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Original Article

Current treatment status of polycystic liver disease in Japan

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Aim: Polycystic liver disease (PLD) is a genetic disorder characterized by the progressive development of multiple liver cysts. No standardized criteria for the selection of treatment exist because PLD is a rare condition and most patients are asymptomatic. We here aimed to clarify the status of treatment and to present a therapeutic strategy for PLD in Japan.

Methods: From 1 June 2011 to 20 December 2011, we administered a questionnaire to 202 PLD patients from 86 medical institutions nationwide.

Results: The patients included 45 men and 155 women, and the median age was 63 years. Two hundred and eighty-one treatments were performed for these patients, as follows: cyst aspiration sclerotherapy (AS) in 152 cases, cyst fenestration (FN) in 53, liver resection (LR) in 44, liver transplantation (LT) in 13 and other treatments in 19. For cases of type I PLD (mild form) according to Gigot's classification, the therapeutic effects of AS, FN and LR were similar. For type II (moderate form), LT demonstrated the best therapeutic effects, followed by LR and FN. For type III (severe form), the effects of LT were the best. The incidences of complications were 23.0% in AS, 28.4% in FN, 31.8% in LR and 61.5% in LT.

Conclusion: Considering the therapeutic effects and complications, AS, LR and LT showed good results for type I, type II and type III PLD, respectively. However, LT for PLD was performed in a small number of patients. In Japan, the transplantation therapy is expected to be common in the future.

Key words: aspiration-sclerotherapy, cyst fenestration, liver resection, liver transplantation, polycystic liver disease

INTRODUCTION

POLYCYSTIC LIVER DISEASE (PLD) is a genetic disorder characterized by the progressive development of multiple liver cysts. PLD includes two different diseases: (i) autosomal dominant polycystic liver disease (ADPLD), which presents multiple cysts in only the liver; and (ii) autosomal dominant polycystic kidney disease (ADPKD), which is associated with multiple renal cysts.[1] Although ADPLD and ADPKD are distinct at the genetic level, the clinical symptoms of both are similar.[2] Most patients with PLD do not require treatment because liver function is maintained during all the stages of the disease. However, some patients with PLD present abdominal distension, abdominal pain and chest compression by extensive hepatomegaly due to an increase in the number of liver cysts and their expansion, which affect performance status (PS) and quality of life.[3,4] In addition, PLD may induce other serious conditions, such as obstructive jaundice or Budd-Chiari syndrome.[3] The purpose of treatment for PLD is to decrease liver volume and alleviate or remove the symptoms caused by hepatomegaly. Common treatments for PLD include cyst aspiration sclerotherapy (AS), cyst fenestration (FN), liver resection (LR) and liver transplantation (LT). However, no consensus on the selection of treatments has been reached. Because PLD is a rare disease and no large cohort study has been performed,

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the long-term outcome after treatment for PLD is poorly understood.[5] In this study, we administered a questionnaire to medical institutions nationwide with experience treating PLD. The aim of the present study was to clarify the current status of treatment and to present a therapeutic strategy for PLD in Japan.

METHODS

Subjects and data collection

THE SUBJECTS WERE PLD patients who had been treated in Japan. The questionnaire was sent to 102 medical institutions that belong to the Liver Cancer Study Group of Japan. The survey was conducted from 1 June 2011 to 20 December 2011. The information collected was as follows: patient age and gender, disease type by diagnostic imaging, presence or absence of polycystic kidney disease (PKD), renal function before treatment, Eastern Cooperative Oncology Group PS before treatment, indication for treatment, method of treatment, sclerosing agent used in AS, treatment-related complications and duration of treatment effect. PLD was classified into three types based on Gigot's classification.[6] Type I (mild form) included patients with a limited number (<10) of large cysts (>10 cm). Type II (moderate form) was represented by patients with diffuse involvement of the liver parenchyma by multiple medium-sized cysts with remaining large areas of non-cystic liver parenchyma. Type III (severe form) patients had extremely high numbers of diffuse cysts that were small to medium in size with little area of liver parenchyma between cysts.[6] The treatment indication was divided into two groups: patients with only subjective symptoms and those with objective symptoms. Subjective symptoms included abdominal pain, appetite loss, dyspnea, movement limitation, fever, leg edema and abdominal discomfort. Objective symptoms included cyst infection, liver dysfunction, compression inferior vena cava, intracavitary hemorrhage, malnutrition, and ascites. Duration of treatment effect was defined as the length of time between treatment and symptom recurrence or next therapy. The patients were censored at the time of loss to follow up.

