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Polyhedral Fenestration Technique Used for Combined Partial Hepatectomy and Cyst Fenestration for Polycystic Liver Disease: A Small Case Series

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Objective: To assess the safety and efficacy of "polyhedral fenestration technique" (PFT), which we newly developed, in combined hepatectomy and cyst fenestration (CHCF) for symptomatic polycystic liver disease (PLD).

Summary of background data: CHCF for PLD has been reportedly less efficacious for its invasiveness because 50% to 70% patients suffered recurrent symptoms after CHCF.

Methods: Patient characteristics, intra- and early postoperative variables were compared between 5 PLD patients undergoing CHCF performed with PFT (PLD group) and 95 patients with diseases other than PLD receiving hepatectomy without biliary reconstruction during the same period (Control group) to assess safety of PFT. Chronological changes in total liver volume (TLV) measured by computed tomography (CT) volumetry as well as recurrent symptoms after CHCF were investigated to assess long-term outcomes.

Results: Although ≧ Clavien-Dindo grade 2 complications were more common in the PLD group than in the Control group (PLD vs Control, 5/5[100%] vs 27/95[28%], p=0.004), patient characteristics, intra-, and early postoperative variables, including ≧ Clavien-Dindo grade 3 complications, were comparable among the 2 groups. Postoperative observational period of the 5 PLD patients ranged 30 to 88 months with a median of 63. CT volumetry revealed that TLV continued to reduce up to 1 year after surgery and thereafter retained less than 0.5 times of preoperative TLV in all patients. Recurrent liver enlargement or recurrent symptoms were not observed in any of the 5 PLD patients.

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Conclusions: Although our case series was very small, newly-developed PFT in CHCF for PLD yielded acceptable safety and excellent long-term outcomes.

Key words: Polycystic liver disease – Combined hepatectomy and cyst fenestration – Operative safety – Surgical efficacy

Polycystic liver disease (PLD) itself is benign and usually asymptomatic. However, considerably invasive surgical procedures, such as combined hepatectomy and cyst fenestration (CHCF) or even hepatic transplantation, are often necessary once it becomes symptomatic.[1–7] However, recurrent symptoms similar to those that were observed in the preoperative period were reported to develop in 50% to 70% patients after CHCF. Furthermore, CHCF has reportedly accompanied severe complications more often than hepatectomy for diseases other than PLD.[1,2,4–7] Considering surgical invasiveness and outcome, the benefit from CHCF for severe form of PLD seemed limited.

That is because we had not performed CHCF for PLD at our institution until 2009. In 2009, however, the Mayo Clinic Group proposed a reasonable therapeutic strategy for symptomatic PLD and showed acceptable outcomes of surgery based on the strategy.[5] Since 2009, therefore, we have applied CHCF to patients with symptomatic PLD. However, previously reported series of CHCF for PLD showed that recurrent symptoms due to the reenlargement of remaining PLD liver were observed in the majority of patients.[1,2,4–6] At the beginning of our CHCF program for PLD, we considered that some modification to the standard CHCF procedure was necessary for reducing the incidence of recurrent symptoms after CHCF. Thus, we developed the "polyhedral fenestration technique" in CHCF. With this technique, we have not experienced any cases developing recurrent symptoms to date although the number of our cases was very small. In this report, we describe the "polyhedral fenestration technique" and results of small case series.

Patients and Methods

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Between December 2009 and December 2014, we performed CHCF for 5 patients with symptomatic PLD. Our therapeutic strategy for PLD basically followed the Mayo Clinic proposal reported in 2009[5] with minor modifications, in which therapeutic methods were selected according to the PLD type determined based on symptoms, cyst characteristics, and the condition of preserved liver sections as shown in Table 1. Regarding the modification to the original proposal, 2 of the 5 PLD patients in the present study corresponded to the Mayo Clinic Type B and thus fenestration alone should have been selected for these 2 patients based on the original Mayo Clinic proposal.[5] However, there were several large grapelike cyst clusters composed of numerous small cysts in their PLD livers. Fenestration alone was considered impractical for such occasions. Thus, we considered that CHCF was occasionally necessitated for such patients with the type B. As such, although section(s), which was almost entirely occupied with the cysts, should be removed; removal of the normal liver parenchyma should be minimized as possible for mitigating the hypertrophy of the remaining liver due to liver regeneration.[8] The main cause of frequent incidence of recurrent symptoms after CHCF was considered as the blockade of fenestration orifice due to postoperative intraabdominal adhesion, by which cyst exudate was dammed up to enlarge the remnant cysts, leading to recurrent symptoms. Thus, in order to prevent the blockade of fenestration orifice due to adhesion, we developed the "polyhedral fenestration technique" and used bioresorbable hyaluronic acid/carboxymethylcellulose membrane (Seprafilm, Genzyme, Cambridge, Massachusetts) extensively surrounding the remaining liver.[9] In brief, the bulkheads between neighboring cysts, including cyst wall and/or thin normal parenchyma between cysts less than 3 mm of thickness, were fenestrated or removed broadly as possible to communicate neighboring cysts each other. Furthermore, separate surfaces of the remaining liver (i.e. upper-, lower-, and liver-cutting surfaces), were penetrated or connected by the fenestrated cysts. In addition, thin bridging normal parenchyma distal to the hepatic hilum, which resulted from remnant cyst fenestration, was partially removed. As a result, several

