

Liver Transplantation is Never... Just Liver Transplantation

İlgin Özden

Başakşehir Çam and Sakura City Hospital, Liver Transplantation and Hepatopancreatobiliary Surgery Unit, İstanbul, Turkey

ABSTRACT

Liver transplantation is a unique operation that has not only saved tens of thousands of lives directly, but has also led to dramatic developments in multiple fields of medicine other than surgery.

Keywords: Liver transplantation, cadaveric, living donor, gene therapy, hepatocyte transplantation

Introduction

Liver transplantation (LTx) is indicated for only a small fraction of patients with liver disease. However, this operation has had tremendous direct and indirect effects on not only surgery, but all fields of medicine—hence the title of this paper. Some of its most striking aspects are outlined here, based on the published literature and the author's personal experience at the İstanbul Faculty of Medicine and Çam and Sakura City Hospital.

1- Standard Treatment of End-stage Liver Disease and Acute Liver Failure (ALF) That Does Not Respond to Intensive Care Treatment

LTx is the only definitive treatment for end-stage liver disease and ALF that does not respond to intensive care treatment (1,2,3).

Although the first consistently successful transplants were performed from 1967 onwards (1), the most decisive event was the adoption of LTx as standard treatment by the American National Institutes of Health in

1983 (4). At the time, the 1-month mortality of the recipients varied between 20% and 40% (4). As Starzl (1) noted, *"In 1989, only six years later, a 17-page article divided between the October 12 and October 19 issues of the New England Journal of Medicine began with the following statement: The conceptual appeal of LTx is so great that the procedure may come to mind as a last resort for virtually every patient with lethal hepatic disease"*.

The current 1-year patient survival figures vary between 85% and 94% (5). In the published literature, the longest survivor underwent LTx for biliary atresia (BA) as a small child and is alive at 42.7 years posttransplant (1). The program at the İstanbul Faculty of Medicine was established by Koray Acarlı in 1991; some of the patients who received transplants in 1992 are leading active lives as of 2021, corresponding to 29 years of survival. Approximately 35,000 liver transplants were performed around the world in 2018 (6). Centers of excellence have reported large series with near-zero hospital mortality and >95% 1-year survival (7,8).

Address for Correspondence: İlgin Özden Prof. MD, Başakşehir Çam and Sakura City Hospital, Liver Transplantation and Hepatopancreatobiliary Surgery Unit, İstanbul, Turkey

Phone: +90 532 415 08 87 **E-mail:** iozden@hotmail.com **ORCID ID:** orcid.org/0000-0001-7360-628X

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2- An Indelible Understanding of Acute Liver Failure

ALF is a life-threatening condition defined by the acute onset of jaundice, coagulopathy and encephalopathy in a patient with no previous liver disease. LTx is the only hope of survival in patients who do not respond to intensive care treatment (2,3). Although prognostic criteria have been proposed, none can represent the grim reality of ALF better than operative findings. The liver of a patient with ALF is shown in Figure 1a. At first glance, everything looks normal. However, the pallor and multiple areas of “dimpling” on the normally smooth capsule (caused by collapse due to necrosis) cannot escape the trained eye. In fact, the entire organ is necrotic. Figure 1b shows one of the small islands of liver tissue which, with the support of the excellent intensive care team, enabled the patient to survive until an organ for transplant became available.

3- An Integral Part of Hepatology Training

There are established indications and criteria for referring patients to liver transplant units and placing them on liver transplant lists (9,10). For example;

“BA patients who are post hepatopertoenterostomy (HPE) should be promptly referred for LT evaluation if the total bilirubin is greater than 6 mg/dL beyond 3 months from HPE (1-B); liver transplant evaluation should be considered in BA patients whose total bilirubin remains between 2-6 mg/dL (1-B)” (10).

