Tohoku J. Exp. Med., 1997, **181**, 235-244

The Outcome of Surgery for Biliary Atresia and the Current Status of Long-Term Survivors

Masaki Nio, Ryoji Ohi, Satoru Shimaoka, Daiji Iwami and Nobuyuki Sano

Department of Pediatric Surgery, Tohoku University School of Medicine, Sendai 980-77

Nio, M., Ohi, R., Shimaoka, S., Iwami, D. and Sano, N. *The Outcome of Surgery for Biliary Atresia and the Current Status of Long-Term Survivors.* Tohoku J. Exp. Med., 1997, **181** (1), 235-244 —— Between 1953 and 1995, 300 patients with biliary atresia underwent surgery at Tohoku University Hospital. The 10-year survival of patients who were operated on in or before 1965 was 9%. But the survival rate went up to 61% in patients operated on between 1976 and 1985. Eighty-five patients including 2 who developed liver failure after Kasai operation and underwent liver transplantation have survived more than 10 years. Eleven of them (13%) have recurrent or persistent jaundice. Of the 30 patients who have survived more than 20 years (10 males and 20 females, age range; 20 to 41 years), 20 underwent hepatic portoenterostomy, 8 underwent hepaticoenterostomy and the remaining 2 underwent hepatic portocholecystostomy. None of these patients has undergone liver transplantation. Twenty-two patients have led near-normal lives. The remaining 8 patients have experienced some troubles due to cholangitis, portal hypertension, intrahepatic gallstones and so on. Two of them are considered as candidates for liver transplantation. While the majority of long-term survivors of biliary atresia have good quality of life, close long-term follow-up is essential even in patients with biliary atresia aged 20 years or more. ——— biliary atresia; hepatic portoenterostomy; hepaticoenterostomy; quality of life; long-term follow-up

Kasai operation is widely accepted as the initial surgical modality for biliary atresia. Although some patients have adequate relief of symptoms after Kasai operation, the others require liver transplantation because of persistent jaundice or because of intractable complications such as portal hypertension. Favorable results of Kasai operation have been reported (Ohi et al. 1990; Imaizumi et al. 1991; Toyosaka et al. 1993; Oh et al. 1995), but the number of patients who survived very long time was not large enough to elucidate the real role of Kasai

Received June 30, 1996; revision accepted for publication November 15, 1996.

Address for reprints: Ryoji Ohi, M.D., Department of Pediatric Surgery, Tohoku University School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-77, Japan.

This paper was presented at 6th International Sendai Symposium on Biliary Atresia, May 20 and 21, 1996, Sendai.

operation. Thus the effectiveness of Kasai operation in long-term survivors remains controversial.

Altman et al. reported that ongoing cirrhosis progressed in the liver of patients even after successful Kasai operation (Altman et al. 1975). Loss of intrahepatic bile ducts in jaundice-free patients was also pointed out by several authors (Callea et al. 1987; Desmet 1990; Nietgen et al. 1992). It is our great concern if these pathological findings means ultimate necessity of liver transplantation for the majority of patients with biliary atresia.

We occasionally experience the cases in which severe portal hypertension develops in spite of no recurrence of jaundice (Ohi et al. 1986). These patients are not very commonly seen, although morphological changes mentioned above might happen in their livers. The results of our clinicopathological study showed that vanishing bile ducts were observed in the livers of both patients with and without jaundice. Pathophysiology of vanishing bile ducts was postulated different between the patients with and without jaundice. Vanishing bile ducts in the patients with persistent jaundice definitely meant bad prognosis. On the contrary, jaundice-free patients whose liver biopsy specimens contained no bile ducts showed favorable clinical courses (Nio et al. 1991).

Long-term follow-up is necessary to properly estimate the real role of Kasai operation. In this paper, we reviewed the surgical outcome as well as the current status of long-term survivors after Kasai operation performed at Tohoku University Hospital.

