Surg. Gastroenterol. Oncol. 2021;26(1):14-18 DOI: 10.21614/sgo-26-319

Domino Liver Transplantation: Current Status

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ABSTRACT

Domino Liver transplant (DLT) is a strategy to address organ shortage and expand the liver donor pool for liver transplantation. Despite offering some unique technical challenges, DLT appears to be a safe and reasonable option to be considered for selected patients who would otherwise not benefit from liver transplantation. However, the benefit of expanding the donor pool must be balanced against the risk of disease transmission.In this review, we present where the DLT currently stands worldwide and our own experience with this procedure.
Key words: liver transplantation, domino liver transplantation, familial amyloidotic polyneuropathy, de novo amyloid polyneuropathy

INTRODUCTION

Orthotopic Liver transplantation (OLT) is an important therapeutic option for patients in a variety of acute and chronic liver diseases. However, the number of organs available for transplant is not enough to supply the demands of the ever increasing waiting list (1,2,3). Domino Liver transplant (DLT) is a strategy to address organ shortage and expand the liver donor pool for liver transplantation (4,5).

This technique was first performed in 1994, in Portugal and allows the explanted liver from one patient to be used in another patient (6,7). The rationale behind this is that some metabolic disorders which can be corrected by liver transplantation leave a structurally normal and well-functioning liver that can be used in another patient (8,9,10).

Familial amyloid polyneuropathy

Received: 05.01.2021
Accepted: 07.03.2021

Familial amyloid polyneuropathy (FAP) is an autosomal-dominant hereditary systemic disease that leads to progressive sensory-motor polyneuropathy (11,12).

Transthyretin (TTR) protein is primarily synthesized in the liver and mutations in TTR gene leads to the formation, aggregation and accumulation of insoluble amyloid fibrils in other organs. To date, over 120

TTR mutation have been described, the most common being the Val30Met mutation (13,14). The deposition of amyloid fibrils leads to progressive loss of superficial sensation, severe autonomic dysfunctions, and cardiac conduction disturbances (15,16).

Since over 90% of TTR Met 30 is produced within the liver, LT will halt disease progression and clinical manifestations (17,18,19).

FAP livers have a normal anatomy and show no abnormal function other than producing variant TTR. FAP patients are usually young, which in combination with a short cold ischemia time, allows excellent conditions for the liver to be used as a graft (10,20).

Medical treatment of patients with TTR mutation-FAP involves disease-modifying targeted therapy to prevent further production of amyloid deposits (21,22). Tafamidis, the most commonly used drug, kinetically stabilizes mutant TTR tetramers and prevents their dissociation into monomers. However, although there is evidence for its effectiveness in delaying neurological impairment, Tafamidis does not seem to halt the progression of FAP entirely. Therefore,liver transplantation (LT) remains a valid treatment option for many patients (15,23,24).

Domino liver recipients

Indications for DLT vary between countries and must take into account factors including age, potential hazards, probability of recurrence, prognosis and priorities in the transplant waiting lists. Many centers select older and more marginal transplant candidates for DLT (25). By December 31, 2017, a total of 1254 domino transplantations were registered in FAP World Transplant Registry. Mean domino recipient age was 55.7 ± 10.2 years, with a median of 57.1 years. Main indications for the DLT recipients included: primary hepatic malignancy (41.4%), alcoholic cirrhosis (19%), cirrhosis secondary to hepatitis B and/or C (17%), metastatic hepatic malignancy (2.3%) and retransplantation (5.3%). (http://www.fapwtr.org)

It is important that the domino recipient is aware of the possibility of developing "de novo" FAP disease. Patients must be assured that, if necessary, they will have the opportunity to receive a cadaveric graft after wards (26,27).

Operative/technical considerations in domino liver transplantation

Classic DLT involves resection of the inferior vena cava (IVC) in the FAP patient, which requires venovenous bypass, because FAP patients are particularly sensitive to hemodynamic changes after caval clamping. In Lisbon, Pena and Barroso developed the 'Double Piggy-back' technique, that allows preservation of the donor´s IVC without the need of caval clamping or bypass. This technique was first performed by our group in 2001 (28).