If LTx are performed at the same institution, the residents and fellows will have opportunities to observe the entire course of the patient’s treatment. If not, the patient will have to be referred to a transplant center. Although this is a good arrangement for the patient, it inevitably creates a huge gap in the education of the trainees because their exposure to patients with liver dysfunction beyond a particular level becomes extremely limited. The maxim “What does not kill you, makes you stronger” holds for all forms of training. Exposure to complicated clinical problems under proper supervision not only provides the fellows with excellent education, but also inculcates a judicious self-confidence that is vital for a successful professional life. Therefore, gastroenterology and hepatology fellows should attend a 3-month rotation at a high-volume liver transplant unit prior to graduation. Since the increasing number of long-term survivors makes it impossible and impractical for the transplant center to follow all patients directly, having an increased number of fellows on rotation would also be beneficial for patients. Some form of holistic collaboration with gastroenterologists, hepatologists

and family physicians would be mandatory, at least for patients without major complications (11).

4- Enhancement of Radiology Training

Any type of major surgery is impossible without strong support from diagnostic and interventional radiology. Living donor LTx (LDLTx) requires accurate delineation of the intrahepatic anatomy for the safe division of a vital organ for transplantation. Expertise in ultrasonography (USG), computed tomography (CT) and magnetic resonance imaging (MRI) are vital. In most centers, patients who receive grafts from living donors undergo Doppler USG examinations twice a day during the first week and once a day during the second. In teaching institutions, this is performed by senior residents under the general supervision of attending radiologists and the transplant surgeon; there is a general understanding that serial examination by a properly supervised junior

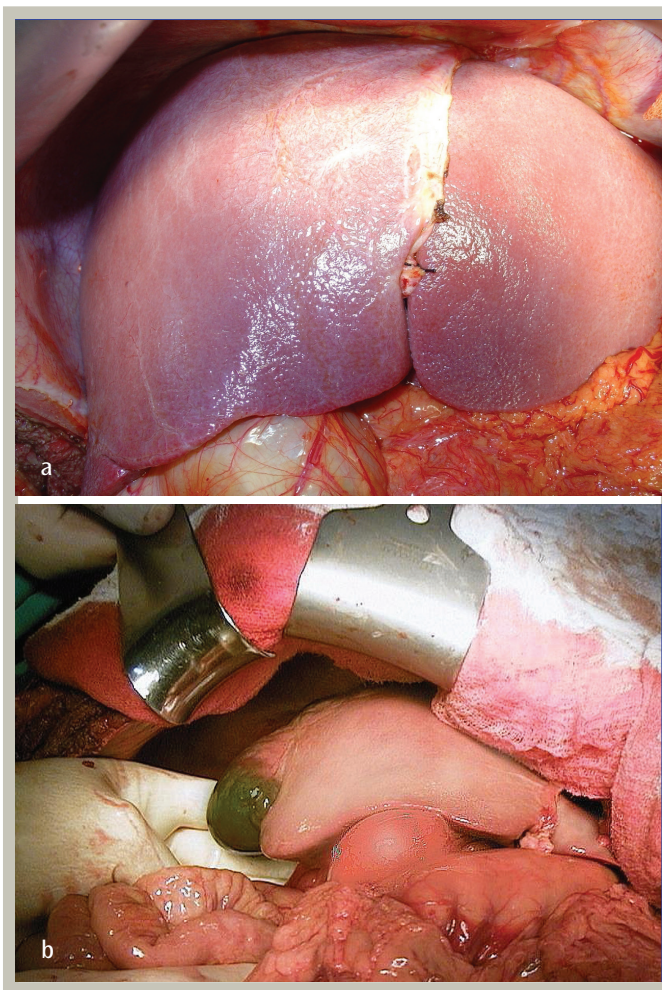


Figure 1. a) Operative photograph of an ALF patient who underwent liver transplantation; the pallor and multiple areas of “dimpling” on the normally smooth capsule are signs of extensive necrosis, b) one of the remaining small islands of viable liver tissue (brown)

physician is more reliable in detecting subtle but important changes, compared to examinations performed by multiple, more senior radiologists. This daily duty provides excellent radiology training with remarkable results, as shown in the following example from the Istanbul Faculty of Medicine.