Three hundred patients underwent corrective surgery for biliary atresia at Tohoku University Hospital between 1953 and 1995. Of the 300 patients, 140 have survived and 160 patients died. Fifteen patients who developed severe hepatic dysfunction after Kasai operation and underwent liver transplantation were included in the survivors.

Procedures

Until 1972, all procedures were basically the same; Kasai's hepatic portoenterostomy, portocholecystostomy or hepaticoenterostomy. Several modifications to prevent cholangitis including Suruga II procedure and intestinal valve(s) method, which have been described elsewhere (Suruga et al. 1981; Tanaka et al. 1991), have been performed since 1972. Liver transplantation has been performed since 1989 in patients who developed liver failure following the initial corrective operation. Eighteen patients underwent liver transplantation until December, 1995.

10-year survival

The age distribution of the survivors is listed (Table 1). Two patients were in their forties, and 3 in their thirties. Ten-year survivors were markedly increasing in number, and 87% of them were jaundice-free.

TABLE 1. *Age distribution of long-term survivors*

Age (years)	Number of patients		
	Jaundice		Total
	Yes	No	
10～19	47	8	55
20～29	23	2	25
30～39	2	1	3
40～	2	0	2
Total	74	11	85

The surgical results were evaluated in each period of time at the initial operation. 10-year survival was 9% in the patients operated on in or before 1965. On the other hand, the survival rate increased to 61% in the latest group of the patients (Table 2). Of 85 patients who had survived more than 10 years, 72 were jaundice-free, and 11 had persistent jaundice. The remaining 2 patients underwent liver transplantation at the age of 9 and 11, respectively (Table 3).

The surgical outcome of the last 10 years

Between 1986 and 1995, 67 patients were operated on, and 41 of them had survived without liver transplantation. Thirty-nine were jaundice-free and 2

TABLE 2. *10-year survival rate*

Year at operation	Number of patients	Number of patients surviving more than 10 years	(%)
～1965	54	5	9.3
1966～1975	87	25	29
1976～1985	93[a]	57	61
Total	234	87	37

[a]Two patients who underwent liver transplantation are included.

TABLE 3. *Patients surviving more than 10 years*

Janudice	Number of patients	%
Without jaundice	74	87
No LTx	72	
After LTx	2	
With jaundice	11	13
Total	85	100

LTx, liver transplantation.

had persistent jaundice. Fifteen patients who underwent liver transplantation had survived (Table 4). The outcome of surgery of the last 10 years shows that still one or two patients died every year with the help of liver transplantation (Table 5).

Current status of patients surviving more than 20 years

The current status of long-term survivors were also assessed in terms of complications including cholangitis and portal hypertension, and quality of life. We presented a paper regarding 21 patients with biliary atresia who had survived more than 20 years (Nio et al. 1996). Thereafter 9 more patients were turned 20, and a total of 30 patients who had survived more than 20 years were analyzed herein. Of 22 patients with noncorrectable type of biliary atresia, 20 underwent hepatic portoenterostomy and the remaining 2 underwent hepatic portocholecystostomy. Eight patients with corrective type of biliary atresia underwent hepaticoenterostomy. In 2 of them hepatic portoenterostomy was subsequently performed as a revision (Table 6). None of these patients has undergone liver transplantation.

Recurrence of jaundice and ascending cholangitis. Following surgery, all the

TABLE 4. *Outcome of surgery for biliary atresia* (1986–1995)

	Number of patients
Alive	
Without jaundice	54
No LTx	39
After LTx	15
With jaundice	2
Dead	11
Total	67

LTx, liver transplantation.

TABLE 5. *Procedures for 30 patients surviving more than 20 years*

Procedures	Number of patients	%
HPE	20	66.7
HE	6	20.0
HPE following HE	2	6.6
HPCC	2	6.6
Total	30	100

HPE, hepatic portoenterostomy; HE, hepaticoenterostomy; HPCC, hepatic portocholecystostomy.