The fundamental rule in total hepatectomy in the PAF patient is to avoid unnecessary mobilizations that may contribute to small periods of warm ischemia. The hilum is minimally dissected, and the common bile duct is divided at its mid length. Cholecystectomy is also performed. Then, the liver is mobilized and freed from the IVC. Accessory hepatic veins greater than 5 mm in diameter are preserved if clamping results in congestion of part of the liver. The right hepatic vein (RHV) and the cuff of middle (MHV) and left hepatic (LHV) veins are isolated. After dissection, the proper hepatic artery is divided at the bifurcation of gastroduodenal and common hepatic arteries, and the portal vein is divided 1cm below its bifurcation. The RHV is transected close to the liver parenchyma using a vascular stapler. The isolated M-LHV cuff is double clamped and hepatic veins are then divided close to the liver surface, completing total hepatectomy. The explanted liver is then perfused with preservation solution through the portal vein and the hepatic artery after opening the RHV stapler line (28,29).

The "Double Piggy-back" technique offers unique technical challenges, since vessels are shared between the donor and the FAP graft. To overcome the problem of short vascular stumps, many techniques of outflow reconstruction of the domino graft have been reported. Graft options to create a "neo" suprahepatic IVC include the use of a cadaveric IVC with or without renal vein, iliac veins, and pulmonary artery, among others. The reconstruction will allow the surgeon to perform the domino liver transplant in a standard piggyback fashion (30,31,32) (*fig. 1*).

Long-term results after domino liver transplantation

DLT is not associated with a higher morbidity or mortality rate in the donor. However, the recipient carries the risk of developing "de novo" FAP disease (33,34).

Early in the development of the technique and according to the natural history of FAP disease, it was assumed that the development of the disease would only become clinically apparent 25 or 30 years after DLT. However, there were concerns about the impact of

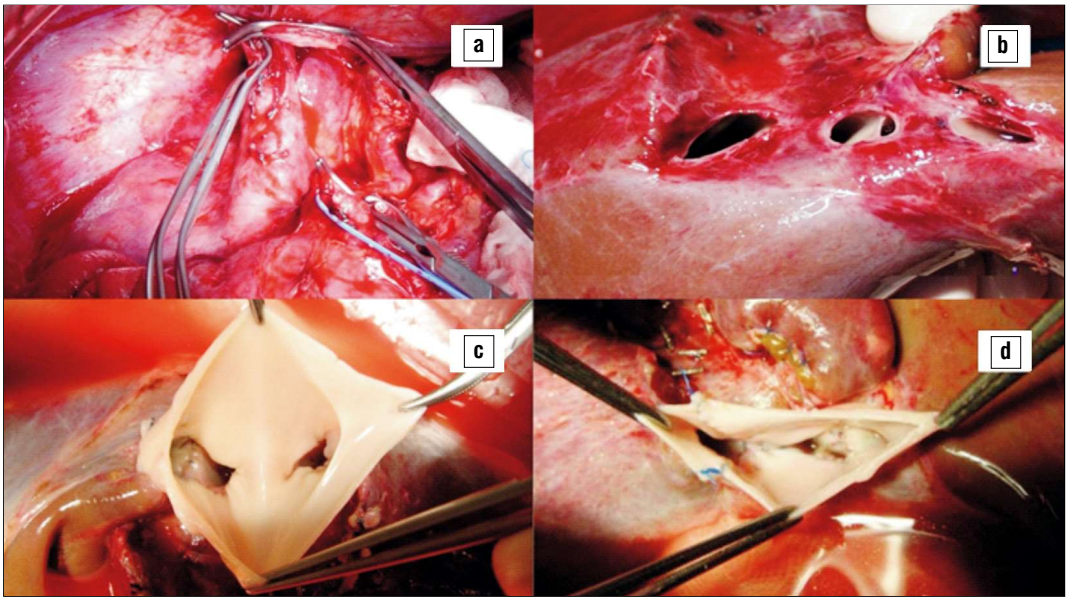

Figure 1 - a: Abdominal cavity after hepatectomy in a FAP liver donor; b: Orifices of the hepatic veins; c,d: "neo" suprahepatic inferior vena cava

