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REVIEW ARTICLE

# Recent advances and problems in the management of pancreaticobiliary maljunction: feedback from the guidelines committee

**Terumi Kamisawa · Hisami Ando · Mitsuo Shimada · Yoshinori Hamada · Takao Itoi · Tsukasa Takayashiki · Masaru Miyazaki**



**Abstract** Clinical practice guidelines on how to deal with pancreaticobiliary maljunction (PBM) were made in Japan in 2012, representing a world first. Using a narrow definition, congenital biliary dilatation involves only Todani type I (except type Ib) and type IV-A, both of which are accompanied by PBM in almost all cases. Prospective ultrasonographic study revealed that the maximum diameter of the common bile duct increased with age. Pathophysiological conditions due to pancreatobiliary reflux occur in patients with high confluence of the pancreaticobiliary ducts, a common channel ≥6 mm long and occlusion of communication during contraction of the sphincter of Oddi. Since PBM can be diagnosed by magnetic resonance cholangiopancreatography, multi-planar reconstruction multi-detector row computed tomography and endoscopic ultrasonography, the current diagnostic criteria should be revised to take these diagnostic imaging modalities into consideration. According to a nationwide survey, biliary cancer occurred in 21.6% of adult patients with PBM with biliary dilatation and 42.2% of patients with PBM without biliary dilatation. In biliary cancer associated with PBM without biliary dilatation, 88.1% were gallbladder cancer. Treatment for PBM with biliary dilatation is prophylactic flow-diversion surgery, but further investigations and surveillance studies are needed to clarify the appropriate surgical strategy for PBM without biliary dilatation.

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

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## Introduction

Pancreaticobiliary maljunction (PBM) is a congenital anomaly in which the pancreatic and bile ducts meet anatomically outside the duodenal wall. Normally, the sphincter of Oddi is 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 sphincter action does not directly affect the pancreaticobiliary junction, allowing reciprocal reflux of pancreatic juices and bile. The reflux of pancreatic juices into the biliary tract (pancreatobiliary reflux) provokes higher rates of biliary tract cancer. PBM can be divided into PBM with biliary dilatation (congenital biliary dilatation) and PBM without biliary dilatation [1–3].

The Japanese Study Group on Pancreaticobiliary Maljunction (JSGPM) formed a PBM clinical practice guidelines committee, which established clinical practice guidelines on how to deal with PBM, with the support of the Japan Biliary Association in 2012, representing a world first [4, 5].

Since the body of evidence-based literature remained relatively small, the guidelines were created based on the consensus of experts, using the medical literature for reference. These guidelines consisted of 46 clinical questions covering distinct aspects of PBM (concepts and pathophysiology, diagnosis, pancreatobiliary complications, and treatments and prognosis). Created to provide assistance in the clinical practice of PBM, the guideline contents focused on clinical utility, and included general information on PBM to improve recognition of this disease. The present paper describes recent topics and problems in the management of PBM that became apparent during the process of creating the guidelines.

## Definition of congenital biliary dilatation

Congenital biliary dilatation is an uncommon anomaly of the biliary system characterized by localized cystic or fusiform dilatation of the common bile duct with or without intrahepatic biliary dilatation and is associated with pancreaticobiliary maljunction [1]. Congenital biliary dilatation used to be known as "congenital choledochal cyst", "congenital bile duct dilatation" or "congenital cystic dilatation of the common bile duct" in Western countries.

In 1959, Alonso-Lej et al. [6] classified extrahepatic bile duct cysts into three types: type I, congenital cystic dilatation of the common bile duct where the intrahepatic tree is usually normal; type II, congenital diverticulum of the common bile duct; and type III, choledochocele, a cystic dilatation of the distal segment of the common bile duct protruding into the duodenal lumen. However, bile duct dilatation was found to not be limited to the common bile duct, but instead also present in the intrahepatic bile duct, classification of the disease became more complex.

Todani et al. [7] refined the classification of bile duct cysts into five types and included the concept of PBM. Type IV-A is a congenital biliary dilatation complicated by intrahepatic duct dilatation. Type V involves single or multiple intrahepatic duct dilatations. Pancreaticobiliary maljunction is not included with types II, III or V. Therefore, in a narrow definition, congenital biliary dilatation involves only type I (except type Ib) and type IV-A.

## Maximum diameter of the common bile duct in adults and children

Until now, a bile duct <10 mm has been idiomatically called a "non-dilated bile duct" in adults, but no data have been accumulated. The maximum inner diameter of the common bile duct was recently prospectively examined in consecutive adults over 16 years old using transabdominal ultrasonography (US) [8]. That investigation revealed a mean diameter for the common bile duct of 4.5 ± 1.4 mm (range, 1–14 mm). The relationship between maximum diameter of the common bile duct and age was as follows: adult common bile duct = 2.83 + 0.03 × age. In all age groups but the 20 s and 30 s, there was statistically significant maximum diameter of the common bile duct among each age group. Mean, mode value and median diameter of the common bile duct increased with age as follows: 20 s: 3.9 ± 1.0 mm; 30 s: 3.9 ± 1.2 mm; 40 s: 4.3 ± 1.2 mm; 50 s: 4.6 ± 1.3 mm; 60 s: 4.9 ± 1.4 mm; >70 s: 5.3 ± 1.6 mm (Fig. 1).

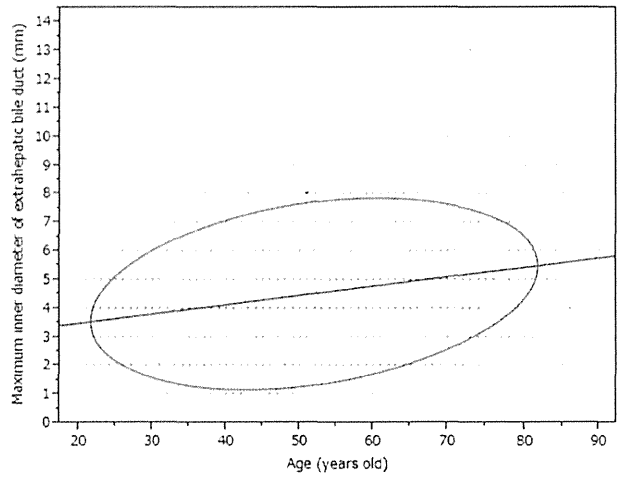


**Fig. 1** Bivariate analysis between age and bile duct diameter in adults [8]. Green: bivariate normal ellipse; red: applying straight line

In the field of pediatric surgery, a common bile duct <6 mm in diameter has commonly been called a non-dilated bile duct [9], but this has been based not on US, but rather endoscopic retrograde cholangiopancreatography (ERCP) data. Maximum diameter of the common bile duct was also examined in children using US [10]. Maximum diameter of the common bile duct correlated significantly with age in months by polynomial expression degree 2 as follows: pediatric common bile duct = 1.64 + 0.014 Month − (3.26 e–5) (Month − 63.0)$^2$. Mean diameters of the common bile duct were 2.4 mm at 5 years, 3.2 mm at 10 years, and 3.7 mm at 15 years. Upper limits of normal for the common bile duct were further calculated as 3.9 mm, 4.5 mm, and 5.0 mm, respectively (Fig. 2). Mean diameter of the common bile duct also increased significantly with height and body weight. Diameter of the common bile duct thus increases in relation to body growth and is not expressed by one value in the pediatric population.

