Review

Current management of portal vein thrombosis in liver transplantation

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ABSTRACT

Nontumoral portal vein thrombosis (PVT) is present at liver transplantation (LT) in 5%–26% of cirrhotic patients [1]. Up to 31% of patients who are found to have PVT at the time of LT, would have had PVT at the time of initial listing, but others develop PVT during the waiting period. Adequate screening and treatment of the PVT on the waiting list for LT is thus essential so that a portoportal anastomoses can be performed at the time of LT. Early PVT (Yerdel Grade I/II) can be usually managed by thrombectomy, whereas Grade III PVT may require a jump graft from the superior mesenteric vein to the graft PV. Complete portomesenteric thrombosis is a huge challenge, and sometimes a cause for denying a LT in these patients, with multivisceral transplant being the only alternative. The presence of spontaneous, or previously surgically created portosystemic shunts like the leinorenal shunt, may serve as a good inflow option (renoportal anastomosis) in these patients to establish a physiological reconstruction. Although challenging, good outcomes are possible in patients with complex PVT if the appropriate surgical technique is chosen to ensure portal inflow and resolution of PHT post LT.

1. Management of portal vein thrombosis on waiting list

PVT can be present at the time of listing for LT, or may arise de-novo on the wait-list. Montenegro et al. [9] analyzed an OPTN dataset of worldwide, given the inferior outcomes.

Adequate portal inflow to the graft is the key factor that determines graft and patient survival after LT [6]. In addition to this, the new liver should also be able to alleviate the pre existing portal hypertension in the recipient, and for this a physiological re-direction of splanchnic blood into the new liver (graft) is essential [7]. This is sometimes not always possible in diffuse PVT, thus giving rise to problems of bleeding, mesenteric congestion and bowel ischemia after LT. This aspect has been recently addressed while proposing a novel classification to guide surgical-decision making during LT [8].

In this update, we have tried to address some of the key issues faced by liver transplant teams when managing patients with PVT; management of these patients on the waiting list for LT, intraoperative management strategies, and short and long-term outcomes post LT.

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134,109 adult patients listed for primary LT between January 2002 and June 2014. Of these, 61,557 patients did not have PVT at listing, and most (57,945) remained without PVT till the time of transplant. On the other hand, 1708 patients were listed with PVT and had PVT at the time of transplant. 3612 patients developed PVT while on the wait-list. Hence, a considerable number of patients who do not have PVT at listing, develop PVT in the waiting period.

Predictors of development of PVT on the wait list include: length of waiting time, age, prior abdominal surgery, hepatocellular carcinoma (HCC), ascites, history of variceal bleeding, non-alcoholic steatohepatitis (NASH), obesity and diabetes mellitus [4,9,10]. Once PVT has been diagnosed and classified according to previous [5,11–17], and novel classifications [8,18], the root question is whether anticoagulation should be instituted in these patients, and if yes, in what doses.

### 1.1. Why to treat?

A spontaneous recanalization of the portal vein during the waiting period is a rare event, while progression of the extent of PVT is an unfortunate reality, occurring in 8.8%–71.4% of patients [4,9]. Montenovo et al. [9] observed that patients with PVT at listing were more likely to be removed from the wait list as a consequence of progression of PVT, thus making them too sick for transplant, compared to those without PVT at listing. Surprisingly, contrary to the above, other Scientific Registry of Transplant Recipients (SRTR) and OPTN data, as well as data from a large single center study showed that the presence of PVT did not increase the risk of wait-list mortality [19,20].

Similarly, variable results have been published with respect to impact of PVT on post operative outcomes. A large series shown that preexisting PVT could represent an independent risk factor for 90-day mortality, and graft failure post LT [4].

Since spontaneous recanalization of PVT is rare and the consequences of PVT progression before and after LT may be fatal, PVT should be probably treated during the waiting period.

### 1.2. How to treat?

At the present, two different options for treatment of PVT are available: anticoagulation and transjugular intrahepatic portosystemic shunt (TIPS).

#### 1.3. 1-Anticoagulation

There is accumulating evidence that cirrhotic individuals with PVT on the waiting list for LT should be treated with anticoagulation therapy [21].

Delay between PVT diagnosis and initiation of anticoagulation seems to be the most important factor predicting recanalization. Indeed, while an interval of <6 months is associated with a higher recanalization rate, withdrawal of anticoagulation is associated with recurrence in up to 38% of patients [19]. Consequently, these studies strongly argue in favor of early initiation, and continuation of anticoagulation [19,21], although the ideal length of anticoagulation is not known.

The choice of the anticoagulation regimen needs to take into account the potential need to reverse the effect of anticoagulation: this can become necessary in cases of acute bleeding, and in all cases undergoing surgery or LT [21]. Therefore, if the decision of initiating anticoagulation is taken, it is wise to recommend screening for varices by endoscopy, and initiation of standard primary or secondary prophylaxis of variceal bleeding before starting treatment [19].

