

ORIGINAL ARTICLE

Portal vein complications after adult-to-adult living donor liver transplantation

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Summary

Successful management of portal vein (PV) complications after liver transplantation is crucial to long-term success. Little information is available, however, regarding the incidence and treatment of PV complications after adult-to-adult living donor liver transplantation (LDLT). Between January 1996 and October 2006, 310 adult LDLTs were performed at our institution. PV thrombus was present in 54 patients at the time of LDLT. The incidence of PV complications, choice of therapeutic intervention, and outcomes were retrospectively analyzed. Among the 310 recipients, PV complications were identified in 28 (9%). Risk factors included smaller graft size, presence of PV thrombus at the time of LDLT, and use of jump or interposition cryo-preserved vein grafts for PV reconstruction. When divided into early (within 3 months, $n = 11$) and late (after 3 months, $n = 17$) complications, the use of vein grafts for PV reconstruction predisposed to the occurrence of late, but not early, PV complications. Portal vein thrombosis occurred more frequently in the early period (eight out of 11, 73%), whereas stenosis occurred more frequently in the later period (14 out of 17, 82%). Surgical interventions were favored in the earlier period, whereas interventional radiologic approaches were selected for later events. Overall 3- and 5-year survival rates were 81% and 77%, respectively, in patients with PV complications and 88% and 84%, respectively, in those without PV complications ($P = 0.21$, log-rank test). PV complications are a significant problem following LDLT with both early and late manifestations. Acceptable long-term results, however, are achievable with periodic ultrasonographic surveillance and timely conventional therapeutic interventions. The use of cryo-preserved vein grafts for reconstructing portal flow should be discouraged.

Introduction

Living donor liver transplantation (LDLT) was devised and established to compensate for the scarcity of donor organs available for deceased donor liver transplantation. The benefits also include improved timing of transplantation and improved graft quality. Various refinements in surgical technique over time have reduced the complications following transplantation. Cumulative experience has produced an equivalent or even improved outcome of

LDLT when compared with that of deceased donor liver transplantation for adult patients [1–3].

The technical difficulties in portal vein (PV) reconstruction as a result of shorter vessel pedicles and limited vessel graft length in LDLT are well recognized [4–7]. Many previous studies have reported the rate and management of PV complications after pediatric LDLT [8–10], but there are few published analyses of PV complications after adult-to-adult LDLT that are based on a large series.

Patients and methods

From January 1996 to October 2006, 310 LDLTs were performed in adults (137 men, 173 women; median age, 51 years) at the University of Tokyo Hospital. The indications for LDLT in these patients included hepatitis C virus cirrhosis ($n = 94$), primary biliary cirrhosis ($n = 63$), hepatitis B virus cirrhosis ($n = 48$), fulminant hepatic failure ($n = 29$), biliary atresia ($n = 18$), primary sclerosing cholangitis ($n = 11$), autoimmune hepatitis ($n = 11$), cryptogenic cirrhosis ($n = 9$), and others ($n = 27$). Model for end-stage liver disease (MELD) score ranged from 6 to 40 (mean, 18). The follow-up period after transplantation ranged from 1 to 138 months (mean, 43 months). Overall 3- and 5-year survival rates were 87% and 83%, respectively.

The selection algorithm and surgical technique for safe live donor surgery were previously described in detail [11–13]. Standard liver volume of the recipient was calculated using Urata's equation [14]. The donors were 180 men and 130 women (median age, 36 years). Their relation to the patients was child ($n = 134$), spouse ($n = 64$), sibling ($n = 55$), parent ($n = 35$), nephew ($n = 12$), or other ($n = 10$). The median duration of operation for the donors was 495 min (315–1760 min). The median blood loss volume was 450 g (90–2000 g). Four percent of the donors encountered complications, i.e., bile leakage, intra-abdominal abscess formation, requiring surgical interventions under general anesthesia. The median postoperative hospitalization was 14 days (5–56 days). The donors have all returned to their normal daily activity.

The immunosuppression regimen consisted of steroid induction followed by tacrolimus and steroid maintenance. Cyclosporine was used in case of tacrolimus intolerance [15,16].