A 34-year-old patient had attended various institutions over three years due to inability to walk in a coordinated manner, dysarthria and non-convulsive fainting episodes that lasted up to 30 minutes and were followed by complete recovery. Episodes of orientation loss and aggression (1-2/month) were reported by his relatives. The results of the standard liver function tests and USG were within normal limits except for increased ammonia levels, noted occasionally. A low-protein diet was partially effective for symptom control. The neurology resident and her supervisor felt that the liver imaging was incomplete without a Doppler USG. The radiology resident who was assigned to the initial examination happened to be physician who had completed her one-month liver transplant rotation. She diagnosed a congenital shunt between the left portal vein and the left hepatic vein by herself and informed her supervisor. A CT angiography confirmed her diagnosis (Figure 2).



Figure 2. The congenital shunt (asterisk) between the left portal vein and the left hepatic vein

5- Enhanced Infectious Disease Training

The rate of development of new antibiotics cannot keep up with the increasing rates of multidrug resistance (MDR). Consequently, infections due to MDR organisms (MDRO) have become important causes of hospital mortality (12,13). One of the most problematic fields is LTx because of the high risk of colonization due to multiple infections during the waiting period. Colonization is the most important risk factor for infection and carries a very high risk of mortality (14). An institution hosting a successful liver transplant program must have established practices for hospital hygiene, quarantine, antibiotic stewardship, and the monitoring and control of colonization, as well as early diagnosis and aggressive treatment of infections due to MDRO. A successful institutional response to this challenge lays an excellent foundation for training residents and fellows in infectious diseases. Of course, LTx is not the only clinical field affected by this problem, but fellows training in gastroenterology and hepatology will certainly reap the benefits listed above.

6- Clues to the Recovery Capacity of the Brain

The prognostication of neurological recovery after transplantation for ALF is a very challenging issue. The available criteria are inadequate for determining which patients will recover without sequelae and which will not (15,16,17). A previously reported case demonstrates that the recovery capacity of the brain may, in some instances, challenge even the basic principles of neurologic examination (18):

“A 9-year-old boy underwent cadaveric transplantation for mushroom poisoning after 5 days of endotracheal intubation. During hilar dissection, after ligation and division of the hepatic arteries and the common hepatic duct, the anesthesiologist reported that pupillary reflex disappeared and the pupillae had become fixed and dilated. A decision whether to abort or proceed had to be made. The liver from a 72-year-old donor had been sent by plane from a distant city and taken to the operation table. It was unlikely that the liver could be used in another recipient. The operation was continued. The graft showed good early function. However, the pupils remained dilated until 10 hours after abdominal closure. Then dilation started to resolve and the pupillary reflex returned. He regained consciousness and was extubated on the 4th postoperative day. However, he was tetraparesic. He was admitted to the ward on the 7th postoperative day. Full functional recovery could be achieved with 4 weeks of intense physical rehabilitation and he was discharged to his home on the 40th postoperative day”...

“Of course, if the disappearance of the light reflex had been noted in the intensive care unit, transplantation would have been cancelled”.

7- Reciprocal Enhancement of Liver Transplantation and Non-transplant Hepatobiliary Surgery

The examples below show that LTx and hepatobiliary surgery should be considered parts of a whole.

LTx is indicated in some patients with hepatocellular carcinoma either as a primary or secondary procedure (salvage operation for intrahepatic recurrence after a hepatectomy) (19). In a situation analogous to the exposure of fellows to patients with moderate-to-severe dysfunction, hepatopancreatobiliary surgery fellows in institutions that do not provide LTx should participate in a 3-month rotation at a high-volume liver transplant unit before graduation.

