepatis with an isolated cyst) during the early postoperative course. We believe that hepaticoenterostomy by anastomosis between the cyst wall and jejunum should be avoided in patients with subtype β, because reported cases and our experience indicate that the minute bile ductules at the porta hepatis may become atretic during the early disease process of biliary atresia.

In our current series, jaundice persisted in five patients following initial surgery, including two who died of pulmonary complications during the early postoperative course. This group also included patients with late operative ages and a patient with mild jaundice who survived more than 10 years. This series included a very limited number of patients in whom jaundice persisted because of advanced liver disease. Thus, we believe that early surgical intervention and appropriate surgical management are very important to achieve excellent short-term results in type I/I cyst biliary atresia.

Regarding long-term outcomes, a considerable number of long-term survivors of even type I developed liver failure necessitating liver transplantation despite good short-term outcomes [13]. The incidence of postoperative cholangitis was significantly higher in subtype β than subtype α. Although no significant difference was observed, more patients in subtype β than in subtype α developed portal hypertension, which required treatments such as EIS and PSE, and more patients survived with native livers in subtype α than subtype β. Based on these results, we believe that there is some possibility that the morphology at the porta hepatis may predict long-term results in type I biliary atresia.

We admit several limitations to this study. The number of cases of both subtypes was insufficient and only the morphology of the extrahepatic bile ducts was considered, and no observations of intrahepatic pathology were made. We will further try to identify prognostic indicators by analyzing the morphology of both extra- and intrahepatic biliary systems by combining information from cholangiograms and pathological evaluations of our accumulated clinical experience.

In conclusion, early employment of appropriate surgery and careful postoperative management are expected to achieve satisfactory short-term results in type I/I cyst biliary atresia. Approximately 40 % of our patients developed liver failure during the postoperative course and proximal subtypes were not sufficient to distinguish good from poor long-term results at this stage. Thus, close long-term follow-up is essential even in type I/I cyst, regardless of the hepatic hilum morphology.

Compliance with ethical standards

Conflict of interest There are no conflicts of interest to declare.

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Long-term outcomes of biliary atresia with splenic malformation☆,☆☆

Masaki Nio *, Motoshi Wada, Hideyuki Sasaki, Hiromu Tanaka, Tomohiko Watanabe

Department of Pediatric Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan

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ABSTRACT

Background: We assessed the long-term outcomes of patients with biliary atresia with splenic malformation (BASM).
Methods: We retrospectively assessed outcomes of 255 patients who underwent the Kasai procedure (KP) at our hospital between 1972 and 2014. Clinical outcomes of 11 patients with BASM (group A: nine with polysplenia, two with asplenia) and 244 patients with isolated BA (group B) were compared.
Results: The incidence of early cholangitis and hepatopulmonary syndrome (HPS) was significantly higher in group A than in group B. Of the 11 group A patients, three died of severe cardiac defects during early infancy. Seven became jaundice free following KP, with three patients subsequently requiring liver transplantation (LTx). Four survived with their native livers for 2, 5, 22, and 23 years, respectively. Overall 20-year survival rates were 63.6% and 66.5% and 20-year native liver survival rates were 29.0% and 47.3% in groups A and B, respectively. No significant difference in cumulative survival rates was observed between both groups.
Conclusions: Long-term outcomes in BASM patients without lethal cardiac defects were comparable to patients with isolated BA. Careful follow-up may be required in patients with BASM because of a potentially higher risk of secondary complications such as HPS.

Biliary atresia with splenic malformation (BASM) is recognized to have a poor prognosis. However, long-term outcomes in this clinical subset of patients are yet to be fully elucidated. Therefore, we assessed long-term outcomes of patients with BASM at our hospital.

1. Materials and methods

We retrospectively analyzed 255 patients who underwent the Kasai procedure (KP) at Tohoku University Hospital between 1972 and 2014. They were divided into two groups: group A comprised 11 patients with BASM (nine with polysplenia, two with asplenia) and group B comprised 244 patients with isolated BA. Subsequently, clinical parameters, including age at surgery, postoperative bile drainage, number of episodes of early cholangitis, requirement for treatment of portal hypertension, and native liver/overall survival rates, were determined and compared between both groups (Tables 1 and 2).

Jaundice clearance was defined as the blood level of total bilirubin <2.0 mg/dl. Early cholangitis was defined as the development of cholangitis before 1 year of age.

The study protocol was approved by the Clinical Research Ethics Board of our institution.

Statistical analyses were performed using the chi-square test or Student's t test, where appropriate. The cumulative survival rates were analyzed using the Kaplan–Meier survival curves, and the statistical difference was assessed using the log-rank test. A probability (p) value of <0.05 was considered statistically significant.

2. Results

2.1. Age at surgery

The mean patient age at surgery was 56.6 days [standard deviation (SD), 28.1 days] and 66.3 days (SD, 22.2 days) in groups A and B, respectively. There was no significant difference between both groups ($p = 0.056$).

2.2. Type of obstruction

The types of extrahepatic biliary obstruction were classified according to the Japanese Society of Pediatric Surgeons [1].

All 11 patients in group A had type III biliary obstruction (atresia at the porta hepatis), whereas 41, 14, and 189 patients in group B had type I/I cyst (atresia of the common bile duct), type II (atresia of the hepatic duct), and type III, respectively ($p = 0.075$). The condition of the bile duct can be further divided into the following subtypes: subtype a, patent common bile duct; subtype b, atretic common bile duct; subtype c, absent common bile duct; and subtype d, unclassified. In group A, 1 patient, 2 patients, 7 patients, and 1 patient had subtypes a, b, c, and d, respectively. In group B, 45, 163, 16, and 19 patients had subtypes

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* Corresponding author at: Department of Pediatric Surgery, Tohoku University Graduate School of Medicine, 1-1, Seiryomachi, Aobaku, Sendai, 980-8574, Japan. Tel.: +81 22 717 7237; fax: +81 22 7174 7240.
E-mail address: mnio@ped-surg.med.tohoku.ac.jp (M. Nio).

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Table 1
Patient Characteristics.

		Group A	Group B	p
No. of Patients		11	244	
Female:Male		6:5	159:85	0.069
Age at the Kasai Procedure (days)	(mean, SD)	56.6, 28.1	66.3, 22.2	0.059
Type*	I/I cyst	0	41	
	II	0	14	0.075
	III	11	189	
Subtype*	a	1	45	<0.001
	b	2	163	
	c	7	16	
	d	1	19	

Type*: I/I cyst, atresia of common bile duct; II, atresia of hepatic duct; III, atresia at porta hepatis.
Subtype*: a, patent common bile duct; b, atretic common bile duct; c, absent common bile duct; d, unclassified.

Table 2
Clinical Course.

		Group A	Group B	p
Jaundice Disappearance	Yes	7	178	0.74
	No	4	66	
Early Cholangitis*	Yes	0	122	0.032
	No	11	122	
EIS*/EVL*		0	16	
PSE*		0	16	
ET* and PSE (both)		0	15	
HPS*/PPH*	Yes	2	8	0.013
	No	9	236	

Early Cholangitis*: cholangitis developing before the age of 1 year.
EIS*: endoscopic injection sclerotherapy.
EVL*: endoscopic variceal ligation.
PSE*: partial splenic embolization.
ET*: EIS and/or EVL.
HPS*: hepatopulmonary syndrome.
PPH*: portopulmonary hypertension.

a, b, c, and d, respectively. Subtype c was the most common in group A, and subtype b was the most common in group B. There was a significant difference in subtype distribution between both groups ($p < 0.001$).

2.3. Jaundice clearance

Jaundice clearance was achieved in seven (63%) and 178 (73%) patients in groups A and B, respectively. No significant difference between both groups was observed ($p = 0.74$).

2.4. Early cholangitis

The incidence of early cholangitis was assessed in each group. Although no patient developed early cholangitis in group A, 122 (50%) patients developed early cholangitis in group B. There was a statistically significant difference in the incidence of early cholangitis between both groups ($p = 0.032$).