Recipient operation

A total of 54 patients presented with portal vein thrombosis (PVT) at the time of transplantation, in whom the thrombus was removed by endovenectomy when possible [17]. Modalities for PV reconstruction were chosen according to the diameter, wall status, and length of the recipient's PV [18]. In brief, when there was no stenosis or vein thrombosis leading to reduced PV flow, direct PV anastomosis without a vein graft was performed using 6-0 monofilament. When the recipient PV branch was stenotic, the vein graft was mounted over the recipient PV, which was incised longitudinally. When the PV trunk was judged inappropriate to function as a conduit because of a narrow diameter or damaged intima, it was sacrificed and the portal conduit was anastomosed to the proximal PV of the recipient near

the confluence of the splenic and superior mesenteric veins (interposition). A venous jump graft from the superior mesenteric vein, as described previously by Tzakis *et al.* [19], but modified using cryo-preserved vein grafts, was indicated for significant PV and proximal superior mesenteric vein thrombosis. Cryo-preserved vein grafts were provided by the University of Tokyo Tissue Bank. The preservation and thawing methods were described previously [20].

Postoperative management and follow-up

Vascular flow in the graft or interposition vein patency was verified by Doppler ultrasonography (SSD 6500; Aloka, Tokyo, Japan) daily until the 14th postoperative day and once a week thereafter until discharge from the hospital [21]. Anticoagulant therapy after LDLT at our institution was described in detail previously [22,23]. To summarize, Dalteparin (25 IU/kg/day) was administered until postoperative day 2, and switched to heparin thereafter. The dose was adjusted according to the level of activated clotting time targeted between 130 and 160 s. Prostaglandin E1 and protease inhibitor were administered intravenously starting immediately after transplantation until the 14th postoperative day. After discharge, Doppler ultrasonography was performed to check the patency and velocities of the PV and hepatic artery flow approximately every 3 months at the outpatient clinic. Computed tomography with contrast was performed routinely at 1 and 3 months after LDLT, and once a year thereafter.

Definition of portal vein complications

Once anomalous flow was suspected by Doppler ultrasonography, multi-detector row computed tomography (MDCT) with contrast medium was performed and three-dimensional reconstruction images were obtained for further evaluation. Conventional angiography with portography was performed only when radiologic interventions were considered. Complications of the portal venous system in this study was defined based on morphologic findings by MDCT study as follows; extra-hepatic PV stenosis or obstruction accompanied by the presence of progressive collateral veins with splenomegaly and/or poststenotic dilation. PV complications found within 90 days after LDLT were defined as early complications and those found thereafter were defined as late complications. Of note, in case of significant radiologic presentations, those with an absence of apparent clinical symptoms, such as anomalous liver function tests or symptoms suggestive of portal hypertension, were also included.

Statistical analysis

Paired continuous data were evaluated by the Mann–Whitney *U*-test. Statistically significant differences between proportions for the two groups in a categorical data set were evaluated by Fisher's exact test or Chi-squared test when appropriate. Actuarial patient survival curves were generated by the Kaplan–Meier method and Log-rank test was carried out for the test of significance. A *P*-value of <0.05 was considered statistically significant. Calculations were performed using STATVIEW 5.0 computer software (SAS, Cary, NC, USA). Data shown are median with range.

Results

Overall PV complications after LDLT

Among the 310 adult-to-adult LDLT recipients, 28 patients (9%) experienced PV complications after trans-

plantation. Comparison of various clinical variables between those with PV complications and those without revealed that smaller graft size, presence of PV thrombus at the time of transplantation, and use of a jump- or interposed grafts for reconstruction were predisposing risk factors (Table 1). Factors such as age, gender, MELD score, ABO compatibility, warm and cold ischemia time, incidence of hepatic artery thrombosis (HAT), cytomegalovirus infection, and biliary complications did not significantly differ between the two groups in this series.

Early and late complications

In 11 patients, the diagnosis of PV complications was made within 90 days (median, 58 days; range, 1–68 days) following LDLT. None of the patients, except for two that had concomitant HAT, presented with elevated liver enzyme levels. Diagnosis was suspected based on direct visualization of the lesion by sonographic examination,

Table 1. Portal vein complications and clinical variables.