Statistical analysis

Statistical analyses were performed using the χ^2-test and the log–rank test. Duration of treatment effect was calculated using Kaplan–Meier estimates. All analyses were performed utilizing GraphPad Prism version 5. Differences at $P < 0.05$ were considered statistically significant.

RESULTS

QUESTIONNAIRES WERE RETURNED by 86 of 102 institutions (collection rate, 84.3%), and 202 PLD patients were included in the analysis. The patients included 45 men (22.2%) and 155 women (76.7%), with a median age of 63 years (range, 39–91 years). Of the 202 patients with PLD, 92 patients (45.5%) had concomitant PKD. Renal insufficiency, namely, abnormal serum creatinine level or hemodialysis, was observed in 34 (16.8%) patients. The type of disease according to Gigot's classification was as follows: type I, 102 patients (50.5%); type II, 67 patients (33.2%); type III, 27 patients (13.4%); unknown, six patients (3.0%). A total of 281 treatments were performed for the 202 PLD patients.

Of the 281 treatments, 152 were AS (54.1%), 53 were FN (18.9%), 44 were LR (15.7%), 13 were LT (4.6%) and 19 were others (6.8%) (Table 1). The most common type of disease for each treatment was type I for AS and FN (57.9% and 45.3%, respectively), type II for LR (52.3%) and type III for LT (61.5%). The PS before treatment was two or less in many of the patients who underwent AS, FN and LR. However, the PS was 3 or more in many of the patients who underwent LT. Moreover, the proportion of patients with renal dysfunction before treatment was high in the LT (53.9%) group compared with the other treatments. Regarding the treatment indication, the frequency of objective symptoms was 25.7% for AS, 28.3% for FN, 45.5% for LR and 76.9% for LT. Treatment-related complications were reported in 23.0% of AS procedures, 28.3% of FN procedures, 31.8% of LR procedures and 61.5% of LT procedures. Severe complications of Clavien–Dindo classification grade IIIb or more were observed more frequently in LT cases (15.4%) compared with any other procedures. The most common complications were fever and abdominal pain for AS, a large amount of ascites for FN, and bile leakage and a large amount of ascites for LR. For LT, cases of death due to early transplant-specific complications such as hepatic necrosis and graft failure were observed. Moreover, various complications, including bile leakage, extensive ascites and renal failure, were reported following LT. Treatment-related death occurred following AS due to sepsis in one case; two cases of treatment-related death were also reported for LT.

Table 1 Characteristics and results according to each treatment

	AS	FN	LR	LT
No. of cases (%)	152 (54.1)	53 (18.9)	44 (15.7)	13 (4.6)
Gigot's classification, *n* (%)				
Type I	88 (57.9)	24 (45.3)	17 (38.6)	0
Type II	45 (29.6)	22 (41.5)	23 (52.3)	3 (23.1)
Type III	15 (9.9)	5 (9.4)	3 (6.8)	8 (61.5)
Performance status, *n* (%)				
≤2	143 (94.1)	48 (90.6)	42 (95.5)	5 (38.5)*†§
≥3	5 (3.3)	0	1 (2.3)	7 (53.8)*†§
Renal insufficiency, *n* (%)	21 (11.2)	8 (15.1)	7 (15.9)	7 (53.9)*†§
Abnormal serum creatinine	14 (9.2)	6 (11.3)	7 (15.9)	3 (23.1)
Hemodialysis	3 (2.0)	2 (3.8)	0	4 (30.8)*†§
Indication for treatment, *n* (%)				
With objective symptoms	39 (25.7)	15 (28.3)	20 (45.5)*	10 (76.9)*†§§
Only subjective symptoms	107 (70.4)	38 (71.7)	23 (52.2)**	2 (15.4)*†§
Complications, *n* (%)	35 (23.0)	15 (28.3)	14 (31.8)	8 (61.5)*††
Clavien–Dindo grade ≤IIIa	33 (21.7)	14 (26.4)	10 (22.7)	6 (46.2)**
Clavien–Dindo grade ≥ IIIb	2 (1.3)	1 (1.9)	4 (9.1)**	2 (15.4)**††
Mortality	1 (0.7)	0	0	2 (15.4)*†§§