2.5. Portal hypertension

Esophageal varices, hypersplenism, hepatopulmonary syndrome (HPS), and portopulmonary hypertension (PPH) were evaluated to assess portal hypertension. No patient in group A required endoscopic treatment (ET) such as endoscopic injection sclerotherapy (EIS) or endoscopic variceal ligation (EVL) for esophageal varices or partial splenic embolization (PSE) for hypersplenism. In group B, 16 patients underwent EIS/EVL, 16 underwent PSE, and 15 underwent both ET and PSE. Two patients in group A (18%) developed HPS and eight patients in group B (3.3%, six HPS and two PPH) developed conditions associated with portal hypertension ($p = 0.013$).

2.6. Patient outcomes and current status

In group A, two patients with asplenia and one with polysplenia died of severe cardiac defects in early infancy (patients #1, #2, and #4 in Table 3). Of the remaining eight patients, seven became jaundice free following KP; however, three patients subsequently required liver transplantation (LTx) at ages ranging from 18 months to 12 years. Indications for LTx were liver failure and HPS in one and two patients, respectively. Four patients survived with their native livers for 2, 5, 22, and 23 years, respectively.

In group B, a total of 159 patients (109 with native livers and 50 following LTx) survived and 185 patients died, including seven who underwent LTx. Four patients were associated with cardiac defects which were all successfully treated medically or surgically; thus, no patient died of cardiac defects in group B.

Native liver survival and overall survival rates more than a 20-year period were 29.0% and 63.6% in group A and 47.3% and 66.5% in group B, respectively. No significant difference was found in the cumulative survival rate between both groups (Figs. 1 and 2). On exclusion of the three patients with cardiac defects from group A, 20-year native liver survival and 20-year overall survival rates were found to be 40.0% and 87.5%, respectively (Fig. 3).

Currently, four (36.3%) and 109 (44.7%) patients are alive with their native liver in groups A and B, respectively. On exclusion of the three patients with cardiac defects from group A, the native liver survival rate became 50.0% (4/8), which was almost the same as that of group B.

Table 3
Outcome of Group A Patients.

No.	Current Age	Sex	Age at Kasai (days)	Type*1	Associated Anomaly*2	HPS*3	Outcome	Age at Death/LTx*4 (years)
1	*	F	69	III-b	AS, SI, MAL, CD	–	Dead	0.3
2	*	F	40	III-c	PS, SI, MAL, CD	–	Dead	0.12
3	*	F	128	III-c	PS, SI, MAL	–	Dead	1.62
4	*	M	61	III-d	AS, PDPV, MAL, CD	–	Dead	0.33
5	24.6	M	73	III-a	PS, SI	–	LTx*4	1.54
6	23.4	M	33	III-c	PS, SI, MAL	–	Native Liver	–
7	22.8	M	39	III-c	PS, SI	–	Native Liver	–
8	17.5	F	65	III-b	PS, PDPV, MAL	Yes	LTx*4	12.18
9	6.0	M	30	III-c	PS, MAL	–	Native Liver	–
10	5.3	F	45	III-c	PS, SI, MAL	Yes	LTx*4	3.35
11	2.5	F	39	III-c	PS	–	Native Liver	–

Type*1: III: type III; atresia at porta hepatis.
a: subtype a; patent common bile duct, b: subtype b; atretic common bile duct, c: subtype c; absent common bile duct, d: subtype d; unclassified.
Anomaly*2: AS: asplenia. CD: cardiac defect. SI: situs inversus. PS: polysplenia. MAL: malrotation. PDPV: preduodenal portal vein.
HPS*3: hepatopulmonary syndrome.
LTx*4: liver transplantation.

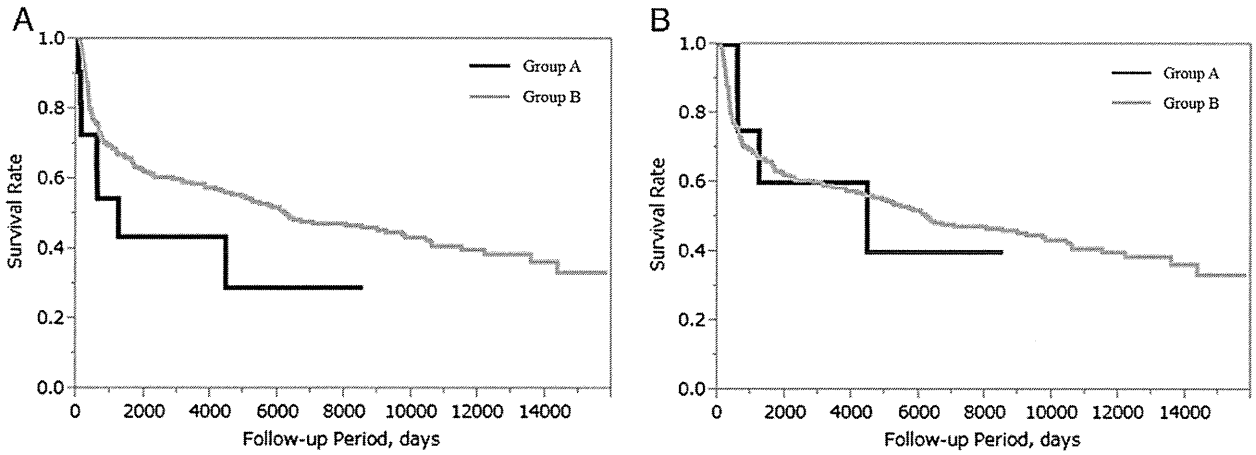

Fig. 1. (A) Comparison of native liver survival: Group A (n = 11) vs. Group B. Although native liver survival rates appeared higher in group B, no statistical difference was observed between groups A and B. (B) Comparison of native liver survival: Group A (n = 8) vs. Group B. On exclusion of the three patients in group A with cardiac defects, native liver survival rates in groups A and B were almost identical.

The ages of survivors with their native liver in group A were 2, 5, 22, and 23 years, respectively.

3. Discussion

According to the Japanese Biliary Atresia Registry (JBAR), 67 patients with splenic anomalies (51 with polysplenia, 12 with an accessory spleen, and four with asplenia) were identified among the total of 2630 patients registered between 1989 and 2011 in Japan [2]; thus, the incidence of BASM in this cohort was 2.5%. In the current study, the incidence of BASM was 4.3%, which was similar to the incidence reported by the JBAR. However, these values were much lower than the incidence, ranging from 7.3% to 14%, reported by studies from Europe and North America [3–7]. The incidence of BASM may intrinsically differ between western countries and Japan. Davenport *et al.* suggested that this discrepancy is attributable to the higher incidence of isolated BA in Southeast Asia and Japan than in western countries and not to the lower incidence of BASM in Asian countries.

The absent common bile duct is a typical finding in BASM patients [8]. In the current study, absent common bile duct, termed subtype c, was the most common subtype in group A patients. On the other hand, fibrotic atresia of common bile duct, termed subtype b, was the most common subtype in group B patients. A significant difference in the distribution of subtypes was observed between the two groups. Although the underlying cause of this discrepancy in subtypes is unknown, it may be attributable to differences in the etiology and/or timing of disease onset between both groups.

In BASM, rates of both jaundice free and overall survival are reported to be lower than those in isolated BA [3,9]. Thus, it has been suggested that BASM defines a subset of BA patients with a poorer prognosis.