Variables	Presence of PV complications after LDLT		<i>P</i> -value
	Yes <i>n</i> = 28 (9%)	No <i>n</i> = 282 (91%)	
Age (years)	52 (19–64)	51 (18–67)	0.59
MELD score	19 (10–30)	18 (6–40)	0.56
ABO nonidentical	8 (29%)	63 (22%)	0.48
GW/SLV (%)	39 (34–61)	46 (22–88)	0.0009
CIT (min)	131 (12–394)	110 (11–250)	0.08
WIT (min)	61 (26–108)	66 (22–237)	0.25
Operation time (min)	970 (725–1990)	890 (640–2405)	0.01
EBL/kg	97 (27–741)	84 (12–961)	0.04
Follow-up period (days)	1212 (6–3573)	1315 (23–4149)	0.70
Graft types, LL/RL/RLSG/others	15/10/3/0	151/112/17/2	>0.9999
PVT* at transplant			
Y	12	42	0.0008
N	16	240	
Use of grafts†			
Y	11	24	0.0001
N	17	258	
HAT after LDLT			
Y	3	7	0.52
N	25	275	
CMV infection			
Y	13	124	0.80
N	14	158	
Biliary complications			
Y	12	99	0.41
N	16	183	

PV, portal vein; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; GW/SLV, graft weight divided by standard liver volume; CIT, cold ischemic time; WIT, warm ischemic time; EBL/kg, estimated blood loss per kilogram body weight of the recipient; LL, left liver graft; RL, right liver graft; RLSG, right lateral sector graft; PVT, portal vein thrombus; HAT, hepatic artery thrombosis; CMV, cytomegalovirus. Parenthesized figures suggest range unless otherwise depicted.

*Portal vein thrombus confirmed at the time liver transplantation.

†Use of either jump- or interposition grafts at the time of liver transplantation.

and all, except for a single case with complete obstruction because of kinking, presented with hepatopetal flow by Doppler ultrasound.

In the other 17 patients, PV complications were found after the first 3 months (median, 13 months; range, 4–96 months). Details of the complications in each group are shown in Figs 1 and 2. Liver enzymes following tests were not significantly elevated in most cases except in those complicated with recurrence of original liver diseases such as hepatitis C or primary sclerosing cholangitis. PVT occurred more frequently in the early period whereas PV stenosis was more prevalent in the later period.

Clinical variables between the two groups are shown and compared in Table 2. Use of either jump or interposition grafts at the time of LDLT was a significant risk factor for late-onset stenosis or obstruction, but not a risk factor for early complications such as thrombosis. The prevalence of PVT at the time of LDLT did not differ greatly between the two groups. Other surgical variables, such as graft size, duration of surgery, and amount of blood loss, did not differ significantly.

Intervention against PVC and outcomes

Among the 11 patients with PV complications in the early period, there were eight with PVT among whom two presented with concomitant HAT within 2 weeks following LDLT. One of these two patients died of graft failure

despite immediate surgical intervention. In the other patient, intervention attempts were abandoned because of the patient's unstable condition and the patient died shortly after the diagnosis. Two patients presented with stenosis, but observation with close follow-up was opted for because of the lack of clinical symptoms. To date, these two patients remain in good condition. In another patient, kinking of the PV caused a complete obstruction of the PV flow, and the patient underwent immediate surgical revision of the anastomosis. Among the six patients with PVT alone, systemic thrombolytic therapy was chosen for one patient with successful outcome, and aggressive surgical intervention was selected for the remaining five patients (Fig. 1). In summary, surgical intervention was selected for seven patients (six thrombectomy and one revision) with successful outcomes except in one case complicated with HAT.

The details of the treatment options identified for the 17 patients with late PV complications are shown in Fig. 2. For nine patients (53%), aggressive treatment was not chosen because of the lack of clinically significant symptoms ($n = 7$) or poor condition because of progression of the original disease ($n = 2$). Three patients with complete obstruction presented with either cavernous transformation or development of collaterals and currently remain asymptomatic. Fourteen patients presented with stenosis, among whom eight underwent aggressive treatment for clinically significant symptoms. Symptoms in these eight patients, such as gastrointestinal variceal bleeding including

