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Living Donor Liver Transplantation

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"*As to diseases, make a habit of two things: to help, or at least, to do no harm.*"

Hippocrates (460 - 377 BC)

1. Introduction

Living donor liver transplantation (LDLT) is probably the most high-profile of all surgical enterprises. At the same time, it is an amazing act of altruism. It requires hard work of dedicated multidisciplinary medical teams coupled with the courage of the patients and their families. The concept of LDLT is based on the following two factors: (1) the remarkable regenerative capacity of the liver, and (2) the shortage of cadaveric organs (Olthoff K, 2003). LDLT has become an acceptable alternative for patients in need of liver transplantation (LT) who are not likely to receive a deceased donor liver transplant (DDLT) in a timely fashion. This is seen especially in countries where cadaveric donation is limited by religious and cultural beliefs, as in Japan, Egypt, Korea, and India (Abdeldayem H, 2010).

This chapter outlines the advantages and disadvantages of LDLT, addresses the moral and ethical issues surrounding this procedure, reviews the evaluation process of the recipient and the donor candidates, highlights controversial indication for LDLT, outlines technical aspects of LDLT, and the middle hepatic vein controversy and reviews donor and recipient outcomes and complications. Where possible, emphasis is placed on the differences in LDLT compared to whole organ DDLT. At the end, the author addresses the issue of living donor mortality and highlights the importance of transparency in LDLT.

2. Historical perspective

Liver transplantation utilizing a partial-liver graft was theoretically proposed for children by Smith in 1969. On 8 December 1988, Raia et al. made the first attempt at LDLT in a four and a half-year-old girl suffering from biliary atresia. In July 1989, Strong et al. performed the first LDLT with long-term success in an 11-month-old boy using segments II and III graft. Broelsch et al. soon followed with publication of the first series of 20 successful cases of LDLT in children at the University of Chicago (Broelsch et al.,1991).

In 1991, Habib et al performed the first LDLT procedure in Africa and the Middle East at the National Liver Institute, in Egypt. They reported the success of their first case in 1993 (Habib et al, 1993). In the same year, Haberal et al. extended LDLT to adult recipients. In their series, they transplanted left-liver grafts to eight patients. In 1994, Yamaoka et al. reported

unplanned adult-to-child LDLT using right liver .In this particular case, the operative procedure was changed from left hepatectomy to right hepatectomy because of unfavorable anatomy of the left hepatic artery.

3. Advantages and disadvantages

In LDLT, the waiting time is reduced, with the ability to perform transplantation when it is medically indicated and the recipient is in the most optimal condition. This ensures better outcome before serious decompensation, disease progression (e.g., hepatocellular carcinoma) or death occurs (Russo M et al., 2004).

LDLT is usually is scheduled on an elective basis, allowing time for completing pretransplant work-up of the recipient and donor. The entire surgical team is more rested since the surgery is planned electively. Extensive workup to exclude other diseases in the donor is made. Details of vascular and liver anatomy are known well before transplant. There will be an opportunity to treat, or at least control, viral hepatitis B or C infection prior to transplantation (in those who can tolerate the medication pretransplant). Bacteremia or sepsis, if present, can be cleared with appropriate antibiotic therapy prior to the procedure (Olthoff K, et al., 2005).

Since the graft is transported between adjacent operating rooms, the cold ischemia time is short. The complications associated with organ preservation are minimized, and primary nonfunction is rare. Another advantage may be related to avoiding the activation of the inflammatory cascade seen in cadaveric livers obtained from brain dead donors, which has been implicated in up-regulation of inflammatory cytokines, adhesion molecules, class II presentation and in affecting microcirculatory flow to the, liver with resultant hepatocellular damage and allograft dysfunction. The age of the living donor is usually young. This avoids the usage of organs procured from terminally ill patient with the possibility of end-organ damage. (Jassem W et al., 2003) In LDLT, there is a potential for better human leukocyte antigen (HLA) matching. Improved matching may have an immunological advantage similar to that observed in living donor kidney transplantation. However, this was not proved (Neumann U et al., 2003).

