RECENT ADVANCES IN SURGERY

12

Editor

Roshan Lall Gupta



JAYPEE

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CHAPTER

Liver Transplantation

Arvinder S Soin, Ravi Mohanka

INTRODUCTION

Liver transplantation has evolved from a risky and experimental procedure to a common life saving operation in surgical practice over last 45 years. The first human liver transplant was performed in 1963,[1] albeit unsuccessfully, followed by similar attempts[2-4] by few enduring surgeons, with similar outcome. The first success, which served as a proof of concept was achieved in 1967.[5] However, in the first 10 years, liver transplantation remained experimental, limited to a few centers, impeded by many problems and poor results, with a 1 year survival of 25-30 percent.[6,7]

Cyclosporine[8] improved the survival to about 70 percent, and liver transplantation was approved as a standard of care in the USA for treatment of end stage liver disease (ESLD) in 1983. Availability of university of Wisconsin (UW) solution,[9] tacrolimus[10] and monoclonal antibodies[11] further improved outcomes.

The Global Scenario

Soon, the demand for liver transplant outstripped the availability of organs and this disparity has widened over the years.[12,13] In the USA, about 6,500 liver transplants are performed annually, although more than 12,000 patients are on the waiting list, and 2000 of them die while on the waiting list.[14] In Europe, about 4000 transplants are performed each year.[12] Prominent centers in South Korea, Japan and Hong Kong each perform about 120 – 300 transplants annually.[15,16] Other active liver transplant centers are in China, Brazil and Turkey. While centers in USA and Europe mostly perform deceased donor liver transplants (DDLT), organ donation rates are very low in Asia,[17] and living donor liver transplantation (LDLT) is predominant. The success of LDLT can be attributed to the large experience and innovative surgical techniques that have been pioneered in South Korea, Hong Kong, Japan and India.[15,16,18]

The Indian Scenario

In India, liver transplantation has so far been attempted at 26 centers but very few of these perform the procedure regularly.[18] The success of LDLT

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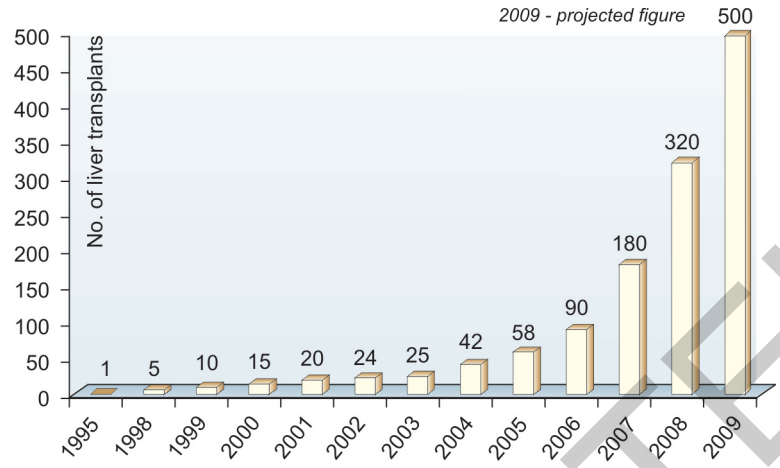

Fig. 2.1: Liver transplantation in India: Annual trends

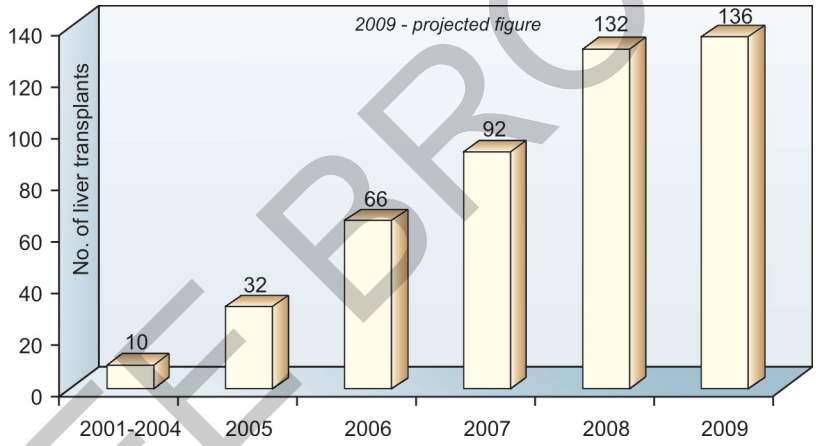

Fig. 2.2: Liver transplantation at SGRH: Annual trends

in India in last 4 years has not only led to rise in number of transplants and centers, but also has helped in establishing confidence in the procedure amongst patients and physicians alike. In 2008, more than 300 transplants were performed countrywide, and this number is likely to rise to around 500 in 2009 (Fig. 2.1, *source: personal communication*). We at Sir Ganga Ram Hospital (SGRH) have seen a steady rise in number of transplants to the present level of around 140 annually (Fig. 2.2).