These standard values for maximum diameter of the common bile duct in each age will be useful for diagnosing PBM with or without biliary dilatation.

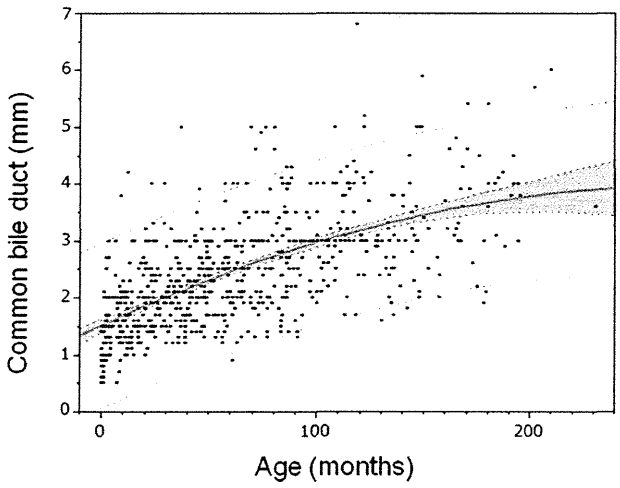


**Fig. 2** Bivariate analysis between age and bile duct diameter in children [10]

### High confluence of pancreaticobiliary ducts

Some patients with a relatively long common channel are not classified as showing PBM because the sphincter of Oddi includes the pancreaticobiliary ductal junction. As the average length of the common channel was reported as 4.4 mm [11], high confluence of pancreaticobiliary ducts (HCPBD) was defined as a disease state in which the common channel length was ≥6 mm and communication was occluded when the sphincter was contracted (Fig. 3) [12].

Reflux of contrast medium into the pancreatic duct was detected in 86% of HCPBD patients who underwent postoperative T-tube cholangiography. Elevated amylase levels in the bile were observed in all cases, although the average levels were significantly lower than those in PBM patients. Gallbladder cancer was associated with 8% of HCPBD patients. Similar to PBM patients, hyperplastic change with increased epithelial cell proliferative activity and K-ras mutations was also detected in the non-cancerous epithelium of the gallbladder of HCPBD patients [3, 13, 14]. A relatively long common channel also appears to be an important risk factor for the development of gallbladder cancer. However, since differences exist between HCPBD and PBM without biliary dilatation in other features, such as the sex most affected, age at diagnosis, bile amylase levels, and incidence of accompanying gallbladder cancer, so HCPBD should at this stage be managed as a disease entity independent of PBM in terms of the appropriate therapeutic strategies.

### Revision of diagnostic criteria of PBM

Diagnostic criteria of PBM were proposed by JSGPM in 1987, and were slightly revised in 1990 [1]. Although no significant changes have been made to the definition of PBM, diagnostic modalities have advanced recently. 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 ERCP, percutaneous transhepatic cholangiography, or operative cholangiography. However, ERCP can cause adverse effects such as pancreatitis.

Magnetic resonance cholangiopancreatography (MRCP) has become popular as a non-invasive method for obtaining high-quality images of the pancreaticobiliary tree, and is replacing diagnostic ERCP for many pancreatobiliary diseases. Many PBM cases can be diagnosed on MRCP based on findings of an anomalous union between the common bile duct and pancreatic duct in addition to a long common channel. MRCP is thus useful for diagnosing children and screening for PBM. However, accurate diagnosis of PBM is difficult in cases with a relatively short common channel [4, 5].

Pancreaticobiliary maljunction can be diagnosed if the junction outside the wall can be depicted by high-resolution multi-planar reconstruction multi-detector row computed tomography. Three-dimensional drip infusion cholangiography computed tomography images can define biliopancreatic reflux in PBM, and the morphology of the intra- and extra-hepatic ducts [4, 5].

Because of its high resolution, endoscopic US (EUS) can be used to diagnose PBM by depicting the pancreaticobiliary junction outside the duodenal wall. In addition to the pancreatic and bile ducts, the muscularis propria of the duodenum and pancreatic parenchyma can be examined by EUS, confirming that the pancreaticobiliary junction lies outside the duodenal wall irrespective of the length of the common channel. Furthermore, the bile duct and gallbladder can be studied in detail in a series of scans following the diagnosis of PBM [4, 5].

The current diagnostic criteria should thus be revised to take these diagnostic imaging techniques into consideration.

### Biliary cancer associated with PBM

Clinical features particularly focusing on the associated biliary cancers were clarified, using data from 2,561 PBM patients with and without biliary dilatation collected by the JSGPM and the Committee for Registration, at 141 medical institutions during the 18 years from 1 January 1990 to 31 December 2007 [15, 16].

Biliary cancer occurred in 21.6% of adult patients with PBM with biliary dilatation and 42.2% of adult patients with PBM without biliary dilatation. In patients with biliary cancers in association with PBM, the location ratio of the

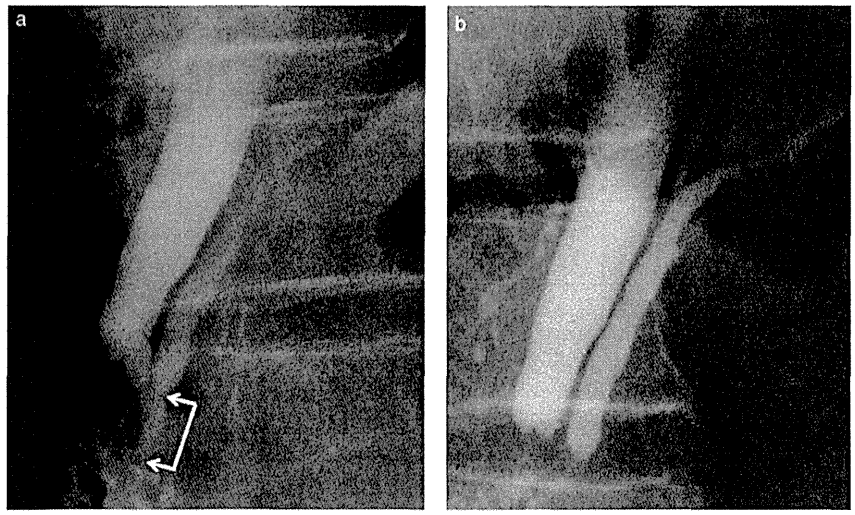


**Fig. 3** (a) Endoscopic retrograde cholangiopancreatography of a patient with high confluence of pancreaticobiliary ducts and a common channel 8 mm in length (arrows). (b) Communication between the pancreatic and bile ducts was interrupted with sphincter contraction [4, 5]