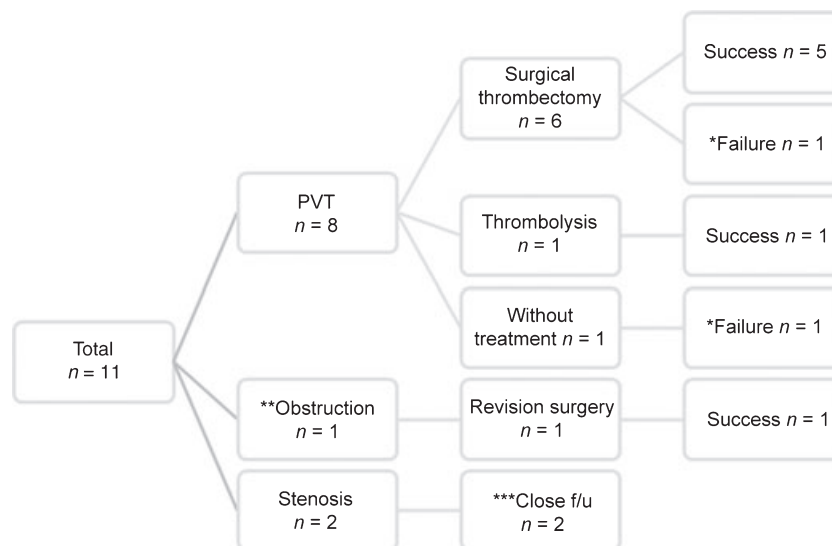


Figure 1 Early portal vein (PV) complications after adult-to-adult living donor liver transplantation. *Two patients with portal vein thrombosis (PVT) presented with concomitant occurrence of hepatic artery thrombosis (HAT). One patient died of graft failure despite surgical recanalization of the hepatic artery and portal vein. In the other patient, intervention attempts were abandoned because of unstable condition. The patient died shortly after the occurrence of concomitant HAT and PVT. **Complete obstruction because of kinking of the PV was surgically revised. ***Two patients presented with PV stenosis by radiologic studies, but remain completely asymptomatic. Both are currently under close surveillance.

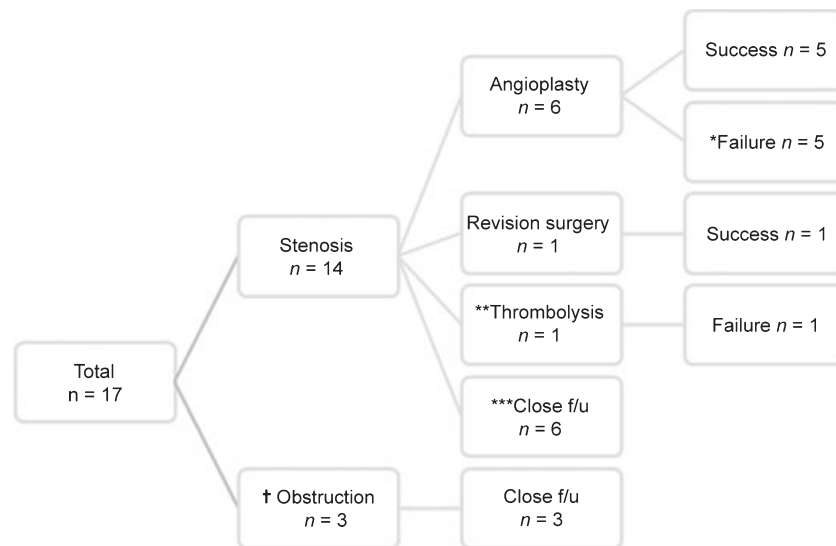


Figure 2 Late portal vein (PV) complications after adult-to-adult living donor liver transplantation. *Angioplasty was performed, but failed in one patient. Further intervention was postponed because of the patient being critically ill from a recurrence of hepatitis C. **Stenosis complicated with PV thrombosis. Systemic thrombolytic treatment was initially carried out but resulted in urinary tract bleeding and no further intervention was planned. ***No significant clinical symptoms were recognized and the patients are currently under close follow-up. †Complete obstruction of the main portal flow with the development of cavernous transformation was recognized. The patients remain asymptomatic and are currently under close follow-up.

esophageal or small bowel bleeding, formation of ascites, progressive pancytopenia, or hepatic coma, were typically because of portal hypertension. Angioplasty was performed using an interventional radiologic approach in six patients with successful outcomes except in one case. In the remaining six patients, four are currently under close follow-up because of the lack of apparent clinical symptoms. In one patient, stenosis was complicated with PV thrombus formation. Systemic thrombolytic treatment was initially performed but resulted in urinary tract bleeding and no further intervention was planned. Surgical revision was performed in one patient.