The prognosis of patients with BASM appeared to be dependent on the presence of associated cardiac defects in our study. When the three patients with fatal cardiac defects who died during early infancy were excluded from the analysis, the long-term native liver and overall survival rates of the remaining patients were comparable to those of isolated BA patients. BASM patients tended to have better clinical courses with respect to the incidence of early cholangitis and the requirement

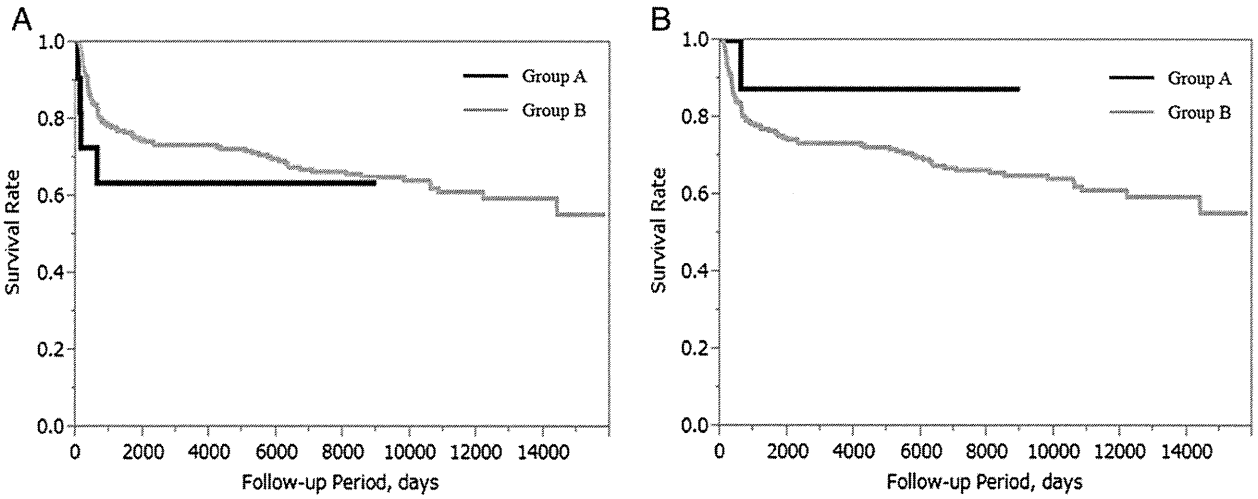

Fig. 2. (A) Comparison of overall survival: Group A (n = 11) vs. Group B. No statistically significant difference in cumulative overall survival was observed between groups A and B. (B) Comparison of overall survival: Group A (n = 8) vs. Group B. On exclusion of the three patients in group A with cardiac defects, the overall survival rate in group A was consistently higher than in group B. No statistical difference was observed between groups A and B.

for treatment of portal hypertension, such as EIS/EVL or PSE, unless they had associated cardiac defects. However, Davenport *et al.* [3] reported no significant difference in native liver survival between BASM patients with and without significant cardiac disease.

A high incidence of HPS was found in this study. The association of HPS and PPH with BASM was previously reported [3,10]; however, the mechanisms underlying this association are currently unknown.

In the current study, the outcomes of BASM were found to be no worse than isolated BA unless these were severe associated cardiac defects, a finding contradicting previous studies. However, considerable biases may have been present in our study; only older cases had associated cardiac defects, the age of all native liver survivors were 23 years or younger, and the number of patients with BASM was small. Further studies are required to elucidate the true influence of splenic malformation on postoperative outcomes of KP.

In conclusion, we found the prognosis of BASM and isolated BA patients following KP to be similar, unless severe associated cardiac defects were present. We believe these findings that indicate long-term management of BASM patients following the Kasai procedure should be similar to that of isolated BA patients. A careful follow-up to monitor the development of secondary pulmonary vascular disorders such as HPS is recommended.

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■ 特集 知っておきたい脾臓の話題

胆道閉鎖症術後遠隔期の諸問題

佐々木 英之* 田中 拡 渡邊 智彦 仁尾 正記

はじめに

胆道閉鎖症（BA）は1950年代に葛西手術が開発され，その後の術式ならびに術後管理の進歩により，その治療成績は向上してきた。それに伴い，長期の自己肝生存例も増加している。胆道閉鎖症全国登録（JBAR）では，全登録数2,792例中1,705例（61.1%）に葛西手術による黄疸消失を認めた。またJBARのKaplan-Meier生存率曲線では，20年自己肝生存率が48.5%である[1]。またJBARにおける自己肝生存例の追跡登録によると，10年目では食道静脈瘤が27.0%，脾機能亢進症が37.9%，20年目では食道静脈瘤が34.6%，脾機能亢進症が36.4%に認められていた[1]。また北米のグループスタディであるChildhood Liver Disease Research and Education Network（ChiLDREN）による検討でも，脾機能亢進症は1～25歳までの計163例中57例（35.0%）に認められると報告されている[2]。当科における20年以上自己肝生存を得ている92症例の検討でも，20例（21.7%）がなんらかの続発症を抱えていた[3]。その続発症のうち，主なものの一つは門脈圧亢進症である。

本稿ではBAの自己肝生存例における門脈圧亢進症，とくに脾腫・脾機能亢進症に焦点をあてて述べる。

Ⅰ．門脈圧亢進症

門脈圧亢進症は肝硬変の進行に伴い発症するため，黄疸消失例では中長期的に注意を要する続発症である。症候としては，消化管の静脈瘤形成と脾機能亢進症，ならびに続発性肺血流異常がある。BAを含めた肝硬変に伴う脾腫の発生機序としては，肝内の抵抗増加に伴い門脈圧が亢進し，脾臓のうっ血により生ずると考えられてきた。組織学的には，静脈血のうっ滞の結果としての脾洞の拡大と増生が観察される一方で，近年のPETを用いた検討では脾臓の局所血流量は増加し，組織学的にも脾柱の増生，脾柱筆毛動脈の拡張，脾索毛細血管の脾洞との吻合など，脾動脈の血流増加を示す所見が認められる。つまり，肝硬変に伴う脾腫はうっ血のみではなく，肝硬変に伴うhyperdynamic circulationによる脾動脈血流増加も関与していることが考えられる[4]。

Ⅱ．脾機能亢進症

1．消化管静脈瘤

門脈圧亢進により脾硬度が上昇することが知られており，脾硬度と門脈圧亢進症の症候との関連の報告がみられる。門脈圧亢進症で脾硬度が上昇する機序としては，脾血流の増加とうっ血による脾内圧上昇と，脾索の過形成や線維化が脾硬度上昇に影響していると推測されている。

種々の肝疾患において，脾硬度と食道静脈瘤の関連性の報告が認められる。BAと脾硬度とについては，論文としては発表されていないが，2014年の第41回日本胆道閉鎖症研究会において「胆道閉鎖症における肝・脾硬度測定による食道静脈瘤の予測診断能」という演題で発表が行われ，脾硬度と食道静脈瘤の関連について発表がなされた。今後さらに検討がなされるものと期待される。

2．続発性肺血流異常

肝硬変に伴う続発性肺血流異常の発症は重要な

Hideyuki Sasaki Hiromu Tanaka Tomohiko Watanabe Masaki Nio
* 東北大学大学院医学系研究科小児外科学分野
〔〒980-8574 仙台市青葉区星陵町1-1〕

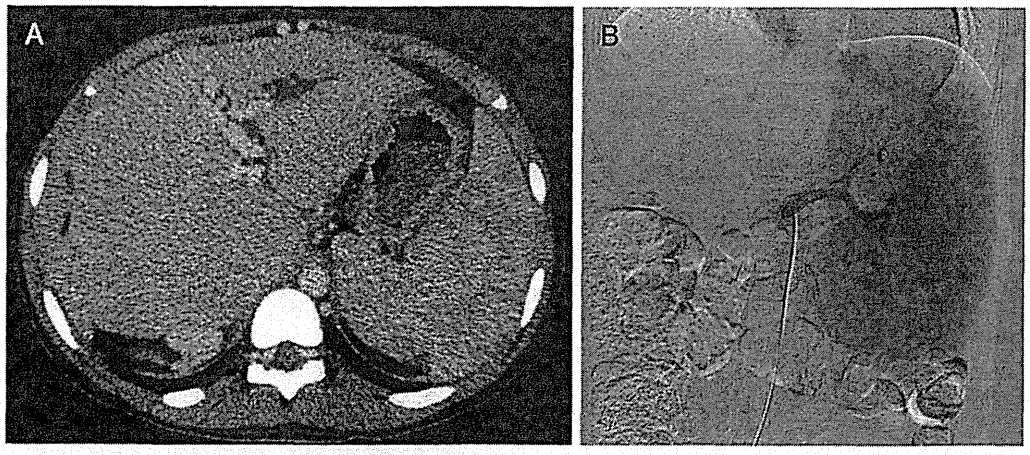

図 1 PSE 前の CT (A), PSE 前の血管造影 (B)