*$P < 0.01$ vs AS, **$P < 0.05$ vs AS, †$P < 0.01$ vs FN, ††$P < 0.05$ vs FN, §$P < 0.01$ vs LR, §§$P < 0.05$ vs LR.
AS, aspiration sclerotherapy, FN, cyst fenestration, LR, liver resection, LT, liver transplantation.

The procedures of LR according to Gigot's classification are showed in Table 2. Lobectomy was performed in approximately half of type I and II PLD patients. The details of LT cases are demonstrated in Table 3. Twelve cases for living donor transplantation and one for domino transplantation were included. The indications for LT were progression of PLD in 10 cases and coexisting hepatocellular carcinoma in three cases. Although nine cases were associated with PKD, there was no case of kidney transplantation performed simultaneously. Seven donors were patients' relatives, and no donor was affected with PLD (data not shown).

The duration of treatment effect was analyzed according to the type of disease. The median follow-up period for all treatments was 16 months (range, 0–215). In the treatment of type I PLD, the 5-year efficacy rates for LR, FN and AS were 77.8%, 78.9% and 56.6%, respectively, but there were no significant differences between these procedures (Fig. 1). For type I patients, the AS procedures were analyzed according to the sclerosing agent used, which included ethanol in 48 cases (31.6%), ethanolamine oleate (EO) in 38 cases (25.0%), minocycline in 34 cases (22.4%) and no drug in 22 cases (14.5%). Regarding the duration of treatment effect, EO was better than the other reported drugs and had a therapeutic effect comparable to LR (Fig. 2). For type II patients, surgical treatments (i.e. FN, LR and LT) had a significantly better effect than AS. The 5-year efficacy rate was 79.1% for FN, 90.2% for LR and 100% for LT; there was no significant difference among these surgical treatments (Fig. 3). For type III patients, the surgical treatments also had a significantly better effect than AS. The 5-year efficacy rate of LT was 75%, which was significantly better than FN. However, there was no significant difference between FN and LR (Fig. 4).

Table 2 Procedures of liver resection

	Lobectomy	Segmentectomy	Partial resection	Total
Type I	9	5	3	17
Type II	10	7	6	23
Type III	1	1	2	4
Total	20	13	11	44