Survival rate of the patients with PV complications

Three patients died during the initial hospitalization following transplantation. The cause of death was concomitant HAT and PVT ($n = 2$, on the eighth and 10th postoperative day) and pneumonia ($n = 1$). Late death occurred in three patients. The cause of death was pneumonia ($n = 1$), heart failure ($n = 1$), and anaphylactic reaction to OKT3 ($n = 1$) administered for steroid-resistant acute cellular rejection. Overall 3- and 5-year survival rates of patients with PV complications were 81% and 77%, respectively, and in patients without PV complications they were 88% and 84%, respectively (Fig. 3). The differences in survival rates were not statistically significant ($P = 0.21$, log-rank test).

Discussion

Despite several reports on the incidence of PV complications after LDLT in the pediatric population [8–10,24], there are few reports of PV complications in a large adult-to-adult LDLT series. In this study, we described the overall incidence, therapeutic options chosen, and the immediate outcomes in our adult series. We also analyzed the background clinical variables to identify risk factors that may be involved in the occurrence of such complications between those with PV complications and those without PV complications, and also between those with early PV complications (within 3 months post-LDLT) and those with late PV complications (after 3 months post-LDLT).

When compared with the general population of LDLT recipients, smaller graft size, pre-existing PVT, and use of either jump- or interposition grafts for PV reconstruction were associated with a higher risk of PV complications. The transplantation surgery duration was longer and blood loss was moderately greater in cases with pre-existing PVT. Similar results have been reported previously [25]. Unlike in the case of deceased donor liver transplantation, native hepatic arteries, the PV, and the bile duct must be preserved as long as possible in the course of recipient hepatectomy in LDLT for anastomosis. This requires meticulous surgical maneuvering, which results in increased blood loss and procedure duration, especially

Table 2. Comparison between early and late PV complications.

Variables	PV complication after LDLT		P-value
	Early (n = 11)	Late (n = 17)	
Age (years)	53 (21–64)	50 (19–62)	0.32
MELD score	20 (15–27)	17 (10–30)	0.19
ABO nonidentical	18 (2%)	41 (7%)	0.25
GW/SLV (%)	38 (34–61)	40 (34–56)	0.92
CIT (min)	127 (20–235)	147 (12–394)	0.88
WIT (min)	58 (45–85)	65 (26–108)	0.43
Operation time (min)	935 (725–1485)	1082 (765–1990)	0.40
EBL/kg	82 (27–741)	108 (80–389)	0.10
Follow-up period (days)	441 (6–3573)	1356 (670–3393)	0.01
Graft types, LL/RL/RLSG	5/5/1	10/5/2	0.35
PVT* at transplant			
Y	4	8	0.70
N	7	9	
Use of grafts†			
Y	0	11	0.0009
N	11	6	
HAT after LDLT			
Y	2	1	0.54
N	9	16	
CMV infection			
Y	6	7	0.70
N	5	10	
Biliary complications			
Y	5	7	>0.9999
N	6	10	

PV, portal vein; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; GW/SLV, graft weight divided by standard liver volume; CIT, cold ischemic time; WIT, warm ischemic time; EBL/kg, estimated blood loss per kilogram body weight of the recipient; LL, left liver graft; RL, right liver graft; RLSG, right lateral sector graft; PVT, portal vein thrombus; HAT, hepatic artery thrombosis; CMV, cytomegalovirus.

Parenthesized figures suggest range unless otherwise depicted.

*Portal vein thrombus confirmed at the time liver transplantation.

†Use of either jump or interposition grafts at the time of liver transplantation.

when there are coexisting adhesions and collaterals with pre-existing PVT.

It is not clear how smaller graft size increases the likelihood of PV complications. Unlike the case in whole liver transplantation, engrafting a partial liver graft is followed by regeneration of the liver, resulting in gradual changes in the position and angles of vascular anastomosis. Regeneration itself, however, seems to be an insignificant factor, because regeneration of the graft is near optimal at 3 months after LDLT [26]. In fact, differences in graft size between patients with early PV complications and late PV complications were not statistically significant. Hence, this issue awaits future investigation.