Indications for Liver Transplantation

Broadly, liver transplantation is indicated in either acute or chronic terminal liver disease, metabolic liver disease, or hepatocellular carcinoma

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Table 2.1: King's college criteria for acute liver failure (ALF)[19]

Acetaminophen induced liver failure
Arterial pH < 7.3
Or all of the below
Prothrombin time: international normalized ratio (INR) > 6.5
Serum creatinine > 300 µmol/L (> 3 mg/dL)
Encephalopathy: grade III or IV
Non-acetaminophen acute liver failure
INR > 6.5
Or 3 of the following 5 criteria
Patient age < 10 or > 40 years
Serum total bilirubin > 300 µmol/L (> 17.5 mg/dL)
Time from onset of jaundice to development of coma > 7 days
INR > 3.5
Drug toxicity, Non-A-E hepatitis

Table 2.2A: Model for end stage liver disease (MELD) and pediatric end stage liver disease (PELD) scoring system

MELD = 9.57 x Log_e [serum creatinine (mg/dL)] + 3.78 x Log_e [serum bilirubin (mg/dL)] + 11.2 x Log_e [INR] + 6.43
PELD = 0.480 x Log_e [serum bilirubin (mg/dL)] + 1.857 x Log_e [INR] – 0.687 x Log_e [serum albumin (g/dL)] + 0.436 [if the patient is < 1 year old] + 0.667 [if the patient has growth failure (≤ 2 Standard deviation)]

(HCC). In acute liver failure (ALF), King's college criteria (Table 2.1) are widely used to predict outcome[19] (including our center) and determine the need for transplant. In chronic liver disease (CLD), transplant listing is primarily based on two systems (Table 2.2A: MELD and PELD; Table 2.2B: CTP) that estimate the severity of cirrhosis and its complications such as hyper-bilirubinemia, coagulopathy, renal dysfunction, ascites, encephalopathy and hypo-albuminemia. Refractory variceal hemorrhage, hepato-pulmonary syndrome, hepato-renal syndrome are some other common indications (Table 2.3). Liver transplantation is also the best therapeutic modality for HCC patients without extra-hepatic or hepatic vascular spread.

Contraindications to Liver Transplantation

Contra-indications for liver transplant are malignancy with extra-hepatic or macro-vascular involvement, cholangio-carcinoma (except in approved

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Table 2.2B: Child-Turcotte-Pugh (CTP) score

Criteria \ *Points*	*1*	*2*	*3*	*Units*
Serum total bilirubin	< 34 (< 2)	34 – 50 (2 – 3)	> 50 (> 3)	µmol/L (mg/dl)
Serum albumin	> 350 > 35	280 – 350 28 – 35	< 280 < 28	µmol/L g/l
Prothrombin time Prolongation (INR)	< 4 (<1.7)	4 – 6 (1.71 – 2.2)	> 6 (> 2.2)	Seconds (No unit)
Ascites	None	Controlled with diuretics	Refractory	No unit
Hepatic encephalopathy	None	Grade I – II	Grade III – IV	No unit

Grading

Class	*Score*
A	5 – 6
B	7 – 9
C	10 – 15

Table 2.3: Indications for listing patients with chronic liver disease for liver transplantation

MELD* score of 15 or more
CTP** score of 9 or more
Patients with lower disease score with
- Refractory ascites
- Refractory portal hypertensive hemorrhage
- Spontaneous bacterial peritonitis
- Recurrent hepatic encephalopathy
- Hepato-renal syndrome
- Hepato-pulmonary syndrome
- Biliary cirrhosis
- Diuretic-induced nephropathy
- Partial portal vein thrombosis
- Compromised quality of life
- Growth retardation or failure to thrive in children

*MELD: Model for End stage liver disease, **CTP: Child-Turcotte-Pugh

clinical trials), active, uncontrolled or refractory infection outside the liver, severe cardiopulmonary or other co-morbid conditions, active psychiatric illness or lack of psychosocial support, active alcohol or other substance abuse, or anticipated major technical difficulty e.g. portal vein thrombosis or dense adhesions. However, with increasing experience and improvement in surgical techniques, technical contraindications are now considered relative.