Table 3 Detail data of liver transplantation cases

Case no.	Sex/age(y)	Type	PKD	HD	Indication for LT	Donor state	Donor relationship	Liver graft	Postoperative complication	Prognosis (months)/ outcome
1	F/56	III	+	+	Abdominal pain	Living	Son	Right lobe	Ascites	84/alive
2	F/70	III	−	−	Liver failure	Living	Daughter	Right lobe	None	71/alive
3	M/51	III	−	−	Liver dysfunction, dyspnea	Living	Wife	Right lobe	Liver failure, graft failure	0/death†
4	F/60	ND	+	−	Malnutrition, abdominal pain	Living	Husband	Right lobe	Acute rejection	108/death‡
5	F/66	ND	+	+	Infection and rapture of cysts	Living	Son	Right lobe	Bile fistula, abdominal abscess	147/alive
6	M/70	II	−	−	Comorbidity (HCC)	Living	Nephew	Right lobe	Drain site hemorrhage	108/alive
7	F/61	III	+	−	Abdominal, low back pain	Living	Husband	Right lobe	None	102/alive
8	F/72	II	+	−	Comorbidity (HCC)	Living	Son	Right lobe	None	91/alive
9	F/51	III	+	−	Liver dysfunction, malnutrition, dyspnea	Living	Husband	Right lobe	MOF, graft necrosis	0/death†
10	F/54	II	+	+	Budd–Chiari syndrome	Living	Husband	Left lobe	Ascites, peritonitis	12/alive
11	M/63	III	+	+	IVC compression, malnutrition, dyspnea	Living (domino)	Domino	Whole liver	None	105/alive
12	F/63	III	+	+	IVC compression, malnutrition, cyst infection, dyspnea	Living	Daughter	Right lobe	Renal failure	101/alive
13	M/64	III	−	+	Comorbidity (HCC)	Living	Son	Right lobe	Renal dysfunction	12/alive

†Treatment-related death.
‡Death due to subarachnoid hemorrhage.
HCC, hepatocellular carcinoma; HD, hemodialysis; IVC, inferior vena cava; LT, liver transplantation; MOF, multiple organ failure; ND, not described; PKD, polycystic kidney disease; Type, disease type of PLD according to Gigot's classification.

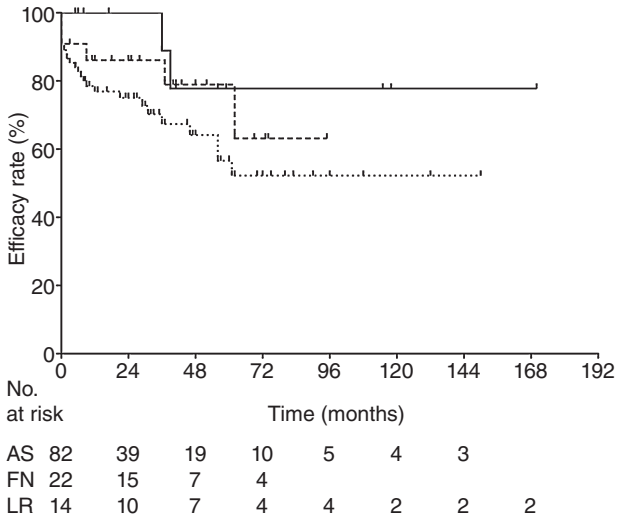

Figure 1 Duration of treatment effect in type I polycystic liver disease (PLD). There was no significant difference between treatments. However, there was the tendency toward a good effect for liver resection (LR), cyst fenestration (FN) and aspiration sclerotherapy (AS). ·····, AS ($n = 88$); - - - -, FN ($n = 24$); ——, LR ($n = 17$).

DISCUSSION

THE CHOICE OF treatment is difficult for PLD. LT is currently the only radical therapy for patients with PLD.[7,8] However, careful consideration of the indication for LT is needed because liver function is maintained even in the patient with symptomatic PLD.[3,9] Additionally, organ donation is limited, particularly in Japan. Instead, AS, FN and LR are generally performed to treat symptomatic PLD. The goals of treatment for PLD are to alleviate the abdominal symptoms and prevent symptom recurrence by decreasing liver volume.[3] These treatments do not change the natural course of the disease, and therefore, the symptoms usually recur due to the growth of new cysts or the re-growth of treated cysts. Hence, it is important to choose an appropriate treatment according to the condition of each patient. When classifying the form of PLD, the system proposed by Gigot *et al*. is often used.[6] This classification system is based on the number and size of the liver cysts and the amount of remaining liver parenchyma. It reflects the severity of the disease and is useful when choosing treatment options. Recently, some reports regarding PLD treatment have recommended AS, FN and LR for type I or II PLD and LT for type III PLD; even so, no standardized criteria for the selection of treatment exist.[1,3,5,10–12] In the present study, we clarified the treatment status for PLD in Japan by conducting a nationwide survey and evaluated the therapeutic effect of each treatment and its associated complications according to disease types.