続発症の一つである。その発症には，エンドセリンや一酸化窒素などの因子の関与も示唆されている。門脈肺高血圧症の発症には，門脈圧亢進症に伴う hyperdynamic circulation による高心拍出状態に伴う肺循環における shear stress をきたし，肺血管のリモデリングをきたすという説や，エンドセリンなどの液性因子の関与などが考えられている。エンドセリンは血管収縮因子であり，ET-1，2，3の3つのアイソフォームがある。肝硬変患者では末梢血の ET-1 濃度の上昇が認められる。また肝硬変において，脾臓はエンドセリンの産生に関与しているという報告も認められる[5]。さらに門脈肺高血圧症では，エンドセリン血中濃度が高かったという報告もある[6]。

また ChiLDREN での検討では，肝肺症候群を 163 例中 8 例（4.9%）に認めていたが，8 例中 6 例では脾機能亢進症を伴っていた[2]。当科の検討でも，続発性肺血流異常を認めた 6 例中 3 例に部分的脾動脈塞栓術（partial splenic embolization：PSE)を要する脾機能亢進症を認めていた[7]。その観点での脾機能亢進症の制御も，今後の研究のテーマとなりうると思われる。

Ⅲ. 脾機能亢進症に対する処置

一般的には肝硬変に伴う脾臓への処置を行う目的としては，脾機能亢進症に由来する血小板減少の改善，門脈圧亢進症（胃食道静脈瘤，出血傾向）の改善，生体肝移植における small-for-size syndrome における門脈圧，門脈血流のコントロールがあげられる[8]。

脾機能亢進症においては脾臓での過剰な血流貯留，溶血により貧血が生じ，脾臓での血小板貯留の増加，半減期の減少，脾臓での血小板の破壊亢進により血小板減少が生ずる[8]。

脾機能亢進症に対しては，BA の小児例では脾摘後重症感染症の発症予防目的で PSE が選択される[9]。当科における PSE の適応としては，① 脾腫，② 血小板数が 10 万以下で減少傾向が進行する場合，③ 臨床的出血症状ありの 3 点が揃う場合としている（図 1)。

PSE は塞栓率 70～80% を目標に行い，塞栓物質はゼルフォームを用いている（図 2)。

PSE 後の疼痛，発熱は高頻度に認められるものの，解熱鎮痛剤で対応は可能である。また脾膿瘍合併のリスクも指摘されているが，当科では術後に十分な抗菌薬を投与することで，その発生をみていない。

脾臓への処置を行うと，門脈血流の血行動態に変化がみられる。一般的には，門脈血流は減少するとする報告が多い。しかし当科の経験において，PSE 後に食道静脈瘤の増悪を認めた症例もあり，注意を要する。当科では PSE 前後に上部消化管内視鏡検査を施行し，静脈瘤の変化に注意している。

比較的早い時期に重症な脾機能亢進症がみられても，PSE により，その後の安定した経過が望める[9]。

成人の肝硬変症例に対して PSE を施行し，その

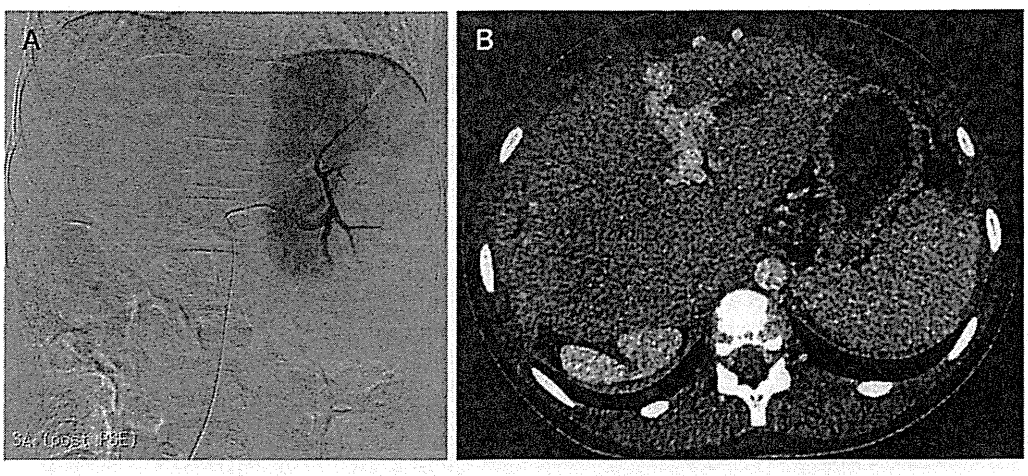

図 2 PSE後の血管造影（A），PSE施行後1年のCT（B）

後のアシアロシンチによる肝予備能評価で改善が認められたとする報告もある[10]。すなわち，肝臓と脾臓との臓器相関（肝脾相関）の観点から，脾腫が肝硬変の増悪に与える影響を考慮すると，脾機能亢進症への適切な介入はより意義が大きいと考えられる。年長児から成人では，脾摘後重症感染症について危険性が低下するため，PSEか脾摘かの選択は，肝病態や治療の見通し，肝移植を要する可能性などで決定される。PSEと脾摘とを比較した場合に，PSEでは脾機能亢進症が再発することが懸念される。当科の検討では，36例中11例（30.6%）でPSE後に再び血小板減少が認められた[9]。しかし，脾機能亢進症の再発の有無はその後の予後に影響を与えていなかった[9]。

背景の肝硬変が高度な場合は肝移植が必要となるが，正確な肝病態ならびに合併症管理が行われれば，消化管出血ならびに脾機能亢進症のみで肝移植となることはまれである。

おわりに

BAにおける脾腫・脾機能亢進症について述べた。前述のとおり，本症における脾機能亢進症は適切に管理を行えば，それのみで肝移植の適応となることはない。さらに，近年の脾臓の免疫や循環に対する機能の解明に伴い，脾機能亢進症の制御により本症の良好な自己肝生存を得る可能性を高めることも期待される。今後のこの方面からの研究の一助となれば幸いである。

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■ 特集 トランジション

トランジションの問題点と学会の取り組み

尾花和子[*1] 八木 實[*2] 田口智章[*3] 仁尾正記[*4]

はじめに

小児期発症疾患を有する患者の成人期にむかっての診療について，個々の患者にふさわしい成人医療への移り変わり，すなわち移行期医療（トランジション：transition）が注目されている。トランジションとは，小児期に特殊な治療を要する疾患にかかった症例に対し，発達的，医療的に適切な診療を継続し，成人期においても個人の状況にふさわしい医療体制を構築することと考えられている。小児期に手術治療を受ける外科疾患においても，診療技術の向上により治療成績は向上したが，疾患や症状が継続したり，機能不全や合併症のため継続的な医療が必要なまま思春期や成人期を迎える症例もある。本稿では，小児外科疾患のトランジションにおける問題と，日本小児外科学会や連携する学会での取り組みについて述べる。

Ⅰ．トランジションとは

海外では，疾患を有する小児は children with special health care needs (CSHCN) と総称され，慢性的に身体的，発達的，感情的，行動的にリスクを有し，一般の小児に比しより多くの医療サービスを必要とするものと定義されているが，1980～2000年代初期にかけてCSHCNに対する医療ニーズに応えるべきという認識が高まり，トランジションという概念が提唱された。トランジションは，小児期から成人期医療へ移行するプロセスであり，適切な時期にトランジションを進めることで，成人としての役割や機能の受け入れが促進されると考えられている。