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Etiology of Liver Diseases Requiring Liver Transplantation[20] (Table 2.4)

Hepatitis C (HCV) is the most common indication for liver transplant and constitutes about 40 percent of transplants in USA,[21] 15 percent in Europe,[12] 3-4 percent in Asia[15] and 30 percent at our center. Graft re-infection after transplant is universal,[22] however, treatment of recurrent HCV with pegylated interferon and ribavirin has improved virologic and histologic responses after transplant.[23] Earlier concerns about faster recurrence in LDLT[24,25] have not been borne out in recent series.[26]

Hepatitis B (HBV) generally constitutes about 6-7 percent of transplants,[12,27,28] but almost 80 percent in South Korea[15,16] and 15 percent at our center. In 1980s liver transplant for HBV was associated with universal graft re-infection, rapidly progressive disease recurrence and

Table 2.4: Etiology of liver diseases requiring liver transplantation[20]

- **Primary biliary cirrhosis:** primary biliary cirrhosis.
- **Primary sclerosing cholangitis:** Crohn's disease; ulcerative colitis; cholangitis with no bowel disease.
- **Alcoholic liver disease:** Lae¨nnec's cirrhosis.
- **Autoimmune disorders:** cirrhosis (drug or industrial exposure; cryptogenic; idiopathic); chronic autoimmune hepatitis (etiology unknown; postnecrotic).
- **Hepatitis C and similar infections:** postnecrotic cirrhosis (non-A, non-B; type C; type D; types B and C; types B and D); Lae¨nnec's cirrhosis (postnecrotic; other).
- **Hepatitis B:** postnecrotic cirrhosis (HBsAg-positive).
- **Acute hepatic failure:** acute hepatic necrosis (drug exposure; hepatitis A; hepatitis B; HBsAg-positive; non-A, non-B hepatitis; hepatitis C; hepatitis D; hepatitis B and C; hepatitis B and D; other acute viral infection);etiology unknown.
- **Cancers:** primary liver malignancy (hepatoma; fibrolamellar hepatocellular carcinoma; cholangiocarcinoma; hepatoblastoma; hemangioendothelioma; hemangiosarcoma; angiosarcoma).
- **Metabolic disorders:** alpha-1-antitrypsin deficiency; glycogen storage disease type 1; glycogen storage disease type II; hemochromatosis; hemosiderosis; hyperlipidemia type II; homozygous hypercholesterolemia; primary oxalosis or oxaluria; hyperoxaluria; tyrosinemia; Wilson's disease or other copper disorder; urea cycle disorder; Crigler-Najjar syndrome; Wolman's disease; protoporphyria; Niemann-Pick disease; abetalipoproteinemia; Gaucher's disease; Osler-Rendu-Weber disease; carbamoylphosphate synthase deficiency; amyloidosis; Wiskott-Aldrich syndrome.
- **Other liver diseases:** cirrhosis (postnecrotic hepatitis A); secondary biliary cirrhosis (Caroli's disease; choledochal cyst; other); familial cholestasis (Byler disease; other); cholestatic liver disease not listed above; neonatal hepatitis; biliary atresia (extrahepatic biliary atresia; hypoplasia; Alagille syndrome; other); congenital hepatic fibrosis; cystic fibrosis; Budd-Chiari syndrome; benign tumor (hepatic adenoma; polycystic liver disease; other); liver disease induced by total parenteral nutrition or hyperalimentation; graft-versus-host disease; trauma; biliary stricture or stenosis; idiopathic adult ductopenia; unknown.

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patient survival of less than 10 percent. Hepatitis B Immune-globulin (HBIg) and effective anti-viral agents i.e. lamivudine, adefovir and entecavir have reduced graft re-infection rates to < 5 percent[29] and even allowed transplantation of HBcAb +ve livers into low risk patients.