LDLTx requires a very high level of expertise on intrahepatic and hilar anatomy. This can be attained not by experience in whole-organ cadaveric transplantation but in complex hepatectomies and hepatobiliary resections for oncological surgery. In this sense, hepatobiliary surgery sets the stage for success in LDLTx, as has occurred in countries in the Far East. Conversely, experience in LDLTx enables a team to perform aggressive hepatobiliary surgery precisely and safely, as illustrated in the following example. The MRI and CT angiography of the patient with perihilar cholangiocarcinoma (Istanbul Faculty of Medicine) are shown in Figure 3. The tumor had divided the biliary tree into at least three compartments, encased the left portal vein and invaded the left and possibly right hepatic arteries. The patient had an accessory right posterior artery that the tumor had not involved. Upon laparotomy, the tumor was

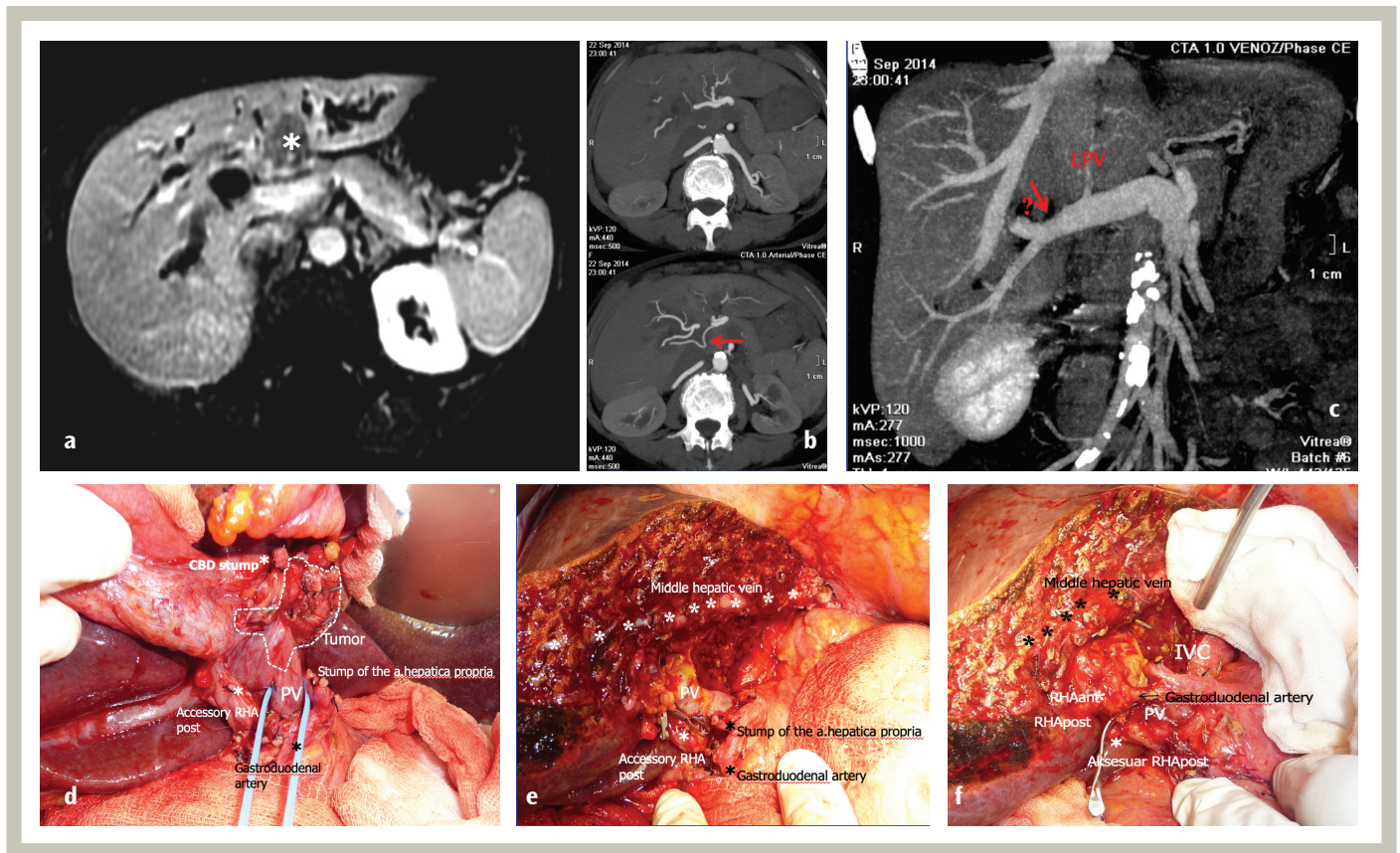


Figure 3. a) Perihilar cholangiocarcinoma (asterisk), b) Involvement of the left and middle hepatic arteries; there is an accessory right posterior hepatic artery (arrow). c) Encasement of the left portal vein branch, suspected involvement of the right branch (arrow). d) The right and left hepatic arteries, the posterior wall of the main portal vein and the left portal vein branch were involved; the accessory right posterior hepatic artery (RHA post) was not. e) Doppler USG showed arterial signals in the right posterior section only. The vascular clips are on the right anterior and posterior branches of the right hepatic artery, f) anastomosis to the branching area would entail risk of thrombosis; the right anterior hepatic artery was reconstructed using the gastroduodenal artery (arrow)

USG: Ultrasonography

found to have invaded the main portal vein and right and left branches of the hepatic artery. The accessory artery was preserved. Left hepatectomy, caudate lobectomy and resection & reconstruction of the portal vein were performed. The right hepatic artery had to be cut at a point that was very close to the division of the anterior and posterior branches; reconstruction near this bifurcation was deemed to carry a high risk of thrombosis. Doppler USG showed arterial signals in segments 6 and 7 (posterior section) but not in 5 and 8 (anterior