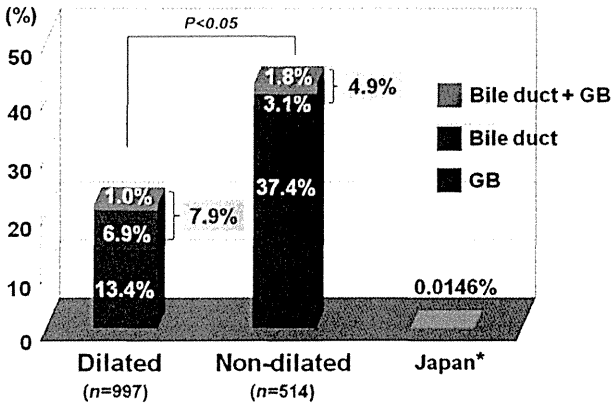


**Fig. 4** Location of biliary tract cancer in adult pancreaticobiliary maljunction (PBM) patients according to biliary dilatation [16]. *Cancer incidence: Cancer Control and Information Services, National Cancer Center, Japan

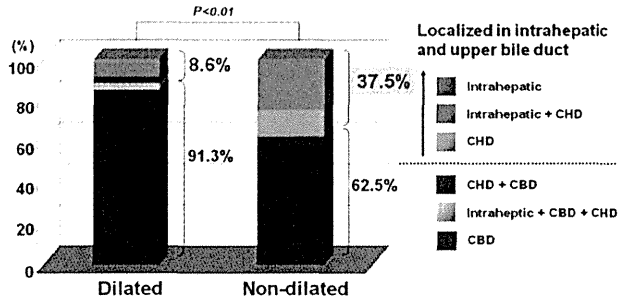


**Fig. 5** Location of bile duct cancer according to biliary dilatation [16]

bile duct cancer and gallbladder cancer were 32.1% and 62.3% in PBM patients with biliary dilatation, and were 7.3% and 88.1% in PBM patients without biliary dilatation, respectively. Regarding the occurrence rate of each biliary cancer, bile duct cancer was seen in 6.9% and gallbladder cancer was seen in 13.4% in patients with PBM with biliary dilatation, and in 3.1% and 37.4% in patients with PBM without biliary dilatation, respectively (Fig. 4). Hence, the location of biliary cancers differs between adult patients with and without biliary dilatation, but gallbladder cancer is significantly predominant. Interestingly, cancer incidence rates in Japan reported by The Japan Cancer Surveillance Research Group [17] showed biliary tract (gallbladder and bile duct) neoplasm occurring at a rate of 14.1 per 100,000 population. The overall incidence of biliary cancers with PBM is more than 200 times higher compared to the risk in the general population, even in bile duct cancer associated with patients without biliary dilatation.

In addition, focusing on the location of the bile duct cancer, total occurrence rates of intrahepatic and hepatic duct cancer were 8.6% in bile duct cancer patients with PBM with biliary dilatation and 37.5% in bile duct cancer patients with PBM without biliary dilatation (Fig. 5). Significant differences in the location of bile duct cancer were found between adult PBM patients with and without biliary dilatation.

Regarding the associated age of cancer onset, in patients with PBM with biliary dilatation, mean age of patients with biliary cancer was approximately 10 years older than that of patients without biliary cancer (benign, 41.3 ± 17.2 years; gallbladder cancer, 60.1 ± 10.4 years; bile duct cancer, 52.0 ± 15.0 years). Likewise, in patients with PBM without biliary dilatation, mean age of patients with biliary cancer was also approximately 10 years older than that of patients without biliary cancer (benign, 47.7 ± 16.1 year; gallbladder cancer, 58.6 ± 9.6 years; bile duct cancer, 63.3 ± 10.6 years). However, these patients may develop biliary cancers 15–20 years earlier than patients without PBM [17].

Regarding the coexistence of biliary stones, the incidence of concomitant stones in adult patients with associated biliary cancers was 13.0% in patients with PBM with

biliary dilatation and 10.6% in patients with PBM without biliary dilatation; lower than the ratio in the biliary cancer population without PBM [18].

Regarding amylase levels, in the gallbladder, amylase levels of cancer patients with PBM with biliary dilatation were significantly lower than those of benign patients with PBM with biliary dilatation, although amylase levels of cancer patients with PBM without biliary dilatation were similar to those of benign patients with PBM without biliary dilatation. In cancer patients, no significant differences in amylase levels were apparent regardless of biliary dilatation. In the bile duct, no significant differences were observed between any groups.

The former period was defined between 1990 and 1999, and the latter period was between 2000 and 2007. In the former period, the frequency of biliary cancer was 19.2% in patients with PBM with biliary dilatation, and 41.3% in patients with PBM without biliary dilatation. In the latter period, the frequency of biliary cancers was significantly increased to 25.0% in patients with biliary dilatation. In patients with PBM without biliary dilatation, the frequency of biliary cancers was also increased from 41.3% to 44.8% in the latter period. In patients with PBM with biliary dilatation, the ratio of biliary cancer localization differed significantly between the former and latter periods. In particular, the frequency of bile duct cancer was increased in the latter period (9.3%) compared with the former period (5.5%). In patients with PBM without biliary dilatation, the ratio of biliary cancer localization also differed between the former and latter periods. Frequencies of bile duct cancer (from 2.7% to 3.6%) and gallbladder combined bile duct cancer (from 1.1% to 3.0%) tended to increase in the latter period.

## Surgical strategy of PBM without biliary dilatation

Once the diagnosis of PBM is established, immediate prophylactic surgical treatment is recommended before the onset of malignant changes. Cholecystectomy and resection of the extrahepatic bile duct, as so-called "flow-diversion surgery", is an established method of standard surgical treatment for PBM with biliary dilatation. However, whether prophylactic resection of the extrahepatic bile duct should be performed for PBM patients without biliary dilatation remains controversial.

Considering that 88.1% of biliary cancers associated with PBM without biliary dilatation were gallbladder cancer [15, 16], and histopathological features such as hyperplasia, metaplasia, and dysplasia with occasional K-ras and/or p53 gene mutations are detected in noncancerous lesions of the gallbladder epithelium [19, 20], prophylactic cholecystectomy is strongly recommended to prevent gallbladder cancer in PBM patients without biliary dilatation. Many institutions have been performing prophylactic cholecystectomy alone, and no bile duct cancer has been reported to develop in such patients, even after a long-term postoperative follow-up [21, 22].

However, some surgeons have recommended that both the extrahepatic bile duct and gallbladder should be excised in PBM patients without biliary dilatation, because of the risk of developing bile duct cancer. An analysis of 1361 PBM patients described bile duct cancer as a complication with an incidence of 4.0% in PBM patients without biliary dilatation, similar to the 5.2% incidence in PBM patients with biliary dilatation [23]. In addition, the incidence of bile duct cancer in PBM patients, even those without biliary dilatation, is extremely high when compared with the incidence of biliary tract cancer in the general population. Indeed, the histopathological changes of carcinogenesis observed in PBM patients with biliary dilatation, such as *K-ras* and/or *p53* gene mutations, are also reportedly seen in PBM patients without biliary dilatation [24]. Moreover, the development of bile duct cancer in PBM patients without biliary dilatation who have undergone cholecystectomy alone without bile duct resection has been reported [25].