Hepatocellular cancer (HCC) constitutes about 10-25 percent of transplants.[12,14,16] At our center, 23 percent of the transplant recipients had HCC (most with underlying cirrhosis). Liver transplant is the best therapeutic modality for patients with HCC because it can potentially achieve complete tumor clearance and eliminate the risk of new lesions in cirrhotic liver. Early results were disappointing with high tumor recurrence and unacceptable mortality. However, when transplantation was restricted to patients with single tumor < 5 cm or upto 3 lesions < 3 cm each, 75 percent survival could be achieved,[30] thus, Milan criteria were laid down. With better patient selection, multi-modality treatment (including trans-arterial chemo-embolization [TACE], radio frequency ablation [RFA], ethanol injection and cryosurgery), priority to HCC patients on waiting list and early transplant with LDLT, excellent outcomes have been achieved lately.[31,32]

Alcoholic liver disease constitutes 12-18 percent of transplants in USA and Europe,[12,27,28] about 3 percent of in Asia[16] and 22 percent at our center. Active alcohol abuse, concerns of recidivism or compliance are common reasons for denial of transplant listing. About 8 to 20 percent patients resume drinking after transplant[33] and have poor long-term survival.[34] In UK, all patients are required to follow up at de-addiction centers to reduce recidivism rates.

Acute liver failure (ALF) constitutes about 3-9 percent of transplants[12,14,16] and is commonly due to acetaminophen toxicity, hepatitis A (HAV) or E (HEV). At our center, 6 percent of LDLT are performed for ALF, predominantly due to HAV or HEV infection, drug-induced ALF, or in children, Wilson's disease.

Cholestatic liver diseases (primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC) and secondary biliary cirrhosis) constitute about 8-25 percent of transplants.[12,14,15] Non-alcoholic steato-hepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD) are increasing[35] indications for liver transplant. Metabolic diseases like Wilson's disease and hemochromatosis constitute about 3-6 percent of transplants.[12,14,15] If the cause of ESLD is obscure despite extensive testing, they are labelled as cryptogenic, which constitutes about 2-10 percent of transplants.[15,27,28] Approximately 5-20 percent liver transplants (9% at our center) are performed in children,[12,16,22] biliary atresia being the most common indication.[15]

Prioritization on the Waiting List

The demand-supply mismatch has necessitated various systems for allocation of available organs based on principles of equitable and fair

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distribution. In the USA, MELD and PELD scores (Table 2.2A) are used to prioritize liver allocation. In Europe, organ allocation in various geographical areas is governed by different organ exchange organizations e.g. United Kingdom Transplant (UKT), Eurotransplant, Scandiatransplant and others. They follow either patient-directed or center-directed allocation algorithms. While deceased donor organs are considered as a public resource and therefore systematically allocated, living donations are patient directed, generally to a family member. Patients with fulminant liver failure (FHF) or complications of liver transplant i.e. primary non-function (PNF) or hepatic artery thrombosis (HAT) get priority and emergency status on the waiting list. Potential LDLT recipients at large volume centers such as ours are prioritized by disease severity, waiting period and presence of HCC.

In order to overcome the scarcity of organs, various attempts have been made to increase donation rates, expand the donor pool and optimize use of available organs, such as, reduced size grafts,[36] split liver transplantation,[37] use of extended criteria donor (ECD) organs and living donor liver transplantation (LDLT).[38] In Europe, about 5 percent of liver transplants are done with reduced grafts, 4 percent with split grafts, 0.4 percent as auxiliary and 0.4 percent domino transplants. In USA, about 3.8-4.4 percent liver transplant are done with split grafts and 0.9 percent with reduced grafts.[12,13,27] In USA and Europe, LDLT constitutes only a small percentage of liver transplants (4 percent and 1.6 percent, respectively),[13,14] however, in Asia LDLT is predominant, and many variations of partial living donor grafts are used for transplantation.[15]

SURGICAL TECHNIQUES

Deceased Donor Liver Transplant

Liver Recovery from Deceased Donor (Fig. 2.3)

The goal of this operation is to perfuse all abdominal organs with cold preservative solution (UW or HTK) through celiac trunk and superior mesenteric artery (SMA), followed by recovery of organs preserving their vascular supply.