section). The posterior branch of the bifurcation was sacrificed (since the accessory artery was already providing adequate arterial perfusion) to achieve a “cylindrical” inflow. There was a gap between the main hepatic artery and the right anterior branch and also a size discrepancy. The gastroduodenal artery was divided and used to provide inflow to the right anterior section. The patient survived for 4 years and 9 months. Of course, this type of operation can be performed by a team that is not active in transplantation. However, our team’s extensive experience in LDLTx enabled us assess the preoperative situation, use the intraoperative Doppler USG to make a final decision on the intrahepatic arterial perfusion and implement it without hesitation, because such decisions are common in LDLTx.

A much lesser known but extremely powerful approach is the possibility of keeping transplantation as a backup procedure during a complicated hepatectomy. While this has been reported with a cadaveric donor (20), the availability of a living donor offers much greater versatility. For example, a 2-year-old boy attended the Çam and Sakura City Hospital with extensive hepatoblastoma limited to the liver; he had undergone intensive chemotherapy with a good response (Figure 4a). However, the lesion looked marginally resectable on imaging; it extended into the right lobe and invaded the pedicle of the right anterior section near its origin (Figure 4b). It had involved the middle and left hepatic veins and regression of the tumor under chemotherapy had caused traction of the suprahepatic part of the inferior vena cava (Figure 4c). The caudate lobe surrounded the vena cava completely. A left trisectionectomy was planned; maximum effort had to be spent to preserve the enlarged right inferior hepatic vein, because there was a possibility that the right superior hepatic vein would have to be sacrificed (due to traction of the vena cava by the tumor). His mother was prepared as a living donor. The tumor was resected by our team (Erdem Kinacı, Melih Akin, İlgin Özden) with negative surgical margins in an 8-hour operation. If the tumor had been evaluated as inoperable or if we had encountered an intraoperative catastrophe, we would have immediately switched to transplantation. He has had no evidence of recurrence at 3 months.