These advantages, though, need to be weighed against the fact that a healthy person is being exposed to an extensive abdominal surgery with its potential for morbidity and mortality. The incidence of biliary complications in the recipient are said to occur more frequently than in DDLT. LDLT recipients are also exposed to slightly higher risk of hepatic artery thrombosis. The so called “small-for-size syndrome”, may occur if careful size-matching between the donor and the recipient is not made. Additionally the donor has to face financial and emotional consequences. The donation will limit the functionality of the donor for weeks or months after the surgery (Abdeldayem H et al., 2009).

4. Moral and ethical issues

Primum non nocere "First do no harm”, a fundamental medical precept of Hippocrates, is an important philosophy believed in medicine. LDLT challenges this tenet, because a healthy individual undergoes a major operation for no physical benefit to himself or herself. Perhaps there is no greater ethical dilemma than to operate and remove an organ from a perfectly healthy individual to help another (Abdeldayem H et al., 2009). It seems that the

general public strongly believes that it is the donor's sole right to donate an organ and this decision should rest with the donor. In liberal societies everyone has the right to participate in dangerous activities according to his or her will, but the transplant procedure involves an 'accomplice'; the transplant surgeon. Yet, for surgeons the principle according to the Hippocratic Oath is to 'do no harm'. Does a surgeon have an obligation to remove a person's organ upon request? (Mazaris E; Papalois V, 2006)

4.1 Donor's motivation

It is important that donors feel they are gaining something by donation so as to be sufficiently motivated and that their profit is of an emotional or moral nature (Sauer P et al., 2004). Donor motivation may be influenced by the type of relationship to the recipient and personal and religious beliefs and values. Donor motivations may include, a desire to help, a feeling of moral duty, a perception that donation is something that he or she is expected to do, and an increase in self-esteem from doing good deeds. Donors may imagine themselves in the recipient's situation, especially siblings, who are sure that the latter would act accordingly if they were in a similar state. That may be the case for parents as well. Spouses may be motivated by self-benefit from their companion's improved health and the improvement of the couple's quality of life (Lennerling A, et al, 2004). The reasons for donation must be thoroughly explored by the team and the donor. The social worker must assess whether the volunteer's decision is made freely without any undo pressure or coercion, and whether motivation is consistent with the donor's values and previous behaviors. Pressure may be more likely when the recipient's death is imminent without a transplant and when no other donor options exist (Lennerling A, et al, 2004).

4.2 Informed consent

Individuals considering living donation must be free to decide how much and what sort of risk is acceptable for them. Potential donors cannot make such decisions if they are not first provided with proper informed consent regarding the risks they are undertaking and potential implications their decision may have on the recipient. The person who consents to be a live donor should be competent, willing to donate, free from coercion, medically and psychosocially suitable, fully informed of the risks, benefits and alternative treatment available to the recipient. The professional who provides informed consent for donation should be a neutral third person. A transplant centre may have reasons for wanting an organ donation to go ahead: transplants are their source of income; they are able to increase their prestige and conduct research (Abdeldayem H. et al., 2009; Steiner R & Gert B 2000).

Issues to be fully explained to the potential donor include:

1. The technical elements of the evaluation process, surgery and recovery, short- and long-term follow-up care.
2. The risk for complications and death to both the donor and the recipient.
3. Medical uncertainties, including the potential for long-term donor complications.
4. Unforeseeable consequences that might change the donor's life, e.g. employment, and insurability, and expenses to be borne by the donor.

5. Expected outcome of transplantation for the recipient.
6. Any alternative therapies available to the recipient.
7. The specific experience and statistics of the transplant centre.

4.2.1 Informed understanding

The donor must demonstrate informed understanding. This is best achieved with written and verbal presentation of the necessary information in lay language and in accordance with the person's educational level. The potential donor must demonstrate their understanding of the essential elements of the donation process, particularly the risks of the procedure. Adequate time should be allowed for the potential donor to absorb the information, and ask questions. This may require several consultations. The donor's family/ loved ones are given the opportunity to discuss their concerns (Trotter J et al., 2007). The donor should be given a period of time to review the decision to donate (Abdullah K et al, 2005). It is very important to inform the prospective donor that he or she can choose not to proceed with the surgery without the risks of coercion or consequences. If the donor is not accepted, the reasons are kept confidential. Most transplant centers will inform the recipient that the donor is not suitable on medical grounds, even when the actual reason may be different. This is done to protect the donor and to avoid any deterioration in the relationship with the recipient (Trotter J et al., 2007). The team must establish that there is no donor monetary compensation and no coercion to donate by family or others. The potential donor's disclosure and consent process should be completely documented.