The Japanese clinical practice guidelines for PBM, as an answer to the clinical question of operative procedures for PBM without biliary dilatation, state that "There is no fixed strategy on the prophylactic resection of the extrahepatic bile duct for prevention of bile duct cancer" [4, 5]. In the clinical practice guidelines for the management of biliary tract and ampullary carcinomas, both of these opinions are mentioned, but no recommendations are given [18].

## Conclusions

Several advances in diagnostic imaging and understanding of the pathophysiology of PBM have been made, and the current diagnostic criteria should be revised accordingly. Further investigations and surveillance studies are needed to clarify appropriate surgical strategies for PBM without biliary dilatation.

**Conflict of interest** None declared.

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TOPICS

# Diagnostic criteria for pancreaticobiliary maljunction 2013

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**Abstract** Pancreaticobiliary maljunction is a congenital malformation in which the pancreatic and bile ducts join anatomically outside the duodenal wall. The diagnostic criteria for pancreaticobiliary maljunction were proposed in 1987. The committee of The Japanese Study Group on Pancreaticobiliary Maljunction (JSGPM) for diagnostic criteria for pancreaticobiliary maljunction began to revise the diagnostic criteria from 2011 taking recently advanced diagnostic imaging techniques into consideration, and the final revised version was approved in the 36th Annual Meeting of JSPBM. For diagnosis of pancreaticobiliary maljunction, 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, percutaneous transpehatic cholangiography, or intraoperative cholangiography; magnetic resonance cholangiopancreatography; or three-dimensional drip infusion cholangiography computed tomography. 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. Pancreaticobiliary maljunction can be diagnosed also by endoscopic ultrasonography or multiplanar reconstruction images provided by multi-detector row computed tomography. Elevated amylase levels in bile and extrahepatic bile duct dilatation strongly suggest the existence of pancreaticobiliary maljunction.

**Keywords** Common channel · Congenital biliary dilatation · Pancreaticobiliary maljunction

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The Japanese Study Group on Pancreaticobiliary Maljunction

This article is a secondary publication based on a study that has been already accepted and will be first reported in Japanese in the JBA (Journal of Japan Biliary Association).

## Introduction

Pancreaticobiliary maljunction was first reported in 1916 [1]. Babbitt demonstrated cholangiopancreatography of pancreaticobiliary maljunction in patients with congenital biliary dilatation and considered the two abnormalities involved from etiological aspects in 1969 [2]. Since then, the concept of pancreaticobiliary maljunction has been gradually understood and widely recognized. The Japanese Study Group on Pancreaticobiliary Maljunction (JSGPM) was properly founded in 1983. JSGPM and its committee

for diagnostic criteria for pancreaticobiliary maljunction proposed the diagnostic criteria of pancreaticobiliary maljunction in Japanese in 1987 [3]. The slightly revised version was published in English in 1994 [4]. JSGPM established clinical practice guidelines on how to deal with pancreaticobiliary maljunction, with the support of the Japan Biliary Association in 2012, representing a world first [5].

Although no significant changes have been made to the definition of pancreaticobiliary maljunction, diagnostic modalities have recently advanced. Taking these diagnostic imaging techniques into consideration, the committee of JSGPM for diagnostic criteria for pancreaticobiliary maljunction (T Kamisawa [chairman], H Ando, Y Hamada, H Fujii, T Koshinaga, N Urushibara, T Itoi) began to revise the diagnostic criteria from 2011, and final revised version was approved in the 36th Annual Meeting of JSPBM (2013 September).

## Diagnostic criteria for pancreaticobiliary maljunction 2013

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.

## Comments

Pancreaticobiliary maljunction is defined as a congenital malformation in which pancreatic and bile ducts meet

anatomically outside the duodenal wall. Normally, at the duodenal papilla, the duodenal papillary sphincter surrounds the pancreaticobiliary junction from the end of the bile duct, and it regulates the flow of bile while preventing the reflux of pancreatic juices into the bile duct. However, in pancreaticobiliary maljunction, the common channel is longer than normal, which debilitates the effect of the sphincter on the pancreaticobiliary junction, allowing the reciprocal reflux of pancreatic juices and bile. The reflux of pancreatic juices into the biliary tract (pancreatobiliary reflux) provokes higher rates of biliary tract cancer, and reflux of bile into the pancreatic duct (biliopancreatic reflux) may sometimes cause pancreatitis [3–5].

Since no radiological modalities were initially available that could show the status of the pancreaticobiliary junction outside the duodenal wall, pancreaticobiliary maljunction was diagnosed when a lack of effect of the papillary sphincter on the pancreaticobiliary junction was verified on direct cholangiography, such as ERCP. However, ERCP can cause adverse effects such as pancreatitis. MRCP has become popular as a non-invasive method for obtaining high-quality images of the pancreaticobiliary tree, and it is replacing diagnostic ERCP for many pancreatobiliary diseases. Pancreaticobiliary maljunction can be efficiently diagnosed by MRCP. However, such diagnosis may sometimes be difficult in patients with a short common channel, and in babies and toddlers [5]. Because of their high resolution, EUS, MPR images by MD-CT, and intraductal ultrasonography (IDUS) can depict the status of the pancreaticobiliary junction within or outside the duodenal wall [5, 6].

Given that the hydropressure within the pancreatic duct is usually greater than that in the bile duct, pancreatic juice frequently refluxes into the biliary tract in patients with pancreaticobiliary maljunction. The biliary amylase levels in pancreaticobiliary maljunction are often at least 10,000 IU/l [5]. However, the biliary amylase levels are not elevated in some patients with pancreaticobiliary maljunction [7, 8]. Also, age must be considered when evaluating the biliary amylase levels, because the serum amylase levels are low in neonates and babies [8].

It has been reported that bile amylase levels are correlated with the length of the common channel [9, 10]. Elevation of pancreatic enzymes in bile and hyperplastic changes in 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) [5, 11].

Since the maximum diameter of the common bile duct is correlated positively with age, standard values for the maximum diameter of the common bile duct at each age appear appropriate for accurate evaluation of the presence of dilation of the bile duct [12, 13].

Although there are several classifications such as the one classifying the disease into three types based on how pancreatic and bile ducts join [4], or the new Komi's classification [14], they should be standardized in the near future.