TABLE 6. *Recurrence of jaundice in 30 patients surviving more than 20 years*

Recurrence of jaundice	Number of patients	%
No	25	83
Yes	5	17
Temporary	2	
Persistent	3	
Total	30	100

patients were relieved of jaundice. But jaundice has recurred in 3 patients (a 32-year-old female, a 24-year-old male and a 20-year-old female). The total bilirubin concentrations were around 10 mg/100 ml in the 20-year-old female, and between 2.0 and 4.0 mg/100 ml in the other 2 patients. Two patients (a 24-year-old male and a 20-year-old female) sometimes developed temporary low-grade hyperbilirubinemia accompanied by the elevation of other liver function tests. No recurrence of jaundice was seen in the remaining 25 patients (Table 6).

Fourteen patients encountered episodes of cholangitis postoperatively (Table 7). Four of them had mild or moderate cholangitis necessitating hospitalization at least once in the last 3 years. Three patients were still suffering from cholangitis almost on a yearly basis.

Portal hypertension. Of 11 patients who developed portal hypertension, esophageal varices and/or hypersplenism, 5 required treatment as follows (Tables 8 and 9). Four of them with severe portal hypertension underwent splenectomy and proximal splenorenal shunting in or before 1985. Prophylactic endoscopic injection sclerotherapy (EIS) was employed in 3 patients including 2 who developed recurrent varices following splenorenal shunting.

A 24-year-old male who had hypersplenism was considered as a potential candidate for partial splenic embolization (PSE).

Portal hypertension is obviously a major sequela of biliary atresia, which could be an only reason for reference for liver transplantation. The careful

TABLE 7. *Cholangitis in 30 patients surviving more than 20 years*

Cholangitis	Number of episodes of cholangitis (per year)	Number of patients	%
No	—	16	53
Yes		14	47
	No episode in the last 3 years	7	
	Less than once	4	
	Once or more	3	
Total		30	100

TABLE 8. *Portal hypertension in 30 patients surviving more than 20 years*

PH		Number of patients	%
No		19	63
Yes		11	37
	EV	6	
	HSP	1	
	PH+HSP	4	
Total		30	100

PH, portal hypertension; EV, esophageal varix; HSP, hypersplenism.

TABLE 9. *Treatment for portal hypertension*

Procedures	Number of patients
SRS+SPL	4
ELS	3[a]

SRS, proximal splenorenal shunting; SPL, splenectomy; EIS, endoscopic injection sclerotherapy.

[a]Two patients who underwent splenorenal shunting are included.

management for portal hypertension is playing an important role in not only keeping good quality of life of the patient but also delaying the timing of transplantation. Until 10 years ago we had performed splenectomy and proximal splenorenal shunting for the patients with severe portal hypertension. But we recently never perform splenorenal shunting, as it is preferable to employ less invasive techniques especially in young children. Since 1985 we have successfully managed patients with portal hypertension employing EIS and/or PSE (Hayashi et al. 1987). Regarding the indication for PSE in the patient with hypersplenism, when a patient with marked splenomegaly manifests both ongoing thrombocytopenia less than 100,000/ml and clinical hemorrhagic tendency such as epistaxis or suggillation, he/she is considered a candidate for PSE.

Fortunately no patient died of portal hypertension in our series as far as he/she is followed up according to our follow-up protocol.

Other complications. Peptic ulcers were seen in 2 patients. A 24-year-old male recently developed massive duodenal bleeding. His liver function tests were near normal. Another patient (a 22-year-old male) developed a hemorrhagic gastric ulcer during a recent episode of cholangitis. Bleeding was conservatively controlled in both patients. They have never rebled.

Three patients developed intrahepatic stones due to cholangitis. A 23-year-

old male was diagnosed with intrahepatic stones 4 years ago. Although he underwent lithotomy and revision of hepaticojejunostomy, residual stones were revealed postoperatively. He was managed by repeated irrigation with a percutaneous transhepatic biliary catheter. Subsequently his liver function tests have improved.

A 30-year-old female underwent diversion of the Roux-en Y limb because of the intractable cholangitis. Intrahepatic stones were revealed postoperatively. Her general condition improved, while her liver function tests were fluctuating.