Abdomen and chest are opened with a midline incision and sternotomy. Extended Balfour and sternal retractors are placed. Liver is assessed grossly and its arterial anatomy ascertained. The right colon and small bowel is mobilised off the retro-peritoneum to bare the infra-renal aorta and inferior vena cava (IVC). Interior mesenteric vein (IMV) is isolated. The aorta and IMV are cannulated. Aorta is cross clamped below the aortic cannula and in the thorax. Aorta is perfused with preservative solution at 4°C for visceral cooling. The IVC is transected at cavo-atrial junction for blood venting. Sterile ice slush is packed peri-hepatically for surface cooling. Once perfusion is completed, splenic artery and gastroduodenal artery (GDA) are identified and divided away from the hepatic

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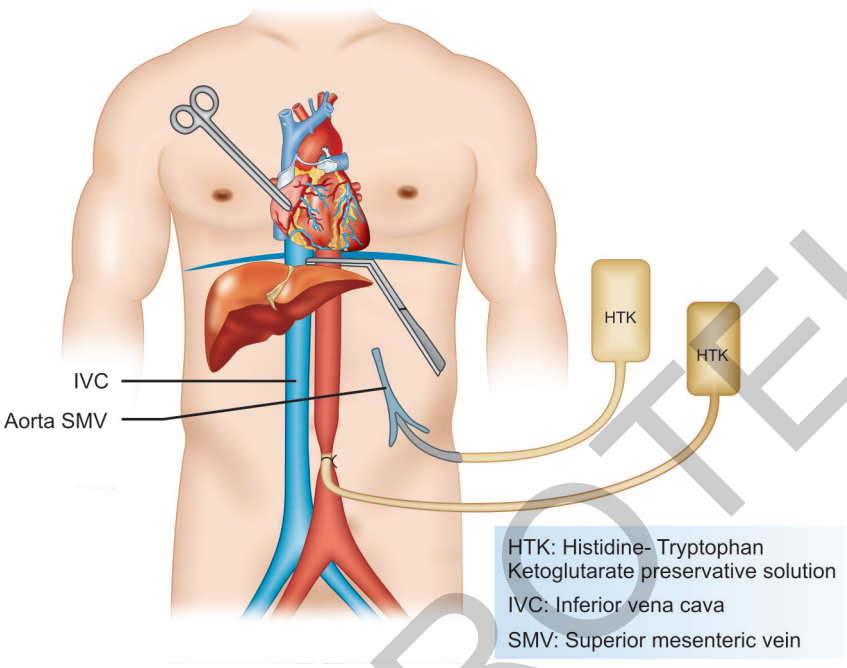

Fig. 2.3: Deceased donor liver recovery

artery. The IVC is transected above the renal veins. Aorta is transected below SMA taking care not to damage renal arteries, dissected from retroperitoneum and transected again in the thorax. Division of cavo-atrial junction is completed leaving a cuff of thoracic IVC. Pericardium and diaphragm are divided around hepatic attachments. Liver is delivered out, stored in preservative solution (UW or HTK solution) and packed in ice.

Liver Recovery after Cardiac Death (DCD)

Steps of recovery are as above; however, donor warm ischemia time is minimized by rapid cannulation and perfusion, because longer ischemia time is associated with poorer graft function and increased biliary complications.[39,40]

Bench Preparation for Deceased Donor Liver Graft

Liver is inspected for gross appearance, uniformity of perfusion, procurement injuries and vascular anatomy. Remaining diaphragm is dissected off, IVC is separated from surrounding tissues and all its tributaries, including phrenic and adrenal veins are ligated. Portal vein (PV) is dissected clean from the surrounding tissue. Superior mesenteric artery (SMA) and left gastric artery (LGA) are examined for accessory

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hepatic vessels. Arterial dissection is done from celiac trunk towards the liver, preserving all hepatic arterial supply and long lengths of splenic artery and GDA. Arterial reconstruction is performed, if required, such that the whole graft is supplied by a common feeder artery, preferably fashioned into a Carrel patch. All extrahepatic branches from PV and hepatic artery (HA) are carefully ligated. Cholecystectomy is performed. Liver is re-packed in cold preservation solution until implantation.