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# 膵・胆管合流異常の外科治療の現状と問題点

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今月のテーマ 膵・胆管合流異常の最前線

# 膵・胆管合流異常の外科治療の現状と問題点

安藤久實[1)]

**要旨**：胆管拡張型膵・胆管合流異常に対する標準術式としての分流手術にはいくつかの問題がある．第1は術後肝内結石で，戸谷IV-A型に発生しやすい．肝門部狭窄に対する処置が重要であるが，その対応には施設間で差がある．第2に分流手術後の癌発生で，戸谷IV-A型に対する治療法の見直しが必要となるかも知れない．第3に胆管非拡張型合流異常に対して肝外胆管切除を行うか否かであるが，胆管癌合併率は4.0%と高率で，胆管温存例に胆管癌が発症したとの報告がみられる．今後とも術後の胆管癌発生の有無，腹痛などの諸症状の経過，胆管炎や肝内結石などの合併症発生の有無などについて，注意深く長期間経過をみていくことが重要である．

**索引用語**：膵・胆管合流異常，先天性胆道拡張症，胆管非拡張型合流異常，分流手術，胆道癌

## はじめに

膵・胆管合流異常（以下合流異常）は，解剖学的に膵管と胆管が十二指腸壁外で合流する先天性の形成異常で，胆管拡張をともなう先天性胆道拡張症（以下本症）と，胆管に拡張を認めない胆管非拡張型合流異常がある[1)]．本論文では，本症と胆管非拡張型合流異常に対するわが国の外科治療の現状と問題点について，主に膵・胆管合流異常診療ガイドライン作成に際して問題となった点を中心に記す．

## I 先天性胆道拡張症に対する外科治療の歴史と現状

本症は1852年にDouglas[2)]が詳細な報告をし，本邦では1905年に佐久間[3)]がretention choledochal cystとして報告しており，また，本症と合流異常との関連については1906年のArnolds[4)]の報告が最初とされ，本邦では1916年の木積と兒玉[5)]による詳細な報告がある．このように，本症には合流異常が認められることが古くから指摘されていたにもかかわらず，Babbitt[6)]の論文を古味[7)]が紹介するまでは，合流異常の合併に注意は払われなかった．

一方，McConnell[8)]によると，治療法としての最初の成功例の報告はSwain（1894年）による胆嚢空腸吻合術であり，次いで外瘻造設後に嚢胞空腸吻合術を施行して救命し得たBrunとHartman（1897年）である．以来，内瘻術は本症の3主徴として挙げられている黄疸，腹部腫瘤，腹痛などの胆管下部通過障害にともなう諸症状を改善するとともに，手術死亡の少ない安全な術式として積極的に受け入れられてきた[9)]．本症は巨大な嚢胞を呈したり胆管炎などを合併した状態で診断されることが多かったため，拡張胆管を膵から剥離することが困難な例が多く，膵管を損傷して膵液瘻を形成したり死に至ったりした例の報告もあり，膵内拡張胆管を摘出することは危険な手技で

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The present state and problems of the surgical treatment for the pancreatobiliary maljunction

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**Figure 1.** 肝門部肝管形成：左右肝管を長軸に沿って切開し（矢印），肝門部胆管の吻合口を幅広くとる．

あるとみなされ嚢胞空腸吻合術が本症の標準術式であった．

しかし，Irwin と Morison[10]により本症の胆管壁から発生した癌症例が，また，本邦でも11歳時に嚢胞十二指腸吻合術を施行された例が18歳時に胆管癌を発生した例が報告され[11]，本症と胆道癌との関連性という新たな問題が提起された．その後も Flanigan[12]，Bloustein[13]，Todani ら[14]によりこの問題が取り上げられ，さらに，Flanigan の集めた症例のうち半数は内瘻術後平均4年で癌が発生していた．また，Valabrega ら[15]は53例の内瘻術後に発生した癌症例を集計し，その66.6％が嚢胞十二指腸吻合術後に発生し，内瘻術から癌発見までは平均10年であったと報告した．Todani ら[16]は内瘻術後10年を経過しないうちに2/3以上の例が発癌し，内瘻術後に癌が発現する年齢は手術を施行されずに発見された癌発症年齢よりも15歳も若年であったと報告した．以来，内瘻術後の癌合併症例が次々と報告されるにつれ，内瘻術は本症に対する治療法としては問題がある術式であり，拡張胆管を切除することが重要であることが認識されるようになったのである．

標準術式としての内瘻術がこのような経過をたどったため，Kasai ら[17]は発癌部位である拡張胆管を切除するとともに，膵液と胆汁との混合を避けるため Roux-en-Y 吻合による肝管空腸吻合を行うべきであると記した．この術式は膵液の逆流を防止するとともに，発癌部位である拡張胆管を切除するため，本症に対する新たな標準術式となった[18]．しかし，拡張胆管を切除する範囲をどこまでとするかについての明確なデータはなく，戸谷Ⅰ型では総肝管で切離しても良いが，戸谷Ⅳ-A型の肝側胆管は可能な限り切除することが重要とされている[1][19]．

他方，膵側胆管の処置に関しては，膵内胆管を遺残させないように膵管合流部直上で切除する必要があるが，拡張の少ない例では胆管と膵管の合流部を確認することは容易ではないので，術中胆道造影を繰り返しながら膵管の位置を確認する必要がある[20][21]．なお，共通管に存在する protein plug を残しておくと，術後に膵炎や膵石形成の原因となり得るため[22]，術中胆道造影で protein plug の残存を確認して完全除去を行うことが重要である．

近年，本症が女性に多いことを鑑み，整容性の面から腹腔鏡下手術が施行されるようになってきた．腹腔鏡下手術は Farello ら[23]が6歳女児に対して施行したのが最初で，小児を中心に多くの報告がなされている．腹腔鏡下手術は腹腔鏡の拡大視による優れた視覚化によって術野の展開が明瞭で，また，手術にともなう癒着や術後の痛みが少なく，腸管蠕動の迅速な再開により経口摂取が早期に可能であるなどの利点がある[24]．しかし，残念なことに，多くの腹腔鏡下手術の報告では後述する肝門部の狭窄に対する処理に触れられていなかったり，膵内胆管の処置が不十分である[24]．腹腔鏡下手術は肝内胆管の狭窄に対する処置や，共通管に存在する蛋白栓の除去などに対して十分な処理がし難いため[25]，現時点では共通管に蛋白栓がなく胆管狭窄のない戸谷Ⅰ型に限定されるべきかも知れない．

## Ⅱ　分流手術後の問題点

拡張胆管を切除して膵液の胆管内逆流を防ぐ分流手術は，本症の標準術式として定着しているものの，いくつかの外科治療上の問題がある．その1つが術後肝内結石の発生で，分流手術後数年から10数年を経過してから発生し，その頻度はおおむね7～8％とされている[26]．また，戸谷Ⅳ-A