the recipient's age and post-transplant immunosuppression on the underlying biological mechanisms and their possible contribution to the earlier development of symptoms in DLT recipient (34,35). Indeed, several subsequent papers described the development of acquired FAP earlier than previously anticipated (26,28,36). In one study from France, 4 of the 91 patients (4.5%) who underwent a DLT with a FAP liver developed "de novo" amyloid polyneuropathy proven by nerve biopsy after a mean delay of 5.75 years (37). A Spanish study describes "de novo" amyloidosis appearing 6-8 years after DLT in 4 out of 31 patients (12.9%). One study from Portugal by our own group, reports that 13 of the 114 patients (11.4%) submitted to DLT developed "de novo" amyloidosis with a median elapsed time until the appearance of clinical features of 75 months (60–121 months) (28,38).

Domino recipients should be maintained on lifelong follow-up and consideration of standardized screening protocols for acquired amyloid in DLT recipients are warranted to develop a management strategy for "de novo" amyloid polyneuropathy (39). Once iatrogenic amyloid neuropathy and systemic amyloidosis are diagnosed, treatment options are limited and retransplantation with a non-domino liver should be considered. However, retransplantation is considered to be a high-risk procedure, due to the comorbidities of patients and the surgical challenges in an already transplanted patient (26,36,40).

While the risks of DLT are unique, several studies suggest that they do not contribute to an elevated mortality rate as compared to receiving organs from deceased donors. In the Domino Liver World Transplant Register, the overall 1-year, 5-year, and 8-year graft survival in DLT recipients was 79.9%, 65.3%, and 61.6%, respectively. Also, several studies found no difference in the rates of acute rejection, perioperative bleeding, vascular complications or biliary complications between domino transplant recipients and cadaveric transplant recipients (8,41,42,43).

Experience with DLT at Curry Cabral Hospital, Portugal

From July 2001 to October 2020, 337 patients underwent a DLT with a FAP liver in our center. The population was composed of 271 men (80.3%) and 66 women (19.7%) with a median age at the time of LT of 57 years. Main indications for the DLT recipients are described in *table 1*. After a median follow-up of 108

Table 1 - Demographic characteristics and indications for liver transplantation in FAP liver recipients

	FAP liver recipients (n=337)
Demographic characteristics	
Female sex, n (%)	66 (19.7%)
Age (years), median [IQR]	57 [10]
Main indications for liver transplantation, n (%)	
Primary hepatic malignancy	147 (43.6%)
Alcoholic cirrhosis	81 (24%)
Cirrhosis secondary to hepatitis B and/or C	53 (15.7%)
Metastatic hepatic malignancy	6 (1.8%)
Retransplantation	15 (4.5%)

Table 2 - Evaluation and monitoring of "de novo" amyloidosis after domino liver transplantation

	FAP liver recipients (n=337)
Clinical signs of acquired FAP	
Neuropathic pain, lack of sensibility, n (%)	85 (25.2%)
Diarrhea, n (%)	19 (5.6%)
Weight loss, n (%)	14 (4.2%)
Time until the appearance of clinical features (months), median [IQR]	108 [40]
Electromyographic evidence of polyneuropathy, n (%)	62 (18.4%)
Demonstration of amyloid deposits in a tissue biopsy, n (%)	55 (16.3%)

months (35–163 months), 85 patients (25.2%) developed clinical signs of FAP disease, most commonly neuropathic pain, lack of sensibility, diarrhea or weight loss. 62 (18.4%) had disease confirmation after repeated neurological assessment and electro-myography. Amyloid deposition was demonstrated in 55 patients either by labial salivary gland, sural nerve, rectal, renal or fat biopsy (*table 2*). 20 of these patients with acquired FAP underwent retransplantation with a cadaveric donor liver. Although in 3 patients the symptoms worsened, 9 of the 20 patients (45%) reported some improvement.

CONCLUSION

In the light of current knowledge, DLT remains a good option in carefully selected patients. Given the known risk of FAP disease transmission, the selection of DLT recipients must consider the status of the patient 7-8 years after transplantation, if a retransplant is necessary. Since acquired polyneuropathy occurs earlier than anticipated, DLT could be considered for extended indications and according to the feasibility of a retransplant.

Conflicts of interest: none

Ethics of approval: none

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