Several reports have recommended FN for the treatment of type I PLD.[6,13] FN, namely, surgical de-roofing of the cyst, is a minimally invasive surgical treatment,[13,14] but, the recurrence rate has been reported to be 20–72%, with a large difference among reports.[15–18] The most common postoperative complication reported by the hospitals was ascites, and its incidence was relatively high at 33–69%. AS involves cyst aspiration followed by injection of a sclerosing agent that destroys the epithelial cells lining the cyst cavity, inhibiting cystic fluid production, and it is also performed primarily for type I PLD.[19,20] The most commonly used sclerosing agent is ethanol, although minocycline and tetracycline are also used. Only mild treatment-related complications were reported for AS with these agents, but AS is impractical because of the high associated recurrence rate, which exceeds 75%.[21] In the present study, the 5-year efficacy rate of AS for type I PLD was only approximately 50%. However, examining the rate according to the sclerosing agent used demonstrated that EO provided an excellent outcome when compared

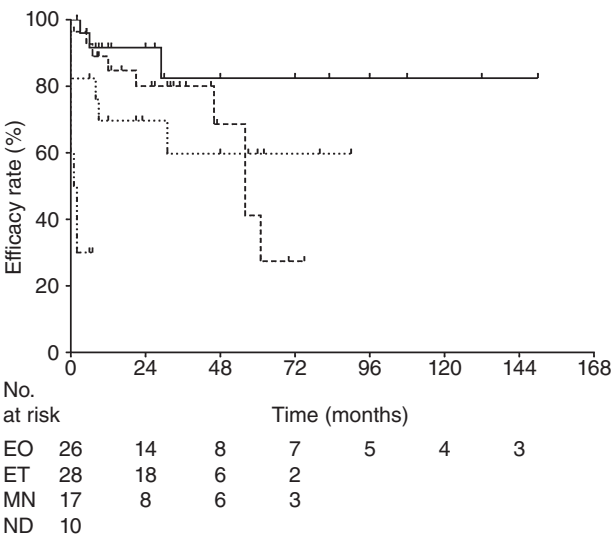

Figure 2 Duration of aspiration sclerotherapy (AS) effect according to the sclerosing agent used for type I polycystic liver disease (PLD). AS with any agent showed a significantly greater effect when compared with no drug (ND) ($P < 0.01$). Ethanolamine oleate (EO) tended to be better than the other evaluated drugs, although there was no significant difference. MN, minocycline. ——, EO ($n = 28$); - - - -, ET ($n = 29$); ·····, MN ($n = 18$); ·····, ND ($n = 11$).

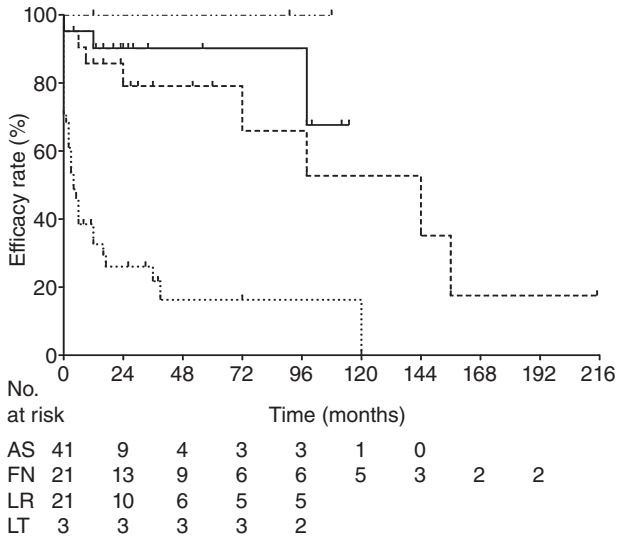

Figure 3 Duration of treatment effect in type II polycystic liver disease (PLD). All surgical treatments showed significantly greater effects compared with aspiration sclerotherapy (AS) ($P < 0.01$; cyst fenestration [FN] and liver resection [LR] vs AS, $P < 0.05$; liver transplantation [LT] vs AS). There was no significant difference between surgical treatments. ·····, AS ($n = 45$); - - - -, FN ($n = 23$); ——, LR ($n = 22$); ·····, LT ($n = 3$).