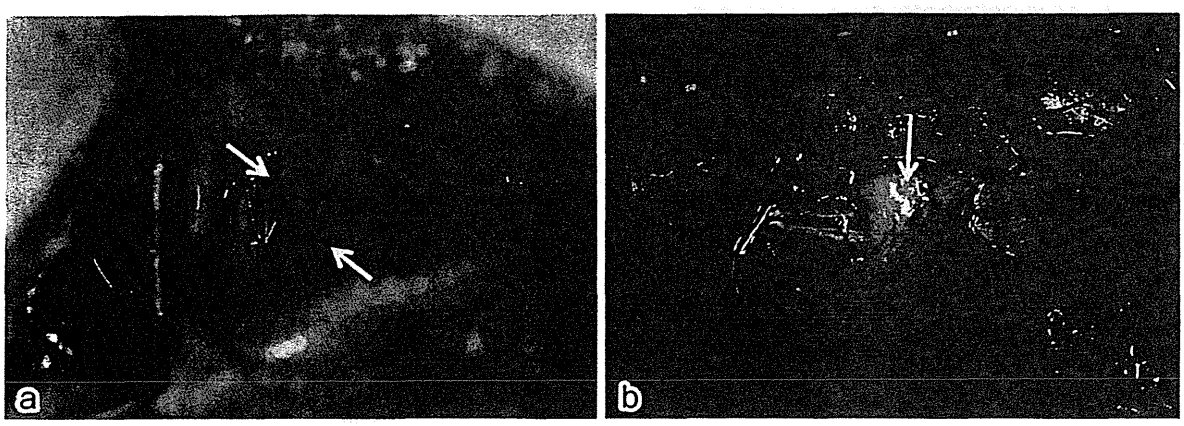


**Figure 2.** a：膜様狭窄．左肝管出口に薄い全周性の膜様物（矢印）があり，左肝管は1/2ほどに狭くなっている．
b：索状狭窄．左肝管の前後壁の間に隔壁のような索状物（矢印）が認められ，これを鉗子ですくい上げている．

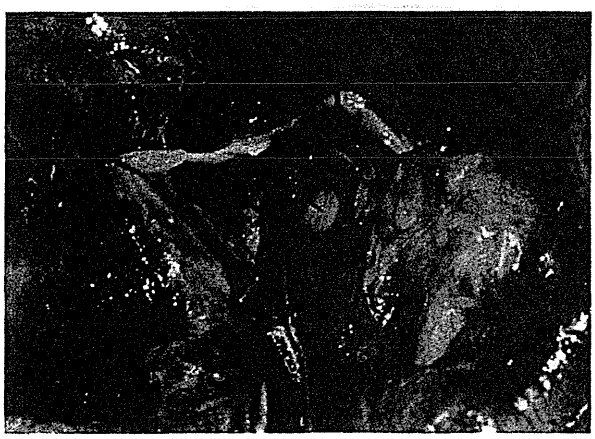

**Figure 3.** 胆管形成：左肝管の膜様の狭窄部を全周にわたって切除・形成した．後区域枝と前区域枝が確認でき，狭窄はなくなっている．

型に発生しやすい[27)28)]．術後肝内結石の発生原因として，Todaniら[29)]は胆管と腸管との吻合部狭窄が重要な因子であるとし，特に戸谷IV-A型では肝内胆管径に対して胆管消化管吻合部の径が相対的に狭窄となるため，肝門部胆管を広く切開して吻合口を幅広くとることを薦めている[30)31)](Figure 1)．これに対して著者ら[32)~34)]は，本症の胆管内に薄い膜が全周性または半周性（膜様狭窄）(Figure 2a)，あるいは胆管の前後壁の間に隔壁のような索状物（索状狭窄）（Figure 2b）が存在するのが戸谷IV-A型の特徴であり，初回手術時にこれらの膜様あるいは索状狭窄を形成・除去しておかないと，胆汁鬱滞と胆管炎が生じて結石が形成されると考えている（Figure 3)．しかし，戸谷IV-A型に対する治療方針は一定しておらず，400名の外科医に対してその対応を調査した結果では，胆管形成を施行する50.8%，肝切除を行う22.8%，放置しておく26.5%と一定していなかった[35)]．

分流手術後に生じる外科治療上の問題の第2は，術後の発癌である．Watanabeら[36)]は23例の分流手術後に発生した胆管癌症例を集計し，分流手術施行例の0.7%に平均9年で癌が発生したことを明らかにした．本邦報告32例の集計では，癌発生部位は肝内胆管8例，胆管消化管吻合部11例，肝側遺残胆管3例，膵内遺残胆管10例とさまざまな部位から癌が生じていた[37)]．さらにKobayashiら[38)]は，分流手術後の発癌例はいずれも戸谷IV-A型であり，拡張胆管を切除しても発癌率に差がないとしており，戸谷IV-A型に対する治療法は現在の標準術式で良いのかという疑問を投げかけている．

### III 胆管非拡張型合流異常例に対する治療上の問題点

全国集計による成人胆管非拡張型合流異常514例のうち，218例（42.4%）に胆道癌が合併しており，そのうち192例（88.1%）が胆嚢癌であった[39)]．胆管非拡張型合流異常においては，胆嚢に膵液逆流をともなう胆汁鬱滞が生じて胆嚢癌を高率に合併するため，予防的胆嚢摘出術が推奨されている[40)]．他方，胆管非拡張型合流異常に対して，

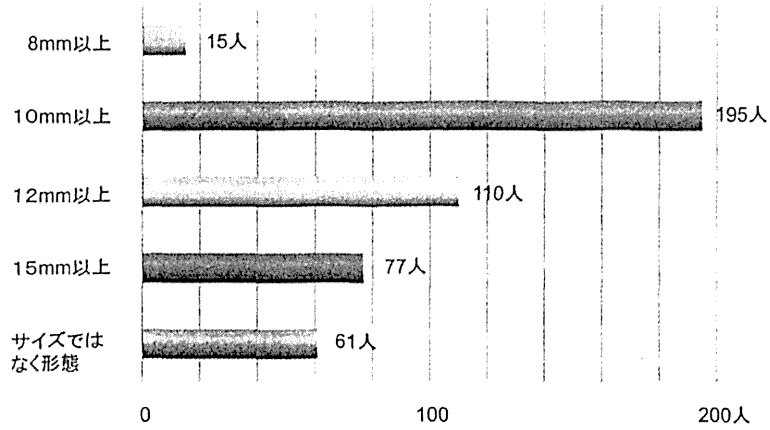


**Figure 4.** 最大胆管横径からみた拡張・非拡張の境界値：アンサーバッドによる調査での成人における最大胆管横径からみた拡張・非拡張の境界値とその人数（文献36より引用改変）.

肝外胆管切除を行うか否かに関しては一定した見解がない．しかし，日本膵・胆管合流異常研究会に登録された1361例の合流異常症例の胆管癌合併率は，胆管拡張型5.2%に対して胆管非拡張型4.0%と大差なく，一般の胆道癌罹患率（0.003～0.01%程度）からみても極めて高率である[41]．また，胆管非拡張型に対する胆管温存例に胆管癌が発症したとの報告が散見されるようになってきた[42)~45)]．これらの点を考慮して，術後長期間を診る小児外科医は，QOLの低下や発癌の危険性など将来にわずかでも禍根を残すことは避けたいと願うため，肝外胆管切除を行う施設が多い[46]．他方，中高年者の多い成人外科では，吻合部狭窄などの危険性を重視する傾向がある．