Chen et al. reviewed 10 studies evaluating the safety and efficacy of anticoagulation for PVT in liver cirrhosis [19]. Most of them were retrospective, had small sample sizes and majority of the patients had partial non-occlusive PVT. In total, 295 patients had been included and treated with different anticoagulation strategies. In 210 (71.2%) patients, improvement in PVT after anticoagulation was observed (complete recanalization in 44%, and partial in the remaining 56%). The reported improvement ranged between 42% and 100% in the different studies [19].

Following anticoagulant drugs have been used in context of PVT, but at the moment there is no consensus regarding the superiority of one over the other:

- Low-molecular-weight heparin (LMWH): LMWH has the advantage of a fixed dose that does not require laboratory monitoring, and it does not affect INR values. However, the inconvenience of daily subcutaneous injections may reduce compliance. LMWH is mainly eliminated by the kidney, so patients with decreased renal function may need dose adjustments
- Vitamin K antagonists (VKAs): VKAs are still the choice for long term anticoagulation with the limitation of regular monitoring of INR. It should be remembered that anticoagulant induced increase in INR tend to overestimate the Model for End-Stage Liver Disease (MELD) scores
- Direct oral anticoagulants (DOACs): DOACS have been recently approved for clinical use in indications different from PVT (i.e., dabigatran, rivaroxaban, and apixaban). DOACs may offer the theoretical advantage of no need for laboratory monitoring. However, the experience with DOACs in patients with cirrhosis is very limited, and until more studies are available, they cannot be recommended for patients with cirrhosis

#### 1.4. Transjugular Intrahepatic Portosystemic Shunt (TIPS)

PVT has been considered for a long time to be a contraindication for TIPS, but increased expertise and improvement in radiological techniques have completely changed this concept. TIPS can be successfully placed in 75%–100% of patients with cirrhosis and Grade I-II PVT [22–24]. The feasibility of this procedure is reduced in patients with portal cavernosa, or when imaging studies are unable to detect patent intrahepatic PV branches.

When TIPS is successfully placed, portal recanalization can be achieved in up to 80% of the patients, and this seems to happen without the need of anticoagulation.

However, patients with significant hepatic dysfunction (e.g., high MELD, total bilirubin > 4 mg/dL, preexisting hepatic encephalopathy) might not be candidates for TIPS due to risk for decompensation, or symptom exacerbation [25].

In summary, since PVT influences the transplantability of the patients and probably the outcome of LT, it should probably be treated by means of anticoagulation and eventually TIPS in patients who need to wait long on the list before LT.

### 2. Intraoperative management of PVT during LT

Intraoperative management of portal vein thrombosis (IOMPVT) is a major challenge for the liver transplant surgeon, not only requiring experience and skill on his part, but also very demanding for the entire team including the anesthesiologists, given the high chances of bleeding and haemodynamic changes during LT.

A transplant surgeon is usually faced with PVT in two settings:

i) the unplanned scenario, where PVT is detected for the first time during the LT, ii) planned scenario, when pre operative scans are available that have detected the presence of, and characterized the extent of the thrombus.

The former scenario is challenging, and sometimes even fatal for the recipient, seldom during surgery (due to non availability of any inflow for the graft or massive bleeding), but more often as a result of re-thrombosis or bleeding after LT. A complete radiological assessment is thus mandatory in every transplant candidate before LT, with liver Doppler and contrast enhanced CT scan or MR angiography.

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The IOMPVT further depends on the extent/grade of PVT. The Yerdel classification [5] which defines the extent of PVT in the PV and superior mesenteric vein, is probably the most suited for the Surgeon to decide on the method of thrombectomy, and establishment of portal inflow for the new graft. The Yerdel’s classification however may be sub optimal in grading diffuse (Grade IV) PVT, as specific aspects like degree of thrombosis of the splenic vein (complete vs. partial), presence of significant portosystemic shunts (like lienorenal shunt, or varices like left gastric vein or pericholedochal) which may serve as inflow to the new graft (renoporal anastomoses, or varico-portal anastomoses) are not defined in this classification. The Jamieson [14] and Charco [15] classification systems aim to denote the extent of thrombosis along the portal system, and also refers to the existence of large portosystemic collaterals, which may help define the surgical strategy during LT. In both classification systems, grade 3 is defined as diffuse thrombosis of the splanchnic venous system with large accessible collaterals, whereas grade 4 includes extensive thrombosis of the splanchnic venous system with only fine collaterals.