Classic Technique of Recipient Hepatectomy (Fig. 2.4A)

Mercedes Benz incision is made. A mechanical (Thomson's or Omnitract) retractor is placed to retract the costal margins upwards and outwards. Falciform ligament, left triangular ligament and gastro-hepatic ligaments are divided in succession, ligating the collaterals and accessory left hepatic artery if present. The hepato-duodenal ligament is dissected in the porta hepatis to isolate and divide hepatic arterial branches, common bile duct and the portal vein. Any accessory right hepatic artery is isolated and divided. In case veno-venous bypass is planned (very selectively used nowadays), PV is cannulated at the time of transection. Femoral vein (FV) and internal jugular vein (IJV) are also cannulated, and the patient is put on bypass, whereby blood from PV and IVC (via the FV) is returned to the superior vena cava (SVC) (via the IJV), aided by a pump. Right triangular ligament is divided upto IVC and the liver is dissected off the diaphragm posteriorly. Supra-hepatic and infra-hepatic (supra-renal) vascular clamps are applied. IVC is then divided between the two clamps and liver is explanted along with the intrahepatic portion of IVC.

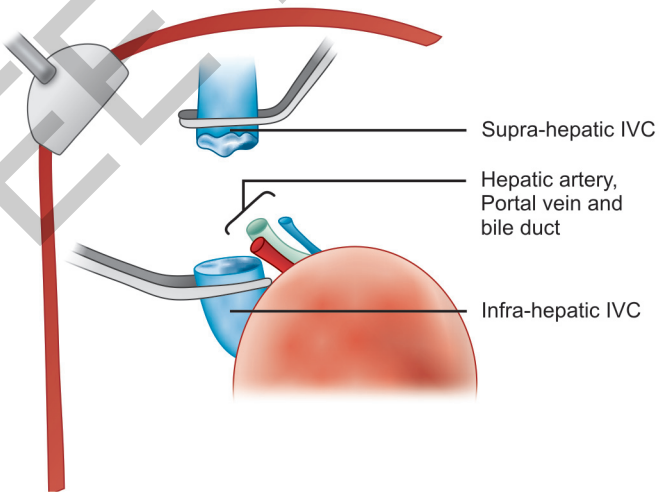

Fig. 2.4A: Classical technique of recipient hepatectomy

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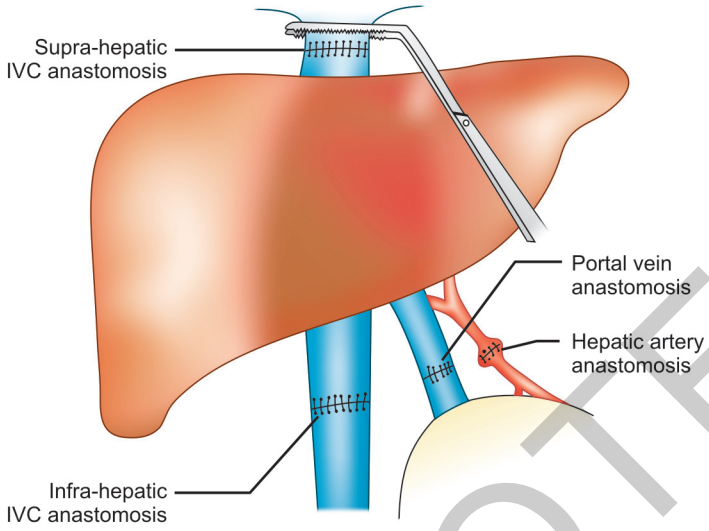

Fig. 2.4B: Classical technique of liver graft implantation

Classical Technique of Liver Graft Implantation (Fig. 2.4B)

Donor supra-hepatic IVC is anastomosed end-to-end with recipient supra-hepatic IVC. Liver graft is flushed via the portal vein with lactated Ringer's solution at room temperature. Donor infra-hepatic IVC is anastomosed end-to-end with recipient's infra-hepatic IVC. Portal vein is clamped, veno-venous bypass discontinued and portal vein trimmed to appropriate length. Donor portal vein is anastomosed end-to-end with recipient portal vein leaving a "growth factor".[41] The new liver is reperfused with portal blood ensuring absence of any air in the IVC. Carrel patch from the donor hepatic artery is anastomosed end-to-end with recipient common hepatic artery or a branch patch of HA with GDA or splenic artery. Donor bile duct is anastomosed end-to-end with recipient bile duct, except in children and patients with PSC, where a Roux-en-Y choledocho-jejunostomy is preferred. Biliary stents and T-tubes are used according to the center policy, but both are increasingly going out of favor.