胆管非拡張型に対する肝外胆管切除に際して留意すべきことは，胆管非拡張の基準が施設によってまちまちなことである．土田ら[35]が行ったアンケート調査によると，成人において最大胆管横径が8mm以上を胆管拡張とする外科医は3.3%，10mm以上が42.6%，12mm以上24.0%，15mm以上16.8%，サイズではなく形態13.3%と分散していた（Figure 4）．一方，日本膵・胆管合流異常研究会診断基準検討委員会が，超音波を用いて小児（740例）ならびに成人（8318例）における胆管径を測定したところ，小児における胆管径の平均は5歳で2.4mm，10歳で3.2mm，15歳で3.7mmであり，これを基準値とした各年齢における正常上限値は5歳で3.9mm，10歳で4.5mm，15歳で5.0mmであった[47]．また，成人での全年齢層における胆管径の平均値は4.5±1.4mmで，これを基準値とした正常上限値は20歳代で6.1mm，60歳代で7.9mmであった[48]．従来，小児では5mm，成人では10mm以上を胆管拡張ありとして取り扱われてきたが，超音波検査と内視鏡的逆行性胆管膵管造影（ERCP）などの胆道造影法の違いによる測定差を考慮したとしても，胆管非拡張型として処理されている例の多くが胆管拡張型である可能性が高い．

## おわりに

膵・胆管合流異常の外科治療として，分流手術が標準術式として行われているが，戸谷IV-A型や胆管非拡張型合流異常に対する治療法は各施設において差がある．これらの差をなくして統一した治療法を確立することも重要であるが，現在行われている治療が内瘻術と同じような経過をたどる危険性もあり得る．われわれに課せられているのは，術後の胆管癌発生の有無，腹痛などの諸症状の経過，胆管炎や肝内結石などの合併症発生の有無などについて，注意深く長期間経過をみていくことであろう．

本論文内容に関連する著者の利益相反
：なし

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# 肝移植

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索引用語：小児肝疾患，成人期肝移植，トランジショナルケア

## 1 はじめに

小児肝移植の適応疾患で代表的なものは胆道閉鎖症で小児肝移植症例の4分の3を占めている．日本肝移植研究会からの報告(2011年版)[1]によれば，胆道閉鎖症にて肝移植を施行した1,723例のうち18歳以上の成人期に移植された症例は163例(9.5%)であったとされている．そのほか，アラジール症候群で3/75例(4.0%)，先天性門脈欠損症で2/25例(8.0%)，先天性代謝性肝疾患(OTC欠損症2/48例，糖原病7/25例，primary hyperoxaluria 5/15例)など小児期から有する肝疾患に対する肝移植は，少なからず成人期において行われている．

こうした成人期に達した小児肝疾患に対する肝移植体制について，一般的には移植適応となった時点で小児外科ないし小児科から成人移植外科へ紹介をしている施設が多いと思われるが，成人期肝移植を一貫して小児外科で担当している施設は九州大学を含めたごく限られた施設のみである．当科における診療体制を紹介するとともに，小児期および成人期肝移植の両者を経験している当科の特性から見えてくる問題点などについて概説したい．

## 2 当科における成人期肝移植

### 1. 肝移植診療体制

九州大学小児外科における肝移植は1996年10月にスタートして以来，現在に至るまで82例に対し再移植2例を含む計84回の生体および脳死肝移植を実施した．小児外科と肝移植というそれぞれの専門性の高さやマンパワーの問題などを理由に胆道閉鎖症をはじめとした小児肝移植適応疾患を初期治療から成人期肝移植に至るまで一貫して同一科において治療を行っている施設は国内でも極めて限られており，当科における肝移植診療体制の大きな特色の1つである．また当科では，多くの場合両親である生体ドナーも小児医療

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**同 消化器・総合外科

表1　当科における小児肝疾患の小児期および成人期肝移植症例の内訳

| | 小児（＜18歳） | 成人（≧18歳） | 計 |
|---|---|---|---|
| 胆道閉鎖症 | 49 | 15（23.4％） | 64 |
| 代謝性肝疾患 | 2 | 1（33％） | 3 |
| Alagille症候群 | 1 | 1（50％） | 2 |
| 先天性門脈欠損症 | 1 | 1（50％） | 2 |
| その他 | 11 | 0（0％） | 11 |

センターに入院しレシピエントと同じ病棟で管理している．周術期の患者家族が抱える精神的不安が軽減されると同時に，医療スタッフ側にとってもドナーとレシピエント双方の情報を共有できることなどのメリットも大きい．

### 2．成人期肝移植例

当科で施行した肝移植82例のうち18歳以上の成人期に施行した症例は18例(22.0％)であった．症例の内訳は表1に示すとおり，先天性門脈欠損症，アラジール症候群，シトルリン血症がそれぞれ1例ずつで，そのほか15例が胆道閉鎖症であった．胆道閉鎖症に限ってみると，23.4％（15/64例）が成人期での移植症例であり，日本肝移植研究会からの全国登録データ[1]（成人期移植例：9.5％）に比較すると成人期肝移植症例が多いのが当科の特徴である．

### 3．成人期肝移植の成績

当科での成人期肝移植の成績は図1に示すとおり生存率100％であり，両群間の有意差はないものの小児期肝移植(84.8％)よりもむしろ成績が良い．

Uchidaら[2]は胆道閉鎖症464例に対する肝移植の検討で，16歳以上のレシピエントでは消化管穿孔，腹腔内出血，胆汁漏の頻度が有意に高く，胆道閉鎖症に対する肝移植は早期に行うべきと結論づけている．一方で，Kyodenら[3]は，胆道閉鎖症症例を同じく16歳以上と16歳未満に分けて検討し，生存率，術後合併症に差が認められなかったことから，すべての年齢において安全に肝移植できるとしており，当科での解析と同様の結論であった．

## 3　成人期肝移植が抱える問題点

### 1．生体ドナーとグラフトサイズの問題

2010年の脳死移植法の改正以来，脳死移植数は若干増えてはいるものの，依然として生体移植に頼らざるをえないのがわが国の移植医療の現状である．

当科における生体肝移植においても同様であるが，一般的に18歳未満の小児肝移植では，ほぼ全例といってよいほどドナーは両親のいずれかである．しかし，成人期を超えてからの生体肝移植となると，必然的に両親の年齢的制約を考慮する必要性がでてくる．かといって，必ずしも兄弟や配偶者がいるとは限らず，若年成人期での肝移植は適切な生体ドナーがいないという状況が生じやすい年代であるといえる．

成人期における生体肝移植では，small-for-size graftに注意を要することはいうまでもない．これに関しては，グラフト肝重量とレシピエント体重比(graft-recipient weight ratio：GRWR)が0.8以上という基準が一般的である．当科での生体肝移植において小児例のGRWRが平均2.21であったのに対し，成人例では平均0.84と有意に低値であった．また，移植グラフトは18例の成人期肝移植症例のうち脳死での全肝グラフトが2例，右葉グラフトが7例，拡大左葉グラフトが9例であり，約半数で右葉グラフトが必要となっていた．成人期移植のドナーは，小児期移植のドナーに比較して手術時間や術後在院日数が有意に