Table 1 Classification of polycystic liver disease with suggested treatment in patients with normal liver function[a]

	Type A	Type B	Type C	Type D
Symptoms	Absent or mild	Moderate or severe	Severe (or moderate)	Severe (or moderate)
Cyst characteristics	Any	Limited number large cysts	Any	Any
Areas of relative normal liver parenchyma	Any	≥2 sections	≥1 section	<1 section
Isosectional portal vein or hepatic vein occlusion of preserved section(s)	Any	Absent	Absent	Present
Treatment	Observation or medical treatment	Cyst fenestration or hepatectomy combined with remnant cyst fenestration	Hepatectomy combined with remnant cyst fenestration	Liver transplantation

[a]This classification system was essentially following the Mayo Clinic Classification, which was reported in the Reference No 5, with minor modification.

fenestration orifices were unified into an orifice, of which the brim formed a polyhedron (Fig. 1). In the standard procedure for cyst fenestration in which only cyst wall was removed for deroofing,[10] the rim of a fenestration orifice formed a plane and thus seemed easily sealed and closed with adhesion. In our technique, the brim of an orifice formed an irregular polyhedron that was considered unlikely to be sealed with adhesion. Furthermore, even though 1 surface of the remaining liver was sealed with adhesion, cyst exudate was expected to run though neighboring cysts connected by the fenestration and subsequently escape from orifices on another surface into the peritoneal cavity. In addition, after completing the CHCF procedure, several sheets of bioresorbable hyaluronic acid/carboxymethylcellulose membrane (Genzyme) were placed extensively to surround the remaining liver.

To assess the safety and efficacy of our CHCF technique, short- and long-term outcomes of surgery were evaluated as follows. Previous series reported that CHCF for symptomatic PLD accompanied frequent early postoperative complications than hepatectomy for diseases other than PLD.[1,2,4–6] Therefore, to assess short-term outcomes, we compared patient characteristics, intra- and early postoperative variables between the 5 PLD patients receiving CHCF and 95 patients with diseases other than PLD receiving hepatectomy without biliary reconstruction performed during the same study period. Regarding long-term outcomes, chronologic changes of the total liver volume (TLV) measured by CT volumetry as well as recurrent symptoms were assessed in the 5 PLD patients. PLD patients were followed monthly until 6 postoperative months, trimonthly until 1 year after surgery, and thereafter annually. At the follow-up visit, patients were asked if they suffered from symptoms similar to those which were observed in the preoperative period. CT evaluation was performed within 1 month before surgery, at 6, 12 months after surgery, and annually thereafter. Liver anatomy and method of hepatectomy was described according to the Brisbane 2000 system of nomenclature of liver anatomy and resections.[11]

Statistical Analysis

Patient follow-up was continued until December 31, 2016. Values were shown as median (range) and/or number (percentage). Differences between groups were assessed by methods for non-Gaussian distribution variables. We used commercial statistics software (SPSS 23.0 for Windows; IBM, Armonk, New York), and two-tailed *P* values less than 0.05 were regarded as significant.

Results

Patient characteristics of the 5 PLD patients were summarized in Table 2. All patients suffered from severe abdominal distension. In addition, abdominal pain was developed in 2 patients, early satiety in 2, lower extremities edema caused by compression of inferior vena cava in 1, and cyst infection in addition to early satiety in case 2. Hepatic function was well preserved in all patients except for mild elevation of serum alkaline phosphatase. Concurrent polycystic kidney was observed in 3 patients whereas renal dysfunction, defined as that with less than 40 mL/minute of actual creatinine clearance, was not observed in any patients. Preoperative TLV