The goal during LT should be to try and establish a physiological inflow of splanchnic blood into the graft [7,8]. This is usually possible in Grade I-III Yerdel, using eversion thrombectomy, thrombo-endoovenectomy, or jump grafts from the recipient PV or SMV to the graft PV. However, in some patients with Grade IV Yerdel PVT, a non-physiological inflow becomes a necessity in order to keep the liver “alive”. It is generally accepted that the latter is associated with higher post operative morbidity and mortality [7].

In living donor liver transplantation (LDLT), IOMPVT is even more complicated due to a very short length of donor portal vein, thus frequently requiring additional vein grafts (autologous veins, cryopreserved vein grafts or cadaveric vessels) to establish continuity. Thus, in many centers worldwide, complex PVT (Yerdel type III and IV) are contraindications for LDLT. High volume centers with large expertise in LDLT especially in Japan, Turkey, Korea, China and India, however, do selectively accept these patients for LDLT [26–28].

3. Tips for IOMPVT: Physiological and non-physiological reconstruction

We would urge the reader to refer to Fig. 5 in the recent publication by Bhangui et al. [8] wherein they have proposed an algorithm for the management of non-malignant portal vein thrombosis in the setting of liver transplantation.

- Grade I and II – Most of those cases are manageable by eversion thrombectomy or resection of the affected part of the portal vein with the thrombus (thromboendoovenectomy) [29–32] (Figs. 1 and 2).

A complete exposure of the entire length of the portal vein up to the spleno-mesenteric junction is essential to guarantee a complete thrombectomy, and ensure a good portal flow.

- Grade III PVT - For thrombi that extend beyond the spleno-mesenteric junction, achieving complete thrombectomy is more demanding, and may not be possible, and safe to do. The better option is to use a jump graft from the superior mesenteric vein (or one of its tributaries. Other splanchnic veins including the left gastric, or splenic may be used for inflow, however, it should be borne in mind, that varices in general have very thin walls and are sometimes difficult to handle during anastomoses.

For a jump graft from the SMV, a mesenteric approach to reach, and expose the SMV is crucial. A Satinsky clamp should be placed over the SMV in order to anastomose the distal part of the venous conduit end-to-side to the SMV, whose proximal end should match well with the graft portal vein. The conduit is then passed through the mesocolon, and placed in an ideal position which would prevent compression or kinking (Fig. 3).

- In an unplanned setting, where PVT is incidentally detected during LT, a detailed intraoperative Doppler ultrasound assessment to evaluate the extent of the PVT, and patency of SMV and splenic vein
is crucial. Complete exposure of portal vein and palpation for the consistency of the thrombus is very important because an acute (fresh) thrombus can be managed easily in most instances, as opposed to a calcified chronic thrombus. Caution has to be exercised when trying to do a thrombectomy in a hard calcified thrombus, as there is a risk of major, uncontrolled bleeding during thrombectomy with major tears in vein walls. Thrombus extension behind the pancreas may require a full Kocher maneuver and isolation of the pancreas (Fig. 4).

- Grade IV–A detailed pre operative evaluation (imaging) is fundamental in order to map out the splanchnic circulation, especially patency of the splenic vein, and more so the presence or absence of a spontaneous or previously surgically created spleno-renal shunt (SRS). The primary goal should be to achieve physiological inflow and drainage (ideally complete, or at least partial physiologic inflow) which would optimize graft function.

  # In the presence of a pre-existing SRS, a renportal anastomoses is the preferred physiological inflow option (Fig. 5). It has the benefit of preserving the retro-hepatic inferior vena cava (IVC), providing portal inflow to the graft, and matching both PV size and flow [33]. Other options, include use of a large gastric vein or pericoledochal varix for portal inflow to the graft. In the presence of a mesocaval shunt that cannot be dismantled, a cavoportal anastomosis can sometimes represent a physiological reconstruction [8].

  # In more complex scenarios, where pre-existing shunts are absent, a combined liver and multi-visceral transplant (MVT) would probably be the best option for physiological reconstruction, especially in Grade 4 (Yerdel) PVT [34,35]. However, the high risk of complications following MVT has prevented widespread use of this technique.

  # In the absence of a clear spontaneous splenorenal shunt, one option is to surgically create a distal spleno-renal shunt (Warren shunt) and then a reno-portal transposition in order to provide a mix of physiological and non-physiological inflow to the liver graft.

  # Non-physiological reconstruction of the portal flow may be divided into three main categories: (a) reno-portal anastomosis (RPA) in absence of spleno-renal shunts (b) cavo-portal anastomosis (CPA) (which includes cavoportal transposition (CPT) and cavoportal hemitransposition (CPHT)), and (c) portal vein arterIALIZATION [33,36,37]. With RPA, there is a risk of persistent portal hypertension, and reduced flow to the graft in this setting. In 1998, Tzakis reported a new approach performing a cavo-portal hemitransposition (CPHT) in order to provide a venous non-physiological inflow to the graft [36]. This approach still very controversial with non optimal outcomes worldwide, the major issue being persistent portal hypertension after the LT, and consequences of inadequate drainage of splanchnic circulation.