一方，国内でも小児診療科の対象年齢を越えて診療が行われており，キャリーオーバー（carry over）とよばれてきたが，近年は欧米同様，トランジションという用語が用いられるようになっている。日本でのトランジション体制は，成育医療の充実のなかで整備が始まったが，その方法として，小児を専門とする医療者から成人を専門とする医療者へ担当が変更されるトランスファー（transfer：転科）と，従来の小児診療科の医療者に継続してかかり続ける場合があるが，それぞれに課題を有している。外科疾患のトランジションについては，疾患を有したまま成人期まで治療を要する場合だけでなく，成人ではあるが小児科が主治医として診療している症例が外科疾患を発症した場合も問題となっている[1]。

Ⅱ．トランジションの対象となる疾患，病態

小児期発症の難治性あるいは慢性の心臓，腎臓，神経，内分泌，消化器疾患などがトランジションの対象となる。小児外科疾患としては，先天性や急性疾患の治療後の臓器の形成不全や機能不全，排泄機能障害，栄養障害などのため長期にわたり治療の継続を必要とする疾患，病態が対象となる。具体的な疾患・病態としては，呼吸機能障害をきたす横隔膜ヘルニアや嚢胞性肺疾患，気管狭窄症，排便機能障害をきたす直腸肛門奇形やHirschsprung病，膀胱直腸障害を呈する二分脊椎症，特別な栄養管理を要する短腸症候群や

Kazuko Obana Minoru Yagi Tomoaki Taguchi Masaki Nio
*1 愛育病院小児外科/日本小児外科学会トランジション検討委員会委員長
〔〒105-0023 東京都港区芝浦1-16-10〕
*2 久留米大学医学部小児外科/日本小児外科学会トランジション検討委員会担当理事
*3 九州大学医学部小児外科/日本小児外科学会前理事長
*4 東北大学医学部小児外科/日本小児外科学会理事長

Hirschsprung病類縁疾患などの腸管不全，胆道系疾患として長期フォローを要する胆道閉鎖症，胆道拡張症，再発や二次がんのリスクを抱える悪性固形腫瘍や，良性ではあるが難治性のリンパ管腫などがある。

Ⅲ．小児外科疾患のトランジションの問題点

小児外科のトランジションに関する問題点を表にあげた。一つ目は，急性期治療後の慢性化の問題で，救命率の上昇により症例数が増加している超低出生体重児，先天性心疾患，小児がん患者，先天性外科疾患などがあげられる。これらの症例は複合する疾患や，合併症や後遺症に対する診療も要することが多く，多領域にわたるフォローを必要とする場合もある。各論については，各疾患の項目を参照していただきたい。

2つ目は経済的支援に関する問題で，ある年齢以降では小児期に受けていた乳幼児医療助成や小児慢性特定疾患などの公費負担が受けられなくなったり，既往歴があるため，治癒後であっても生命保険に加入しにくいことに加え，日常生活の制限や通院などが必要な場合，就労困難となり健康保険料が払えないなどのことが起こりうる。

3つ目は，成人になった症例をどの診療科がみていくかという問題で，成人診療科に転科する，小児系診療科で診療を継続する，双方で併診する，などの方法がある。小児期に発症し成人期にも認められる疾患や，成人期には症状や管理の方法が固定している疾患のなかには，適切な成人診療科での受け皿があり，スムーズな移行が可能なものもある。一方，希少疾患は生涯にわたるシームレスな医療の提供が必要となるが，病気について理解しているのは小児外科医のみとなるため，疾患の種類によっては転科できず，小児外科医が継続医療しなければならない場合があることも事実である。また，小児期からかかわっていると，医療側も家族側も強い信頼関係で結びついてしまい，離れがたくなってしまうという側面もある。成人になると成人特有の疾患が発症したりするため，成人診療科の関与は不可欠だが，疾患はみられるが，原疾患も含めた総合的な診療についての患者のニーズに応えきれない現状もある。

表　小児外科のトランジションが抱える諸問題

1．急性期疾患の慢性化(救命率上昇により症例数増加)
  1) 超低出生体重児 → 合併症，治療の後遺症
  2) 複雑心奇形 → 先天性心疾患の後遺症をもった成人
  3) 小児がん → 再発，二次がん，治療の後遺症
  4) 先天性外科疾患 → 継続治療を要する病態，機能障害
2．経済的支援に関する問題
  1) 小児期に受けていた公費負担（乳幼児医療助成，小児慢性特定疾患など）が受けられない
  2) 生命保険に加入し難い
  3) 就労困難のため，健康保険料が払えない
3．成人期に移行したあとの診療体制
  トランジション症例を誰がみるか？

理想的には，総合病院での主治医は内科医（総合診療医）が担当し，問題のある臓器は臓器別の専門診療科に相談するという診療体制を構築し，小児期の情報は小児科医や小児外科医が詳細に提供するという形が望ましい。図は田口ら[2]が提案したメディカルコンプレックス型の病院であるが，成人の診療ができない小児病院であっても，この形態により患者を中心とした多科，多職種での診療体制が可能となることが期待される[3]。

Ⅳ．小児外科学会のトランジションに対する取り組み

トランジションに関する小児領域の取り組みとして，まず日本小児科学会では2012年に移行期医療に関するワーキンググループが設置され，2013年に「小児期発症疾患を有する患者の移行期医療に関する提言」（案）も発表されたが，そのなかに外科治療を受けた患者に対する特別な議論はなかった。そこで，日本小児外科学会では，成人期医療へ移行する疾患について小児外科の視点で調査・検討を行い，日本小児科学会や成人疾患を担当する日本外科学会などの他学会，公的医療システムや民間支援との連携も視野に入れ，トランジションの課題に取り組む足がかりを作るため，2013年にトランジション検討委員会を立ち上げた。委員会では，トランジションの対象となる疾患について，病態，治療戦略，合併症および後遺症，社会支援，移行期，成人期の問題点などが明らかになるようにガイドブックを作成し，小児診

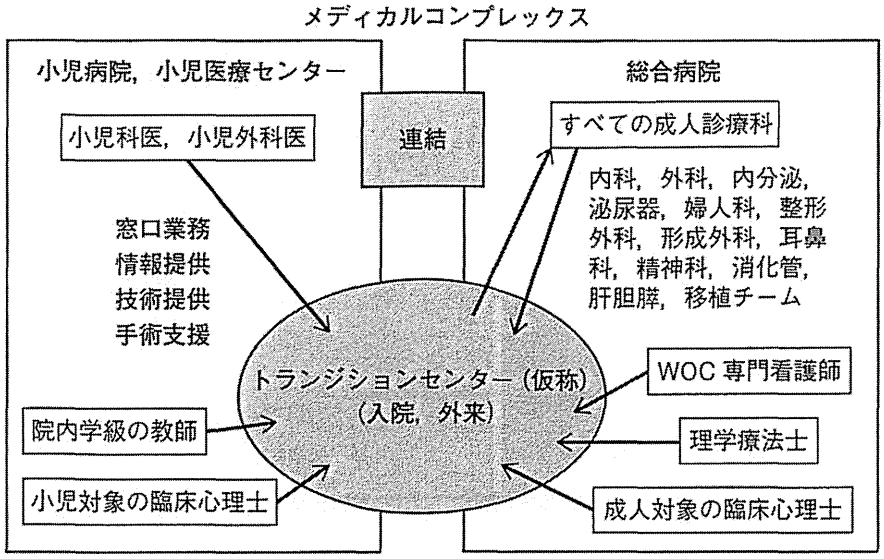

図　メディカルコンプレックス型病院におけるトランジションのイメージ
（田口ら[2]，2013 より引用一部改変）

療科だけでなく成人診療科にも広く認識を深めてもらう活動を開始した。また，日本小児科学会のワーキンググループや，厚生労働科学研究費補助金難治性疾患等政策研究事業にも参画し，情報共有や意見の発信にも努めている。