Piggyback Liver Transplant (Figs 2.5A and 2.5B)

IVC preserving piggyback technique is increasingly being used for DDLT. Initial steps are similar to the classic technique, however, the entire recipient IVC is retained and its patency maintained by dividing the short hepatic veins between ligatures, thus obviating the need for veno-venous bypass. Hepatic veins are clamped and divided. Their stumps are joined together to form a common cloaca and used for anastomosis with supra-

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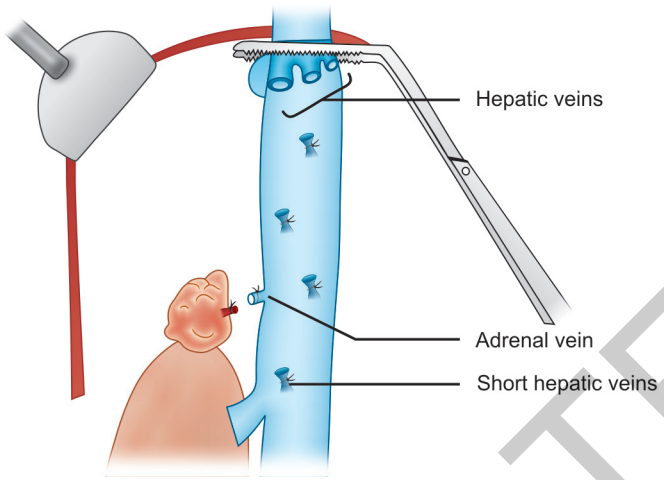

Fig. 2.5A: Piggyback technique of recipient hepatectomy

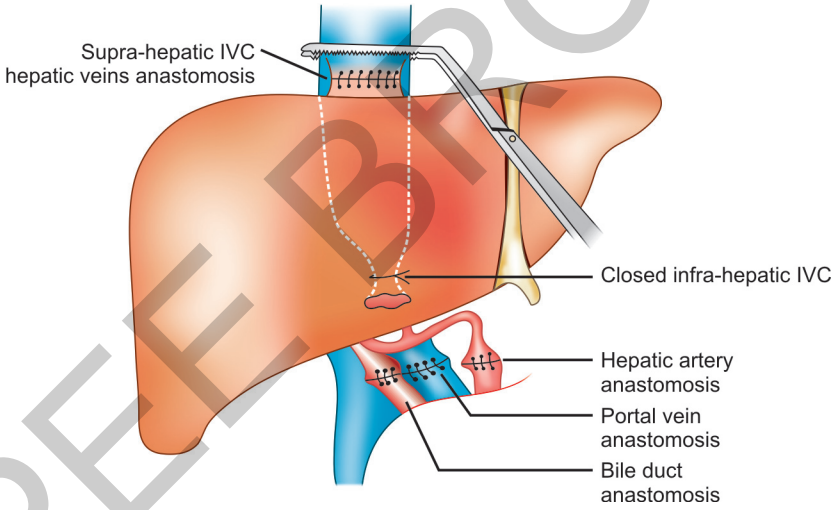

Fig. 2.5B: Piggyback technique of liver graft implantation

hepatic donor IVC. Donor infra-hepatic IVC is closed with a ligature or a vascular stapler. Portal vein anastomosis, reperfusion, hepatic artery and biliary anastomoses are done in the standard fashion.

Living Donor Liver Transplant

Generally left lobe donation is required for children and right lobe for adults.

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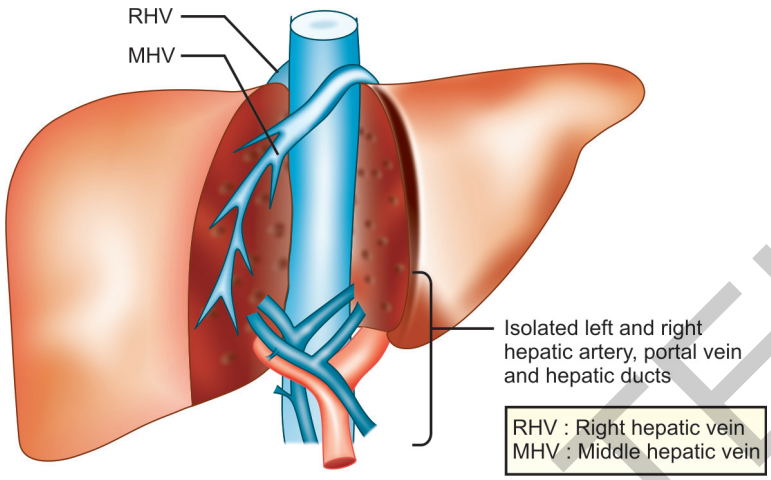