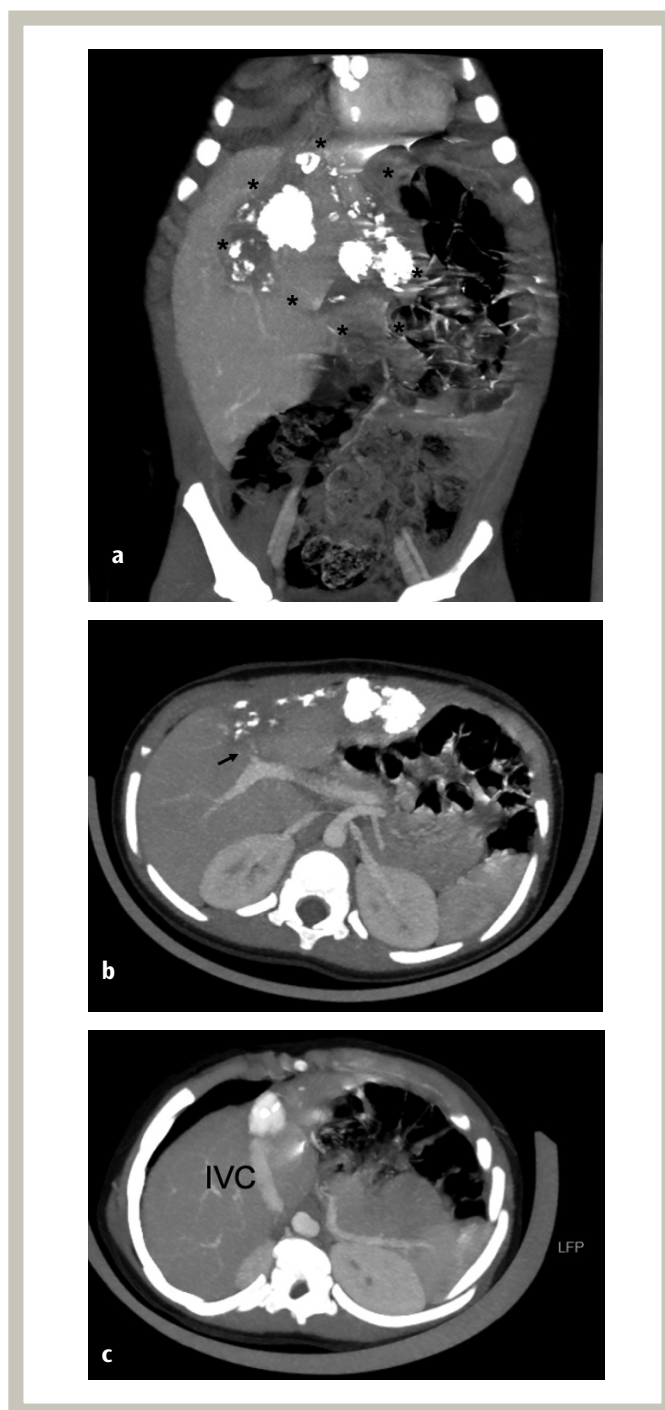


Figure 4. a) A 2-year-old boy who had hepatoblastoma (outlined with asterisks) that was still locally advanced even after a good response to chemotherapy, b) the left lobe tumor extended into the right lobe and involved the right anterior section pedicle near its origin. c) The tumor involved the middle and left hepatic veins extensively and had pulled the suprahepatic section of the inferior vena cava toward itself during regression under chemotherapy
IVC: Inferior vena cava

8- Bridge to the Future

LTx as we know it has saved and will continue to save tens of thousands of lives every year. However, it has a very basic philosophical weakness that will eventually relegate it to history: For the physician to save a life by LTx, somebody must die (cadaveric donor) or be exposed to the risk of living donor mortality. More practical alternatives, such as gene therapy for monogenic diseases (21), antifibrogenic agents to arrest the progression to, and even reverse, cirrhosis (22,23),

and hepatocyte transplantation (24) are in various stages of development. LTx will have to serve as a “salvage” procedure for the failures during the development of the alternatives (24), only to be replaced by them in the long run.

Ethics

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