The other patient, a 24-year-old male, with intrahepatic stones was having severe hepatic dysfunction and portal hypertension, and was considered as a candidate for liver transplantation.

Intrahepatic stones are a serious complication because of their difficulty in management. Since the early diagnosis is a key for successful treatment of intrahepatic stones, yearly basis of diagnostic imaging such as ultrasonography or CT scan is strongly recommended in follow-up of even the patient surviving very long time.

Growth/development. Physical growth was within the normal range in all except one (Table 10). The remaining patient exhibited dwarfism associated with Turner's syndrome. None of the patients were mentally retarded. All of female patients except 2 and all of male patients normally exhibited secondary sexual characteristics. A menstruation was induced by hormonal therapy in the female with Turner's syndrome at the age of 18. The remaining one patient, a 20-year-old female, who had severe liver disfunction and was considered as a candidate for liver transplantation developed primary amenorrhea. Three females got married, one of whom have 2 healthy children aged 2 years and 5 years.

Delayed puberty in patients with biliary atresia was reported by Nakano et al. (1990). This delay might be attributable to liver dysfunction. But the mechanism was not clear. There was no significant relationship between the onset age of menstruation and the severity of liver dysfunction in our series.

QOL of the survivors. Twenty-two patients were leading normal to near-normal lives. The quality of life of the remaining 8 patients was unsatisfactory (Table 11). Quality of life has been poor for one patient with Turner's syndrome.

TABLE 10. *Development in 30 patients surviving more than 20 years*

Developmental delay		Number of patients
Physical	No	29
	Yes	1
Mental	No	30
	Yes	0

TABLE 11. *Eight patients with unsatisfactory QOL*

	Number of patients
Recent episodes of cholangitis	3
Persistent jaundice	2
External biliary conduit	1
Hypersplenism and cholangitis	1
Turner's syndrome	1
Total	8

QOL, quality of life.

Five patients required temporary hospitalization at least once in the last 3 years for complications including cholangitis. The remaining 2 patients developed severe hepatic dysfunction, and were considered as candidates for liver transplantation. Most patients actively participated in social events.

CONCLUSION

Thirty patients have survived more than 20 years in our series. Twenty-two of them are leading normal to near normal lives, while 6 other patients have experienced some complications in the last 3 years, but have well-preserved liver function. Progressive liver disease was not observed in the 22 long-term survivors. The quality of life of these patients is really satisfactory. Kasai operation was regarded as a curative surgical modality at least for these patients. The total number of patients who were operated on in the same period of time (1953-75) was 138. In terms of overall survival rate, it was 22% (30/138) and this would not be satisfying at all. From the viewpoint of survival, the role of Kasai operation appears limited. But over the last 40 years, the outcome of patients following Kasai operation has markedly improved owing to early diagnosis, the refinement of surgical techniques and precise postoperative management. We therefore believe that the patients cured by Kasai operation is increasing in number.

Liver transplantation offers great hopes for survival to patients even after failed Kasai operation. It may be performed as a primary operation in the patient with highly advanced stage of this disease. Living related liver transplantation is widely accepted in Japan, where cadaveric transplantation is still very difficult to perform because no legislation for brain death is prepared yet. However, we should always be aware of problems of transplantation such as rejection, immunosuppression-related disorders including infections and secondary malignancies, and donor shortage. Especially in living donors, difficulty in the second donor and the ethical problem were more serious than in cadaveric transplantation. These problems will hopefully be resolved in the near future. But at this stage, we should do our best to keep the patient's own organ first. Combination of Kasai operation with subsequent liver transplantation, if neces-

sary, is the treatment of choice for patients with biliary atresia (Vacanti et al. 1990; Otte et al. 1994).

In conclusion, we found most patients surviving more than 20 years after Kasai operation were leading almost normal lives. But as severe complications including cholangitis developed in some patients, close long-term follow-up is essential even in patients at the age of 20 or more.

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