with the other drugs, with a result comparable to LR and FN. EO has been used with immense success in sclerotherapy for esophageal varices.[22] Nakaoka *et al*. reported that AS with EO for PLD had a 93.3% success rate with no recurrence during the observation period.[23] They used 5% EO and injected a volume of sclerosant equivalent to 10% of the volume of aspirated cystic fluid. However, there is no consensus on the appropriate concentration and volume of EO for PLD. Considering the therapeutic effects and complications, AS with EO is appropriate as an initial treatment for type I PLD.

Liver resection for type II PLD has been recommended by some reports, and one report noted that LR should be performed even for type III PLD.[11] The recurrence rate following LR has been reported to be 3–33%.[5,24,25] In type II or III PLD, the intrahepatic vasculature and biliary system are severely altered by cysts and the accurate preoperative definition of these structures remains difficult, even with current imaging modalities.[26] Therefore, the postoperative complication rate is high, at 20–83%, and includes ascites, pleural effusion, biliary leakage, hemorrhage and wound infection.[5,11,13,24,25] The present study demonstrated that the postoperative complications of LR include ascites, bile leakage and intra-abdominal abscess, with an incidence of 31.8%. However, the duration of treatment effect for type II PLD was more satisfactory following LR and LT than AS or FN. LT provides a desirable cure as the therapeutic effect is permanent. However, considering the high morbidity associated with LT and the limited number of donated organs in Japan, LR is recommended as the initial treatment for type II PLD.

In previous reports, LT was commonly recommended for type III PLD,[6,27–29] but one report proposed an extended indication of LR to type III.[11] However, LR for type III PLD is associated with difficulty determining the LR line and liver dysfunction caused by the small amount of remnant liver. In addition, most type III patients have a poor PS or renal dysfunction due to coexisting polycystic kidneys. Therefore, it would appear that the use of LR for type III PLD should be prudent. LT is the only radical treatment option for PLD.[8] Although LT carries increased risks of postoperative morbidity and mortality,[5,10,11,13] it has an excellent curative effect if these problems are overcome.[30–32] The outcome of LT for PLD is comparable to that for other liver diseases.[10,27] Therefore, LT appears to be a more appropriate treatment in type III PLD patients in Western countries in which cadaveric donor transplantation is common. However,

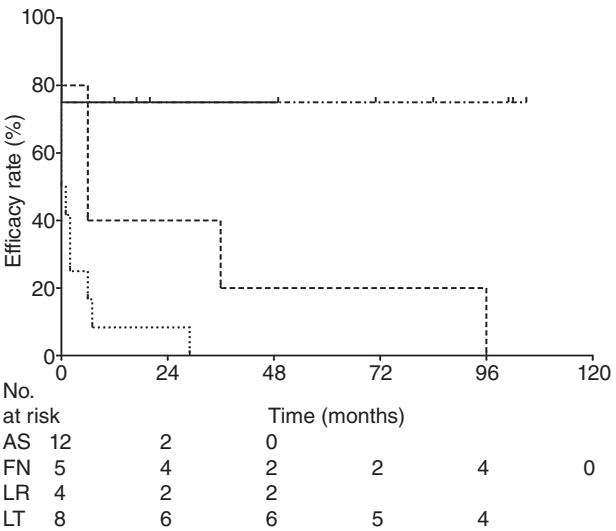

Figure 4 Duration of treatment effect in type III polycystic liver disease (PLD). All surgical treatments showed significantly greater effects compared with aspiration sclerotherapy (AS) ($P < 0.01$; liver transplantation [LT] vs AS, $P < 0.05$; cyst fenestration [FN] and liver resection [LR] vs AS). LT showed a markedly greater effect than FN ($P < 0.05$). There was no significant difference between LR and LT. ·····, AS ($n = 15$); - - - -, FN ($n = 5$); ——, LR ($n = 3$); ·····, LT ($n = 8$).