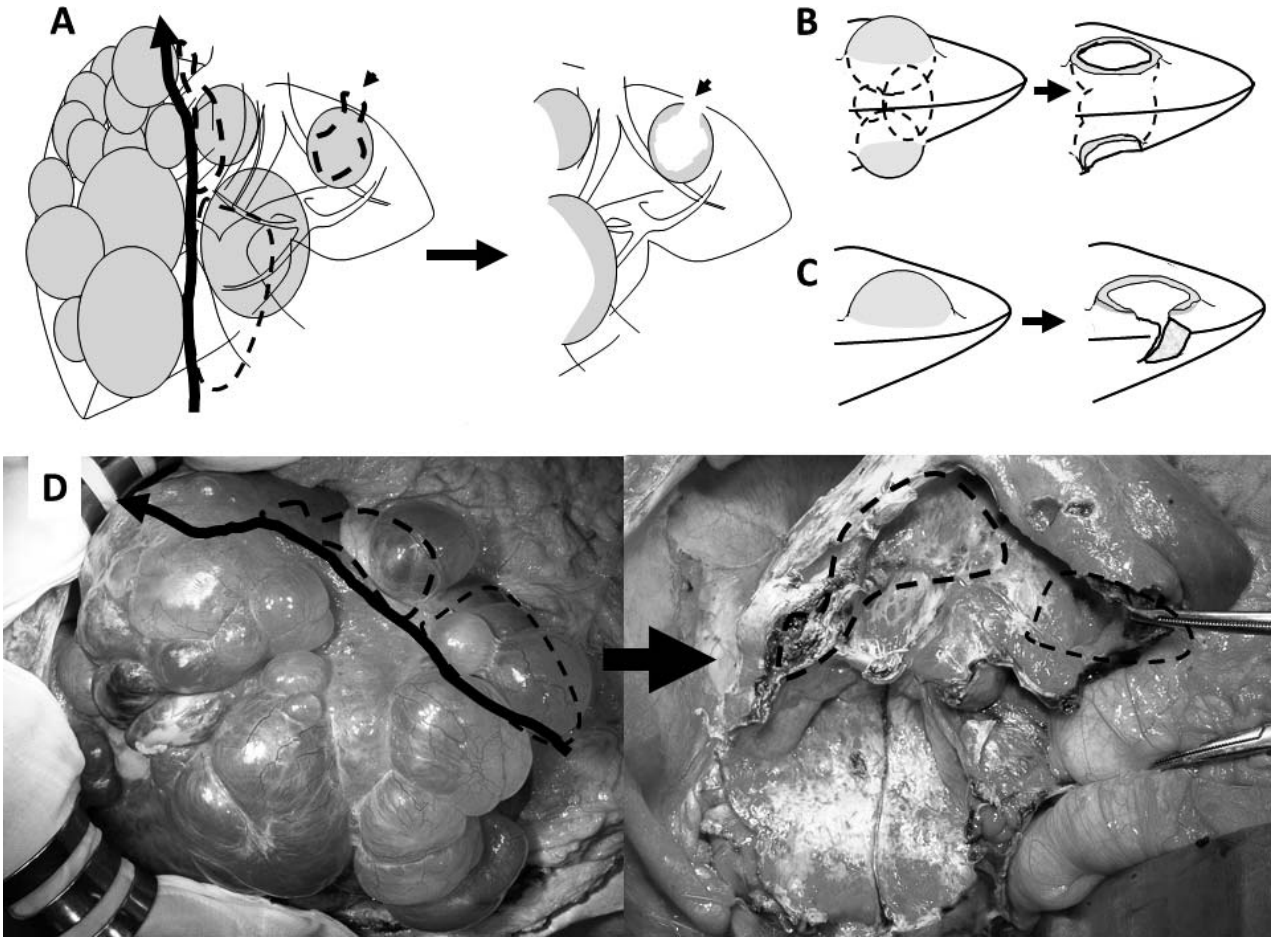

Fig. 1 Schematic of polyhedral fenestration technique and intraoperative photograph of a representative case. Segment(s), which were mostly occupied with cysts, were removed by anatomical resections (A, D). Remnant cysts were treated by fenestration. The bulkheads between neighboring cysts, including cyst wall and/or thin normal parenchyma between cysts less than 3 mm of thickness, were fenestrated or removed broadly as possible for neighboring cysts to communicate each other (B). Separate surfaces (i.e., upper-, lower-, and liver-cutting surfaces), of the remaining liver were penetrated or connected by the fenestrated cysts (B). Furthermore, thin bridging normal parenchyma distal to the hepatic hilum (small arrowheads, A, B), which resulted from remnant cyst fenestration, was removed in part. As a result, several fenestration orifices were unified into an orifice, of which the brim formed an irregular polyhedron.