おわりに

一昨年，日本小児外科学会は設立50周年を迎えたが，この半世紀のあいだに，救命を目指す医療から，長期生存だけでなく生活の QOL の向上も考えていく医療に飛躍的な進歩をとげている。医療に寄り添っていかなければならない疾患もあるが，時期や病態に応じて，患者の利益となるような診療を継続できる環境作りを重視し，トランジションについて正しい理解と支援を行っていけるよう，これからも取り組んでいく。

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The Japanese Society of Gastroenterology

REVIEW

Pancreaticobiliary maljunction and biliary cancer

Terumi Kamisawa · Sawako Kuruma · Taku Tabata · Kazuro Chiba · Susumu Iwasaki · Satomi Koizumi · Masanao Kurata · Goro Honda · Takao Itoi

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Abstract Pancreaticobiliary maljunction (PBM) is a congenital malformation in which the pancreatic and bile ducts join anatomically outside the duodenal wall. Japanese clinical practice guidelines on how to deal with PBM were made in 2012, representing a world first. According to the 2013 revision to the diagnostic criteria for PBM, in addition to direct cholangiography, diagnosis can be made by magnetic resonance cholangiopancreatography (MRCP), 3-dimensional drip infusion cholangiography computed tomography, endoscopic ultrasonography (US), or multiplanar reconstruction images by multidetector row computed tomography. In PBM, the common channel is so long that sphincter action does not affect the pancreaticobiliary junction, and pancreatic juice frequently refluxes into the biliary tract. Persistence of refluxed pancreatic juice injures epithelium of the biliary tract and promotes cancer development, resulting in higher rates of carcinogenesis in the biliary tract. In a nationwide survey, biliary cancer was detected in 21.6 % of adult patients with congenital biliary dilatation (bile duct cancer, 32.1 % vs. gallbladder cancer, 62.3 %) and in 42.4 % of PBM patients without biliary dilatation (bile duct cancer, 7.3 % vs. gallbladder cancer, 88.1 %). Pathophysiological conditions due to pancreatobiliary reflux occur in patients with high confluence of pancreaticobiliary ducts, a common channel ≥6 mm long, and occlusion of communication during contraction of the sphincter. Once the diagnosis of PBM is established, immediate prophylactic surgery is recommended. However, the surgical strategy for PBM without biliary dilatation remains controversial. To detect PBM without biliary dilatation early, MRCP is recommended for patients showing gallbladder wall thickening on screening US under suspicion of PBM.

Keywords Pancreaticobiliary maljunction · Congenital biliary dilatation · Gallbladder cancer · Bile duct cancer

Introduction

Pancreaticobiliary maljunction (PBM) is a congenital malformation in which the pancreatic and bile ducts join anatomically outside the duodenal wall. The sphincter of Oddi is normally located at the distal end of the pancreatic and bile ducts and regulates the outflow of bile and pancreatic juice. In PBM, the common channel is so long that action of the sphincter of Oddi does not directly affect the pancreaticobiliary junction. As a result, reciprocal reflux of pancreatic juices and bile occurs. As the fluid pressure in the pancreatic duct usually exceeds that in the bile duct, reflux of pancreatic juice into the biliary tract frequently occurs in PBM. Persistence of refluxed pancreatic juice injures the epithelium of the biliary tract and promotes cancer development, resulting in higher rates of

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T. Kamisawa (✉) · S. Kuruma · T. Tabata · K. Chiba · S. Iwasaki · S. Koizumi
Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan
e-mail: kamisawa@cick.jp

M. Kurata · G. Honda
Department of Surgery, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

T. Itoi
Department of Gastroenterology and Hepatology, Tokyo Medical University, Tokyo, Japan

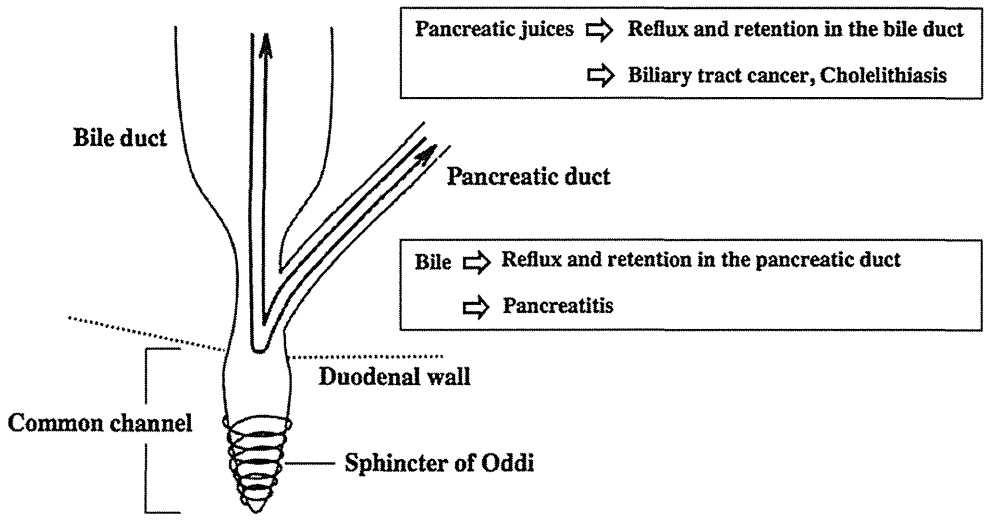

Fig. 1 The pathophysiology of pancreaticobiliary maljunction [3]

carcinogenesis in the biliary tract of PBM (Fig. 1). PBM can be divided into PBM with biliary dilatation (congenital biliary dilatation) and PBM without biliary dilatation [1, 2].

Japanese clinical practice guidelines on how to deal with PBM were created in 2012, as the first in the world [3]. Diagnostic criteria for PBM were revised in 2013, taking recent advances in diagnostic imaging techniques into consideration [4]. Based on the guidelines and new diagnostic criteria, we describe herein recent topics and problems in the management of PBM, with a focus on biliary cancer.

Diagnostic criteria for PBM 2013

Diagnostic criteria of PBM were proposed in 1987 [5], and were slightly revised in 1990 and published in English in 1994 [6]. In 2013, these criteria underwent thorough revision, 23 years to the day since the previous version (Table 1) [4]. Although no significant changes have been made to the definition of PBM, diagnostic modalities have undergone substantial advances in recent years. As no radiological modalities were initially available that could show the status of the pancreaticobiliary junction outside the duodenal wall, PBM was diagnosed when a lack of effect of the sphincter of Oddi on the pancreaticobiliary junction was verified on direct cholangiography such as with endoscopic retrograde cholangiopancreatography (ERCP).

Magnetic resonance cholangiopancreatography (MRCP) has now become popular as a noninvasive method for obtaining high-quality images of the pancreaticobiliary tree, and it is replacing diagnostic ERCP for many pancreatobiliary diseases. Many PBM cases can be diagnosed from MRCP based on findings of an anomalous union between the common bile duct and pancreatic duct in addition to a long common channel [7–10]. MRCP is thus useful for diagnosing children and screening for PBM [7]. However, accurate diagnosis of PBM is difficult in cases with a relatively short common channel (Fig. 2a, b) [11]. In cases with a common channel $\leq$9 mm on MRCP, direct cholangiography is needed to confirm PBM [12]. PBM can be diagnosed if junction outside the wall can be depicted by high-resolution images with multiplanar reconstruction (MPR) provided by multidetector row computed tomography (MD-CT), and endoscopic ultrasonography (EUS) [3, 13, 14].

Amylase levels in bile are markedly elevated (>10,000 IU/l) in most cases of PBM, but are not elevated at all in some cases [15, 16]. Furthermore, elevation of pancreatic enzyme levels in bile and hyperplastic changes to the gallbladder mucosa are sometimes observed in some cases with a relatively long common channel in which the effect of the sphincter reaches the pancreaticobiliary junction (high confluence of pancreaticobiliary ducts) [17–19].