Unlike the case of deceased donor liver transplantation in which longer graft vasculature can be obtained with additional fresh vein grafts [27], LDLT is subject to technical difficulties when an adequate PV length cannot be prepared. To solve this technical problem, we previously proposed the use of cryo-preserved vein grafts. We now

know, however, that using cryo-preserved vein grafts for PV reconstruction is a significant risk factor for subsequent complications [18]. The present findings share some similarities with those of previous reports regarding the use of cryo-preserved veins [8,28]. The rates of vein graft use differed significantly between early and late PV complications (Table 2). More specifically, reconstruction using vein grafts was sustainable over the short term, but was susceptible to complications in the long term (0% vs. 65%). This finding strongly suggests that the occurrence of PV complications following the use of cryo-preserved vein grafts is related to factors other than surgical technique alone, which requires further study. The use of cryo-preserved vein grafts should be avoided when reconstructing the PV, especially in cases in which jump- or interposition grafts are required. Perhaps the method described by Moon *et al.* [29], using the umbilical portion of the left PV is a useful alternative. In cases in which cryo-preserved vein grafts cannot be avoided, meticulous follow-up is recommended.

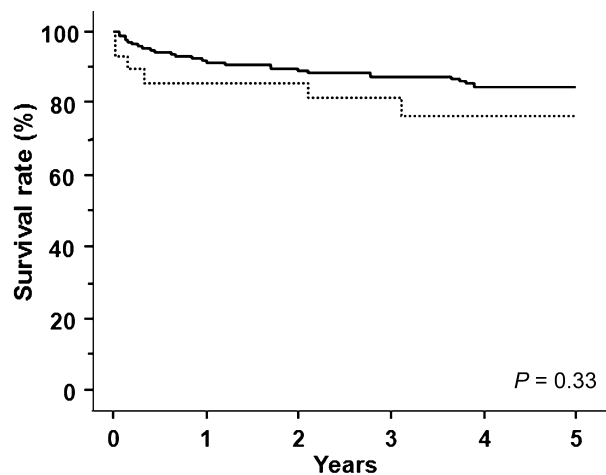


Figure 3 Portal vein (PV) complications and overall outcome after living donor liver transplantation. Overall 3- and 5-year survival rates of patients with PV complications (dotted line) were 81% and 77%, respectively, and in patients without PV complications (solid line) they were 88% and 84%, respectively.

Establishing an efficient surveillance protocol for detecting PV complications after LDLT is an important issue. Recently, significant technologic advancements in computed tomography image reconstruction techniques have been made [30]. MDCT with three-dimensional image reconstruction has become an indispensable tool for evaluating vascular complications in liver transplantation [31,32]. Digital subtraction angiography with portography is now performed only at the time of definite radiologic intervention at our institution. Routine application of MDCT study for screening is, however, unrealistic because of the high cost and impaired renal function in many adult LDLT recipients. At our institution, Doppler ultrasonographic study performed for the first few months remains the standard screening procedure for evaluating hepatic blood flow. This is the least-invasive and easily performed modality that can be accomplished in an out-patient setting. Despite its intrinsic operator-dependant nature [33,34], its usefulness in evaluating hepatic vasculature in surgical settings has been demonstrated [35–38]. Its usefulness for evaluating and managing various vascular complications following LDLT has also been recognized [39–42].

In this series, we defined PV complications by abnormal MDCT findings following screening by Doppler ultrasonographic surveillance. Although our study demonstrates that the use of cryo-preserved vein graft in PV reconstruction is a significant risk factor for late-onset complications, we were unable to recognize characteristic radiologic findings. Identification of such findings is clinically important, but remains a future challenge. Once a

PV complication is diagnosed, a decision must be made as to whether immediate intervention is required, or whether close follow-up is preferable because of the lack of substantial clinical symptoms. Presentation of symptoms related to portal hypertension was a definite sign requiring intervention during the later period after LDLT, whereas a more aggressive treatment was chosen based on the detection of thrombus formation alone in the earlier period. Various modalities, including thrombolytic treatment, ballooning, and stenting, have been reported with satisfactory outcomes [43–45]. We favor a surgical approach for early PV complications and an interventional radiologic approach for late PV complications. The outcomes of the current series suggest that our surveillance and treatment approach is acceptable with overall good long-term survival rates that are comparable between patients both with and without PV complications.

Authorship

YK, ST, YS, YM, JT JK, NK, MM: acquisition of data. YK, ST: analysis and interpretation of data, drafting of the manuscript. ST, YS: critical revision of the manuscript for important intellectual content. YS, MM: funding obtained, study supervision. ST, YS, MM: administrative, technical and material support.

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