only 13 patients underwent LT in the present study. These results indicate that LT for PLD is not common in Japan. Organ shortage is a serious problem in Japan, in addition, the priority of PLD patients as recipient is low, and liver transplants from cadaveric donors are not expected. Therefore, it is not easy to recommend LT as initiation therapy for type III PLD in the present situation in Japan, and accumulation of experiences and discussion are necessary sequentially. On the other hand, the duration of treatment effect following LT for type III PLD was long compared with the other treatments in this study. In Japan, the number of cadaveric transplantation cases increased after revision of the Organ Transplant Law enforced in 2010, thereby increase in LT for PLD is expected. Living donor liver transplantation from a patient's relative may be a restricted treatment option, as PLD is an autosomal dominant disease. In the present study, almost all (12/13) of LT were living donor liver transplantation, of whom seven donors were relatives and five were spouses. The relative donors were four sons, two daughters and one nephew, and none was affected with PLD. Most relative donors were male, which might have been affected by the fact that three-quarters of PLD patients were female. Furthermore, it is possible to perform simultaneous liver and kidney transplantation (SLK) in patients with PKD. A meta-analysis by Drenth *et al*. reported that 42% of patients undergoing LT for PLD underwent SLK.[10] In the present study, there was no case that underwent SLK for PKD. Additionally, the first case of successful SLK was reported in 2013 in Japan.[33] In the current Japanese status, it is difficult to perform SLK even with renal failure, because most transplantation cases are dependent on a living donor. On the other hand, Simpson *et al*. reported that SLK has an immunological advantage over serial transplantation in terms of avoiding the risk of pre-sensitization, when recipients require liver and kidney transplantation.[34] In the future, increase in cadaveric donors would enable PLD patients with PKD to undergo SLK.

Other treatments for PLD include percutaneous transcatheter hepatic artery embolization (TAE). Ubara *et al*. reported that TAE reduced the cyst volume following the selective embolization of the hepatic artery because the blood flow in the liver cysts caused by PLD is predominantly supplied by the hepatic artery.[35] By performing TAE super-selectively, targeting hepatic arterial branches supplying localized hepatic regions replaced by multiple cysts with neither an intact portal vein nor intact hepatic parenchyma, they sought to minimize damage to remaining intact liver. Selection of embolized hepatic regions followed the same judgment process as for LR.[36] Takei *et al*. also noted that TAE decreased the liver volume by approximately 23% and the cyst volume by approximately 30% and that it could be performed for patients with poor general condition who are not candidates for surgical treatment.[36] We were unable to compare TAE with the other treatments in the present study because of the small number of included TAE cases and their short observation periods. Recently, somatostatin analogs were reported as a new treatment option for PLD.[37–39] Somatostatin inhibits fluid secretion and proliferation by reducing cyclic adenosine monophosphate in the cholangiocytes within PLD cysts.[40,41] Previous reports have demonstrated that somatostatin analogs can decrease the liver volume by 3–5% and provide 6–12 months of therapeutic effect. Moreover, it is less invasive than other treatments and can be used for all types of PLD.[26,38,42] Although the accumulation of experience with somatostatin analogs in Japan is required, they are expected to be a treatment option in the future.

In conclusion, considering the therapeutic effects and complications, AS, LR, and LT are good treatments for type I, type II and type III PLD, respectively. However, LT for PLD was performed in a small number of patients. In Japan, the transplantation therapy is expected to be common in the future. In addition, in the clinical setting, it is particularly important that treatment selection should be tailored to a patient's clinical status and that patients are informed that treatments other than LT are not radical treatment options.

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