Since the maximum diameter of the common bile duct correlates positively with age, standard values for the maximum diameter of the common bile duct in each age group appear appropriate for accurate evaluation of the presence of bile duct dilatation [20–22].

Biliary cancer associated with PBM

Incidence and characteristics

Biliary cancers are frequently observed in adult patients with PBM [23–25]. According to a nationwide survey in

Table 1 Diagnostic criteria for pancreaticobiliary maljunction 2013[4)]

I. Definition

Pancreaticobiliary maljunction is a congenital malformation in which the pancreatic and bile ducts join anatomically outside the duodenal wall.

II. Pathophysiology

In pancreaticobiliary maljunction, the duodenal papillary sphincter (sphincter of Oddi) fails to exert any influence on the pancreaticobiliary junction due to the abnormally long common channel. Therefore, reciprocal reflux between pancreatic juice and bile occurs, resulting in various pathologic conditions, such as inhibiting the excretion of bile and pancreatic juice, and biliary cancer, in the biliary tract and pancreas.

III. Diagnostic criteria

Pancreaticobiliary maljunction is diagnosed by either imaging test or anatomical examination.

Imaging diagnosis

a) An abnormally long common channel and/or an abnormal union between the pancreatic and bile ducts must be evident on direct cholangiography, such as endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transpehatic cholangiography (PTC), or intraoperative cholangiography; magnetic resonance cholangiopancreatography (MRCP); or three-dimensional drip infusion cholangiography computed tomography (3D-DIC-CT). However, in cases with a relatively short common channel, it is necessary to confirm that the effect of the papillary sphincter does not extend to the junction by direct cholangiography.

b) Pancreaticobiliary maljunction can be diagnosed if the pancreaticobiliary junction outside the wall can be depicted by endoscopic ultrasonography (EUS) or multi-planar reconstruction (MPR) images provided by multi-detector row computed tomography (MD-CT).

Anatomical diagnosis

It should be confirmed by surgery or autopsy that the pancreaticobiliary junction lies outside the duodenal wall, or pancreatic and bile ducts unite abnormally.

IV. Supplementary diagnosis

The following findings strongly suggest the existence of pancreaticobiliary maljunction.

Elevated amylase levels in bile

Pancreatic enzymes, especially amylase, in the bile within the bile duct and gallbladder obtained immediately after laparotomy, endoscopically or percutaneously are generally at extremely high levels. However, levels close to or below the normal serum value are occasionally observed in patients with pancreaticobiliary maljunction.

Clinical features similar to pancreaticobiliary maljunction, including elevation of pancreatic enzymes in bile, are observed in some cases with a relatively long common channel, showing the effect of the sphincter on the pancreaticobiliary junction.

Extrahepatic bile duct dilatation

Pancreaticobiliary maljunction includes one type that is associated with bile duct dilatation (congenital biliary dilatation), and another that is not (pancreaticobiliary dilatation without biliary dilatation). When cystic, fusiform, or cylindrical dilatation is detected in the extrahepatic bile duct, careful investigations are needed to determine whether pancreaticobiliary maljunction is present.

Standard values for the maximum diameter of the common bile duct at each age are useful for diagnosing pancreaticobiliary maljunction with or without biliary dilatation.

Japan ($n = 2561$) [2], biliary cancer was detected in 21.6 % of adult patients with congenital biliary dilatation and in 42.4 % of PBM patients without biliary dilatation. In patients with biliary cancers in association with PBM, the location ratio of cancers in the bile duct and gallbladder were 32.1 % and 62.3 % in congenital biliary dilatation, and 7.3 % and 88.1 % in PBM patients without biliary dilatation, respectively. The mean age at which PBM patients developed biliary cancer was 60.1 years for gallbladder cancer and 52.0 years for bile duct cancer among patients with congenital biliary dilatation, and 58.6 years for gallbladder cancer in PBM patients without biliary dilatation. Such patients develop biliary cancers 15–20 years earlier than patients without PBM [26].

In PBM patients, biliary cancers frequently develop as simultaneous and/or metachronous double cancers. Of 37 patients with simultaneous double or multiple biliary cancers, 19 patients (51 %) suffered from concurrent PBM [3, 27–31].

The ratio of gallstone detection in PBM patients who developed gallbladder cancer was lower than that in the biliary cancer population without PBM [2, 3, 32]. In our series, the ratios were 10 % and 62 %, respectively [1].

Mechanism of biliary carcinogenesis

The mechanisms of carcinogenesis in PBM appear to be related to the persistence of refluxed pancreatic juice into the biliary tract. Refluxed proteolytic pancreatic enzymes and phospholipase A2 are activated in the biliary tract and strongly cytotoxic substances such as lysolecithin are produced. The resulting chronic inflammation provokes repeated cycles of damage and healing in the biliary mucosal epithelia. These alterations in the mucosal epithelia, in conjunction with DNA mutations, finally promote cancer development and progression (Fig. 3) [1, 3, 33, 34]. The sequence of hyperplasia-dysplasia-carcinoma, regarded as the prevailing mechanism underlying the development of biliary tract cancer in PBM, is thought to differ from both the adenoma-carcinoma sequence and de novo carcinogenesis associated with biliary tract cancer in the population without PBM [35–37].

In our series, the gallbladder mucosa was significantly higher in PBM than in controls. The incidence of epithelial hyperplasia of the gallbladder and the Ki-67 labeling index of the gallbladder epithelium were significantly higher in PBM than in controls. K-ras mutations in the noncancerous epithelium of the gallbladder were detected in 36 % of PBM patients [1, 19]. Considering that increased cell proliferation is linked to the development of cancer by means of tumor promotion and an increased rate of random mutations, the gallbladder mucosa of PBM patients can be considered to represent a premalignant region.

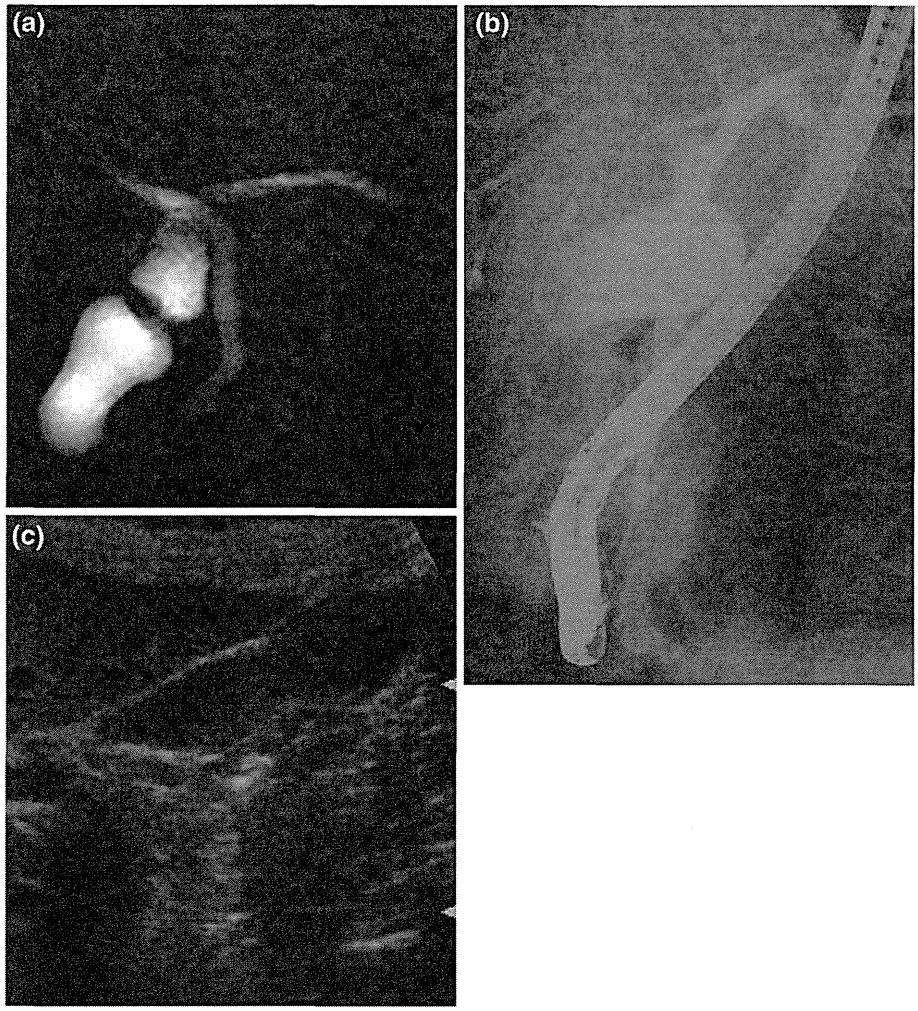

Fig. 2 Pancreaticobiliary maljunction without biliary dilatation was suspected by magnetic resonance cholangiopancreatography (MRCP) (**a**) and confirmed on endoscopic retrograde cholangiopancreatography (ERCP) (**b**). Ultrasonography in this patient showed gallbladder wall thickening (**c**)