Table 2 Patient characteristics

Case	Age, y	Gender	Concurrent PKD	Ccr, mL/min	Classification of PLD			Specific symptoms	Preoperative TLV, mL	Preoperative TLV/SLV ratio, %	History of prior treatment for PLD
					Gigot	Mayo	Qian				
1	49	Female	yes	66	I	B	4	Pain	2530	252	None
2	76	Female	yes	49	I	C	4	Early satiety Cyst infection	1806	187	Aspiration and sclerotherapy
3	62	Male	yes	44	I	C	4	Pain	2720	242	None
4	80	Female	no	54	I	B	4	Early satiety	1488	159	Aspiration and sclerotherapy
5	63	Female	no	89	I	C	4	IVC syndrome	3743	344	Fenestration alone

Ccr, creatinine clearance; IVC, inferior vena cava; SLV, standard liver volume.

Table 3 Comparison of pre-, intra-, and early postoperative variables between 5 patients with PLD and 95 patients with diseases other than PLD

	PLD (n = 5)	Other than PLD (n = 96)	*P* value
Age at surgery, y	63 (49–80)	68 (44–87)	1.000
Gender, Male:Female	1:4	74:21	0.013
Disease indicated for hepatectomy			<0.001
PLD*	5		
HCC		34 (35.8%)	
Liver metastasis		48 (50.5%)	
Gallbladder cancer		6 (6.3%)	
IHCC		4 (4.2%)	
Others		6 (6.3%)	
Preoperative ICGR15, %	6 (4–9)	10 (2–46)	0.093
Methods of hepatectomy			0.926
Hemi-hepatectomy (Bi-sectionectomy)	1 (20%)	22 (23.6%)	
Sectionectomy	2 (40%)	32 (33.7%)	
Segmentectomy	0	16 (16.2%)	
Partial resection	2 (40%)	25 (26.3%)	
Operation time (minutes)	320 (148–352)	304 (82–425)	0.842
Intraoperative blood loss (ml)	450 (10–1800)	290 (10–1800)	0.812
Postoperative complication			
≧Clavien-Dindo grade 2	5 (100%)	27 (28.4%)	0.004
≧grade 3	2(40%)	15 (15.8%)	0.166
30-, 90-day mortality	0	0	
Postoperative hospital stay (days)	21 (4–33)	14 (3–51)	.577

exceeded 1.5-fold of the standard liver volume calculated by Urata's formula in all patients.[12] We found 3 of 5 patients had a history of prior treatment for PLD. Genetic analyses were not performed in any patients because of unestablished clinical benefit.[3,6]

Short-term outcomes

Comparison of perioperative variables between the 5 PLD patients (PLD group) and 95 patients with diseases other than PLD who underwent hepatectomy without biliary reconstruction (control group) showed that most variables did not differ among the 2 groups. However, female gender was significantly more common in the PLD group than in the control group. Operative methods, operation time, and intraoperative blood loss were comparable between groups. No mortality was observed in any groups. Postoperative complications with the Clavien-Dindo grade 2 or severer were more common in the PLD group than in the control group (5/5 [100%] versus 27/95 [28.4%], $P = 0.004$) although the incidence of grade 3 or severer complications [2/5 (40%) versus 15/95 (15.8%), $P = 0.166$] and postoperative hospital stay [21 days (4–33) versus 14 days (3–51), $P = 0.577$] were comparable among the 2 groups (Table 3).

Long-term outcomes

Chronologic changes in ratio of the TLV measured at each time point to preoperative TLV [i.e., (TLV measured at each time point)/ (Preoperative TLV)], of PLD patients showed that TLV reduced significantly up to 12 postoperative months and thereafter retained less than half of the preoperative TLV in all patients (Fig. 2). Postoperative observational period of the 5 PLD patients ranged from 30 to 88 months with a median of 63. During the study period, any of these 5 patients did not complained of symptoms similar to those which were observed in the preoperative period. All patients have been currently alive and doing well. All these 5 patients currently declare their well-being. Current age of the 5 PLD patients ranged 57 to 85 years with a median of 68.

Discussion

Most previous studies of CHCF for PLD followed the fenestration method as introduced by Lin et al. in 1968.[10] In 2009, the Mayo Clinic group reported their largest experience of surgery for PLD in the worldwide English literature and proposed the classification and therapeutic strategy of PLD based on their outcomes of surgery.[5] However, recurrent symptoms after surgery were observed in 73% of