4. Short- and long-term outcomes post LT (Table 1)

Pre-existing PVT may be associated with up to 50% increase in 1-year mortality post LT [1]. Peri-operative outcomes are influenced by the extent of PVT, and intra-operative surgical management. When an end-to-end porto-portal anastomosis can be performed, the results are similar to those in patients without PVT, and 1 and 5-year survival ranges from 84% to 86%, and 65%-80%, respectively [1]. A recent meta-analysis showed that the 30-day mortality after LT was higher in patients with PVT (13%) vs. those without PVT (7%) (OR 2.29; 95% CI 1.43–3.68; P < 0.0001); further, 30-day mortality was higher in those with occlusive (complete) vs. partial PVT (OR 5.65; 95% CI 2–15.96; P = 0.001)38. If not an end-to-end porto-portal anastomosis, at least being able to achieve a physiological inflow to the liver (as detailed above) seems to be the key factor impacting post-operative outcome. A non-physiological reconstruction has been shown to be associated with a significantly higher risk of portal vein re-thrombosis, gastrointestinal bleeding and small bowel obstruction [7]. Utilizing pre-existing porto-systemic shunts, either directly, or using interposition grafts are sometimes the only options to achieve physiological inflow in Grade IV (Yerdel) PVT [8,39]. A recent review showed that PV anastomosis using pre-existing shunts is associated with a post-operative mortality of 16%, and a 5-year survival of 81%. Acute kidney injury represented the most frequent complication in this setting, with an incidence of 20%, while re-thrombosis occurred in 6% of the analyzed population [18]. In patients with no pre-existing shunts MVT is the only option for physiological inflow. Vianna et al. [35] have published the largest series of MVT (25 cases), reporting an incidence of surgical complications of 56%, and post-operative mortality of 28% over a 1–22 month period. Overall, patient and graft survival were reported to be of 80%, 72%, and 72% at 1, 3, and 5 years, respectively.

Among non-physiological reconstruction techniques, early post-operative mortality risk with RPA and CPA is around 25%, with poor 1- and 5-year survival outcome, 60% and 38%, respectively [1]. In a large French series of patients affected by diffuse PVT, 4 cases of RPA in absence of shunts were reported. One patient was reported to be alive and with patent RPA and good liver function at 9 years from LT. Two patients died due to sepsis at 3 months and 3 years after LT, respectively, while 1 patient died at 4 years due to myocardial infarction [33]. RPA may be preferred over CPA in presence of diffuse PVT due to the reduced complications related to IVC patency. CPA is complicated by
high post-operative morbidity. In particular, it cannot solve the problem of mesenteric hypertension and 30–50% of patients have been reported to develop intra-abdominal bleeding and ascites after this procedure. Scarce long-term data is available, and in the largest published series, 15% of patients died during the postoperative period, while 63% were alive at last follow-up. Lerut et al. [40] reported a modified CPA technique, where caval continuity was maintained using a latero-lateral cavo-caval and end-to-side cavo-porto anastomoses, separated only by a double vascular stapler line. This technique may allow the splanchnic blood to be completely diverted towards the alograft and eliminate the low flow in IVC, which would otherwise lead to complications. However, using this technique also, the immediate post operative and long term outcomes were sub optimal. Finally, portal vein arteriulation can be used to either augment portal vein flow, or to completely replace it. Scarce data is available in literature, with only fourteen cases reported till date [8,41].

Re-thrombosis is a potential complication in this setting, and while early re-thrombosis requires emergency re-LT, little data is available on the rate of delayed re-thrombosis. The rate of re-thrombosis in patients with an end-to-end portal anastomosis is less than 5%, therefore a short course of fractionated heparin may be recommended to reduce the risk of early re-thrombosis, while long-term anticoagulation should be recommended in those patients that receive a non physiological restoration of the portal flow [1].

5. Conclusion

In conclusion, although challenging, good outcomes are possible in patients with complex PVT if the appropriate surgical technique is chosen to ensure portal inflow and resolution of PHT, based on extent of the PVT and presence or absence of spontaneous or previously surgically created portosystemic shunts.

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Declaration Conflict of interest

No Conflicts of Interest.

Appendix A. Supplementary data

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References


G. Han, X. Qi, C. He, Z. Yin, J. Wang, J. Xia, et al., Trans- jugular intrahepatic portosystemic shunt for portal vein thrombosis with symptomatic portal hypertension in liver cirrhosis, J. Hepatol. 54 (2011) 78–88.