Treatment of PBM

Once a diagnosis of PBM has been established, immediate prophylactic surgery is recommended before the onset of malignant changes. Cholecystectomy and resection of the extrahepatic bile duct (flow-diversion surgery) is an established standard for the surgical treatment of congenital biliary dilatation [3, 22]. Internal drainage operations have been abandoned because of the high risk of postoperative carcinogenesis.

On the other hand, treatment of PBM without biliary dilatation and without cancer is controversial. Prophylactic cholecystectomy is performed in many institutes, as most biliary cancers that develop in PBM patients without biliary dilatation are gallbladder cancers [38, 39]. However, some surgeons propose excision of the extrahepatic bile duct together with the gallbladder for PBM patients without biliary dilatation [23], because the frequency of bile duct cancer in PBM patients without biliary dilatation is higher compared to that in the general population [2], and K-ras and/or p53 gene mutations are also reportedly seen in the bile duct of PBM patients without biliary dilatation [23, 40].

Strategy for early diagnosis of PBM

Compared to congenital biliary dilatation, PBM cases without biliary dilatation rarely evoke symptoms, and most patients are not diagnosed until the onset of advanced stage gallbladder cancer [1, 38]. Detecting PBM before the development of biliary cancer is important in order to allow for prophylactic surgery. Epithelial hyperplasia of the gallbladder induced by longstanding continuous stasis of the bile intermingled with refluxed pancreatic juice is a characteristic pathological change in PBM patients [41–43]. To achieve early detection of PBM without biliary dilatation, MRCP is warranted in patients showing thickening of the gallbladder wall on screening US under suspicion of PBM (Fig. 2c) [44].

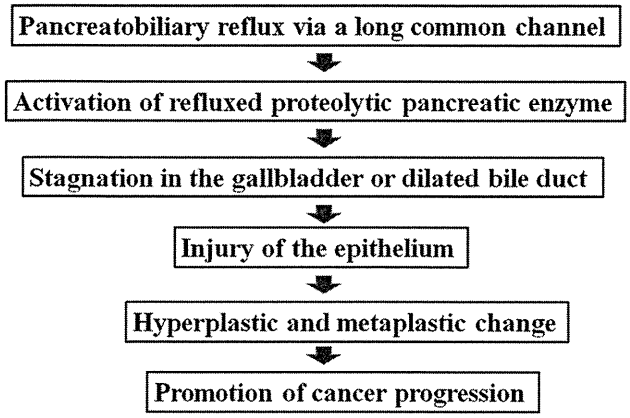

Fig. 3 Mechanism of biliary carcinogenesis in pancreaticobiliary maljunction [1]

High confluence of pancreaticobiliary ducts

The frequency of common channel formation ranges from 55 % to 91 % [17], and the mean length of the common channel has been reported as 4.5 mm [45]. To investigate the clinical significance of a relatively long common channel, we defined high confluence of pancreaticobiliary ducts (HCPBD) as a disease state in which the common channel length is ≥6 mm and communication is occluded when the sphincter of Oddi is contracted (Fig. 4a, b) [17].

In our series of 95 HCPBD patients, reflux of contrast medium into the pancreatic duct was detected in 86 % of patients who underwent postoperative T-tube cholangiography. Elevated amylase levels in bile were observed in all patients, although the mean levels were significantly lower than those in PBM patients. Gallbladder cancer was identified in 11 HCPBD patients (12 %). Similar to PBM patients, hyperplastic changes with increases in both the proliferative activity of epithelial cells and K-ras mutations were also detected in the noncancerous epithelium of the gallbladder in HCPBD patients [1, 18, 19]. A relatively long common channel also appears to represent an important risk factor for the development of gallbladder cancer. However, several differences exist between HCPBD and PBM without biliary dilatation in terms of other features, such as gender predilections, age at diagnosis, incidence of concomitant gallbladder cancer, and biliary amylase levels. HCPBD appears to represent an intermediate clinical condition that is both morphologically and functionally difficult to differentiate clearly from PBM. We consider that HCPBD should currently be managed as a disease entity independent of PBM in terms of the appropriate therapeutic strategies [1, 22].

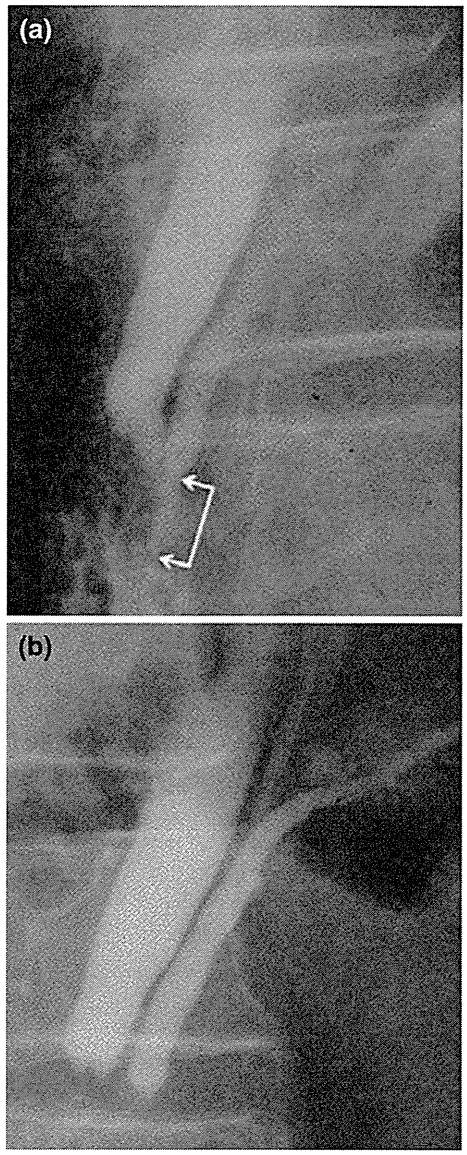

Fig. 4 Images from endoscopic retrograde cholangiopancreatography of high confluence of pancreaticobiliary ducts (HCPBD) [3]. The bile and pancreatic ducts form a common channel (*arrows*) 8 mm long during sphincter relaxation (**a**). Communication between these two ducts is interrupted during contraction of the sphincter of Oddi (**b**)

Conclusions

Biliary cancers occur frequently through proliferative processes provoked by chronic inflammation resulting from the persistence of pancreatic juice refluxed through a long common channel. Once PBM is diagnosed, immediate prophylactic surgery is recommended before malignant changes develop. It is important to diagnose PBM before the onset of biliary carcinogenesis. To achieve early detection of PBM without biliary dilatation, MRCP is recommended for patients showing gallbladder wall thickening on screening US under suspicion of PBM. Further investigations and surveillance studies are also needed to clarify appropriate surgical strategies for PBM without biliary dilatation.

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