Fig. 2.6: Living donor hepatectomy

Living Donor Hepatectomy (Fig. 2.6)

Mercedez benz incision is made, liver is mobilized by dividing the right and left triangular ligaments. For right lobe donation, short hepatic veins between the right lobe and IVC are isolated and divided, preserving any veins larger than 5 mm. Right hepatic vein is isolated for right lobe donation and left and middle veins are isolated for left lobe donation. Cholecystectomy is performed and cholangiogram is done. During hilar dissection, the bile duct and the ipsilateral hepatic artery, portal vein and hepatic duct are isolated. The lobar hepatic artery and portal vein branches are occluded temporarily with a vascular clamp and the interlobar ischemic plane is marked. Liver parenchyma is transected along the ischemic line using cavitron ultrasonic suction aspirator (CUSA), dividing any vascular structures encountered along the transection line. The lobar hepatic duct is divided. Liver is removed by dividing ipsilateral portal vein, hepatic artery and hepatic veins and then perfused with preservative solution.

Bench Preparation for Living Donor Liver Graft

Hepatic veins, artery and portal vein are examined for length, and if required, lengthened using cryopreserved vein grafts. Donor middle hepatic vein (MHV) is extended or neo-MHV is created using vein grafts so that the right anterior segments drain into the IVC.

Recipient Hepatectomy and Living Donor Liver Graft Implantation (Figs 2.7 and 2.8)

Recipient hepatectomy is performed in piggyback fashion as described above, preserving long lengths of hepatic artery, portal vein, bile duct and

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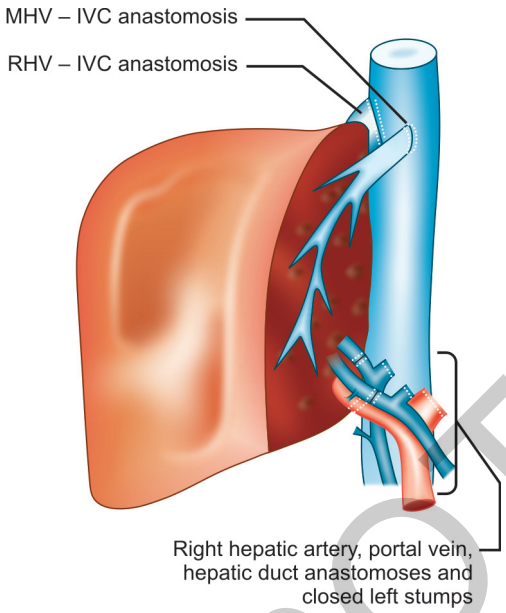

Fig. 2.7: Living donor right lobe graft implantation

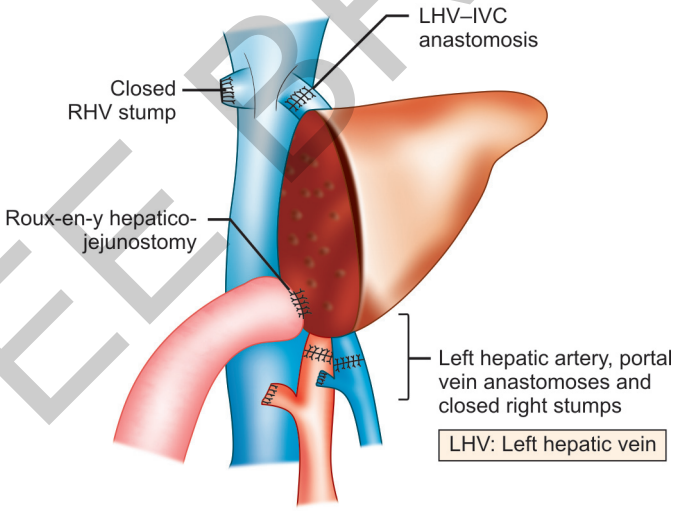

Fig. 2.8: Left lateral segment living donor liver graft implantation

right hepatic vein stumps. For right lobe graft preserving the MHV, wide end to end anastomosis is made between donor right hepatic vein (RHV) and recipient RHV. Extended donor MHV is anastomosed end-to-side with a cavotomy made in the IVC. Any inferior hepatic veins > 5 mm preserved during graft retrieval are anastomosed end-to-side with a

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