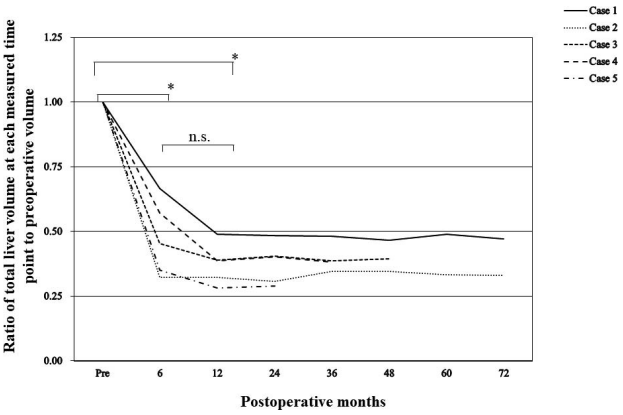

Fig. 2 Chronologic changes in ratio of the total liver volume measured at each time point to the preoperative total liver volume. Chronologic changes in ratio of the TLV measured at each time point to the preoperative TLV [i.e., (TLV measured at each time point)/(Preoperative TLV)], of the 5 PLD patients showed that TLV reduced significantly up to 12 postoperative months and thereafter retained less than half of the preoperative TLV in all patients. Reenlargement of the remaining liver was not observed in any patients.

their surviving patients although the health survey score of these patients was well maintained. In other words, procedural improvement has not been discussed during almost half century despite the relative inefficacy of CHCF for PLD for long-term relief. Hence, we developed the "polyhedral fenestration technique" with extensive use of bioresorbable hyaluronic acid/carboxymethylcellulose membrane (Genzyme) for preventing fenestration from being neutralized by blockade with adhesion, aiming for long-term relief.

The "polyhedral fenestration technique" we developed was designed to make fenestration orifices unlikely to be sealed with adhesion. In addition, escape route of cyst exudate might have been maintained with the communication through the fenestrated cysts and/or parenchymal removal between the fenestration orifices on the upper-, lower-, and/or liver-cutting surfaces of the remaining liver even if one surface was sealed with adhesion. Cyst fenestration for the liver cysts has been considered to work as follows. Cyst exudate escape through the fenestration orifices into peritoneal cavity and be absorbed through the peritoneum.[1,2,4–7,10] Thus, the fenestration continues to work as long as its orifice opens to the peritoneal cavity. In the present study, any patient did not show either re-enlargement of the remaining liver or recurrent symptoms. Most previous studies regarding CHCF for PLD argued its efficacy in their reports on the basis of symptom mitigation without confirming sustained reduction of TLV.[1,2,4–6] Recently, the Mayo Clinic group reported sustained effect of CHCF for liver volume reduction. However, serial analyses of liver volume were available in only one third of their patients and the report did not evaluate recurrent symptoms.[7] In the present study, the long-term relief after CHCF in all patients was confirmed not only by the symptom mitigation but also by the chronologic changes of TLV. Furthermore, the short-term outcomes of surgery were comparable between the PLD and control groups although CHCF for symptomatic PLD has reportedly accompanied severe postoperative complications more often than hepatectomy for diseases other than PLD.[1,2,4–6] These findings support the safety and efficacy of the "polyhedral fenestration technique" we developed in combination with extensive use of the bioresorbable hyaluronic acid/carboxymethylcellulose membrane (Genzyme).

The present study has the 2 limitations as the followings: very small sample size and smallness of the preoperative TLV. Accumulating sufficient sample size needs to take long time due to the rareness of symptomatic PLD. Autosomal dominant polycystic kidney disease (ADPKD) reportedly affects up to 0.2% of the general population, 75% to 90% of which have associated PLD, while isolated PLD has less than 0.01% of the general population.[3,6,7] In addition, PLD is asymptomatic in 80% of affected individuals.[6] Furthermore, it has been reported that the more severe the renal dysfunction, the more likely to be symptomatic the PLD coexisting with ADPKD.[3,6] Therefore, most patients with symptomatic PLD usually consult their attending nephrologists at first.[3,6] Our institution does not have a nephrological division. This may be explainable for very small sample size and absence of severe renal dysfunction in this study population. On the other hand, the median preoperative TLV was 2530 mL in the present study while the median TLV before surgery reported from the Western Countries usually exceeded 5000 mL.[1,2,5,7] The smallness of TLV in the present study compared to the Western reports can be explained by the fact that the standard liver volume was reportedly larger in the Caucasian population than in the Japanese population for the same body size.[12,13] Furthermore, the body size is generally larger in the Western population than in the Japanese population. In addition, our study cohort did not include severe ADPKD cases, which can also explain the relative smallness, as well. We hope that the efficacy of our

technique will be verified in the Caucasian population and/or in patients with the ADPKD-associated PLD. In spite of these 2 limitations, we believe that our procedure will contribute to improve long-term treatment outcomes for patients with PLD. For the time being, hence, we will continue to perform this procedure based on the current strategy.

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