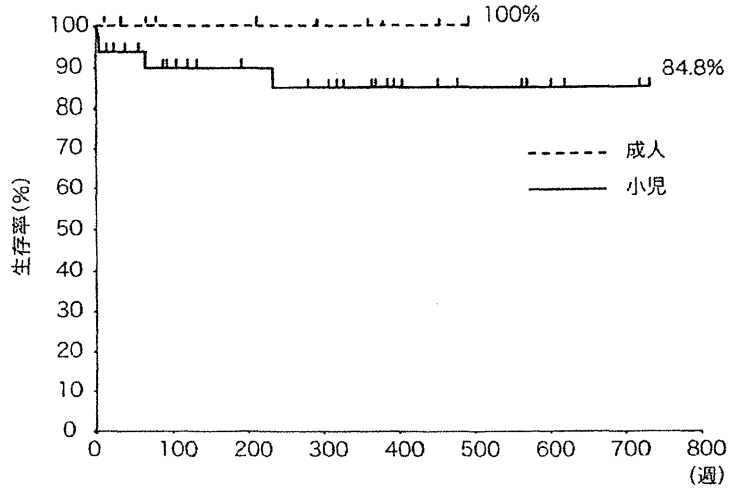


図1　当科における生体肝移植後の生存率

長くなっており，ドナーにかかる負担も大きくなっていることが示された[4]．

**2. 肝肺症候群・肺高血圧症**

Sasakiら[5]の報告によると，胆道閉鎖症の最終的な移植適応理由は，乳幼児などの小児期では圧倒的に黄疸であるが，成人期になると黄疸の割合は減少し肝肺症候群や肺高血圧症など肝硬変に伴う二次的な合併症が直接的な移植適応理由となっている．これらは手術適応やタイミングを知るうえで，欠かすことのできない要因であると同時に患者自身の自覚症状が乏しい場合がある点において注意を要する．重症例では移植そのものが禁忌となる場合があるため，定期的な心電図，心エコー，酸素飽和度測定，血液ガス測定，必要であれば心臓血管カテーテル検査を行い，早期診断を行う必要がある．

当科では，5例の肺合併症(肝肺症候群4例，肺高血圧症1例)を有する患者に肝移植を施行している．移植後は全例が生存しているが，術後人工呼吸器管理の長期化や低酸素血症に伴うと考えられる消化管穿孔など，術後合併症のリスクも高いため注意が必要である．

**3. 移植手術時間と出血量**

当科の胆道閉鎖症に対する肝移植を成人期と小児期で比較してみると，手術時間で有意に成人症例が長くかかっていた(1,016±217分 vs 813±218分)．出血量に関しても成人例で多い傾向は認めたが，有意差は認めていない(147±114.9 mL/kg vs 116.2±131.5 mL/kg)．また，術後血管，胆管合併症の発生率にも有意差を認めなかった[4]．

しかし，小川ら[6]の報告では成人例で有意に術後出血の発生率が高かったとしている．

成人例では長期にわたる胆管炎をはじめとした炎症に伴う強固な癒着と複雑な側副血行路の形成による術中出血のリスク，脾機能亢進症に対する治療歴を有する症例が含まれてくることなどの因子が絡んでいると考えられる．

**4. 消化管穿孔**

当科では移植後消化管穿孔を10例(10/84例：12.0％)経験している．穿孔例の移植時平均年齢は，9.3歳であった．年齢分布をみ

てみると，1歳未満の乳児例が5例あり，残りの5例は18歳以上の成人期移植2例を含めすべて10代半ば以降の症例であった．消化管穿孔の発生は二峰性の年齢分布を示した．乳幼児の腸管壁の脆弱性と，長期経過症例の強固な癒着がそれぞれ起因していると考えられた．穿孔部位は，胃1例，十二指腸1例，小腸6例，結腸2例とさまざまであった．結腸穿孔の2例を含む4例で一時的に人工肛門造設を行った．結果的に10例中2例が死亡したが，穿孔が直接的死因となった症例は経験していない．しかし，McDiarmidら[7]は，術後の消化管穿孔はpatient/graft lossのriskを3～4倍に上昇させる独立因子の1つであると報告している．迅速な対応と躊躇せず人工肛門を造設することが重要であると考えている．

### 5. Non-adherenceの問題

肝移植後の管理において最も重要なことは，免疫抑制剤管理であることはいうまでもない．移植後に思春期・成人期を迎える症例，とりわけ本人の記憶がほとんどない乳幼児期の肝移植を経験した症例においては，本人の病識が乏しく思春期・成人期におけるNon-adherenceの問題が無視できない．免疫抑制剤の内服管理が，両親管理から本人管理に移行していく時期である．Burraら[8]の報告では，小児期に施行した肝移植症例では，移植後のNon-adherence症例が成人症例の約4倍のリスクであったとしている．当科で経過観察中の症例においても，これまでに6/82例(7.3％)でNon-adherenceに起因すると思われる合併症を経験し，うち1例では治療抵抗性の拒絶反応からgraft lossにまで至っている．

患者本人の服薬環境の変化に応じて，その都度，厳重な管理の必要性についての再教育を適宜行うことが重要である．

### 6. Transitional careと医療保障制度

小児肝疾患を原疾患として肝移植を施行した患者の成人期におけるフォローは，いかに行うべきか定まったモデルケースはないのが現状である．当科では，これまで述べてきたように成人期を超えても小児外科で基本的なフォローを行いながら，状況に応じて適宜しかるべき他科にコンサルトをしている．一方で，近年特にこうしたキャリーオーバー症例の成人科へのtransitionの重要性も再認識されている．患者の立場からは，成人になってもいつまでも小児センターへ通院することに抵抗や不安を感じているケースもある一方で，長年通い慣れた小児診療科と主治医から離れることの不安の訴えも非常に多い．Watson[9]は，慣れない成人科へのtransitionを契機に移植患者の外来への足が遠退き，transition期間中に拒絶からgraft lossに至るケースが，35％にも上ったと報告している．Transitional careの導入には，患者本人の明確な病識とさまざまな関連科との協力体制とが不可欠であり細心の注意を要する．このことは，移植患者に限らず，小児医療そのものが抱えている今後の整備すべき課題であるといえる．

小児肝疾患患者の医療費負担軽減を成人期以降も保障する制度の整備も重要な要素である．現在，胆道閉鎖症を例にとれば，小児慢性特定疾患でカバーされているが，20歳を過ぎると公的助成が消失してしまうのが現状である．肝移植をすでに受け免疫抑制状態にあれば，年齢に関係なく身体障害者手帳の交付を受けられる．しかし，こうした現在の保障制度のみでは，十分な医療費助成が受けられない「空白の」状況が発生している．胆道閉鎖症を守る会(青年部)による主に成人患者を対象にした大規模アンケート調査結果(回答