4.3 Donor advocate

In many transplant centers, a donor advocate evaluates the donor independent of the transplantation team. The advocate should not be in contact with the potential recipient and should not be influenced by the severity of the recipient's illness. The donor advocate could be a social worker, psychiatrist, or physician. The primary role of the donor advocate is to protect and promote the interests and well-being of the donor, and to help the donor through the entire process. The advocate should not pre-empt the donor's decision, since the donor continues to possess the ethical and legal right to decide to proceed with LDLT (Chen Y et al., 2003). The donor advocate should be able to answer the following questions. Is the donor adequately informed about the transplant procedure? Is consent truly informed? Is the donor vulnerable in any way to exploitation? Is the donor aware of alternative options for the recipient? Does the donor recognize the possibility of future health problems related to donation? (Trotter J 2000)

4.4 Relationship to the recipient

Reasons for donation are more understandable when there is a close bond between the pair. For genetically unrelated prospective living donors, questions must be tailored to the specific situation to fully understand why the individual wishes to donate.

4.4.1 Live unrelated donation

It has been well established that live genetically-unrelated emotionally-related donors such as spouses, partners or friends can be potential donors for LDLT. There are surgeons

against spousal donation advising that since a good percentage of marriages end in divorce there is no guarantee of a long-lasting loving relationship as a motive for such donation. Friends have been accepted reluctantly as potential donors, despite the fact that they might feel less pressure to donate compared to a family member (Terasaki P. et al., 1997).

4.4.2 Donation by strangers and good samaritan donors

Occasionally, an unrelated (so-called "altruistic") donor may volunteer to be assessed for LDLT, but such a practice is best avoided if possible. The intrinsic reasons for such unreserved altruism, especially in the adult-to-adult LDLT setting, are usually ill-defined prior to the surgery, and may only surface afterward, leading to serious unforeseen problems (Choudhry et al., 2003). The majority of transplant centers disapprove living donation between strangers, expressing doubts about their motivation and commitment to donation, their understanding of the potential risks and their psychological stability.

Such donors may benefit from their act with increased self-esteem and may experience great satisfaction without being coerced by any sense of obligation. It has been proposed that in non-directed donation, the donor and recipient should remain anonymous to each other and probably meet only after the transplant, if they both agree. It has been suggested that true altruists do not need the name of those they help. Yet, the donors might want to see the results of their good deed, and the recipients might want to express their gratitude to the donor. It seems unethical to allow potential donors to specify particular characteristics of the recipient (e.g. sex, religion or race) (Levinsky N, 2000).

4.5 Commercialization of organ donation

It may be said that, living related donation involves a 'highly artificial altruism' according to which everyone is paid, including the transplant team as well as the recipient who gains an important benefit and only the donor is required to be altruistic. On the other hand, shortage of cadaveric organs has led to a worldwide black market for living-donor organs. Of course, it is unethical to sell human organs. A poor donor may be compelled by their financial status to donate, thus making the action non-voluntary. Yet, on the contrary, the donor may be choosing the best from a list of bad options, since it carries significantly less risk than working, for example, under harsh and dangerous conditions. Paid donors are, in their majority, poor and less educated, thus possibly unable to understand the risks involved (Choudhry et al., 2003).

4.6 Paired-exchange programs

A possible way to increase the live-donor pool is the paired exchange programs. In such programs, pairs of potential donors who are incompatible with their recipients donate eventually to each other's recipient. Some have suggested that strict confidentiality should be maintained for each donor-recipient pair because there is a possibility of frustration, anger or resentment between the two pairs, in case one recipient does not have such a good outcome as the other. It is also suggested that both procedures should be performed simultaneously in order to avoid the possibility of one donor refusing after the other donor

procedure had already been performed (Park K et al, 1999). Psychological evaluation should be more meticulous to ensure that the donors are acting voluntarily. With the advances in immunosuppression and plasma-exchange techniques, such programs may be unnecessary, since ABO- incompatible transplants may be possible.

4.7 Orphan graft

The possibility of being unable to transplant a liver graft (orphan graft) into the intended recipient because of intraoperative death or other causes should be included in a prospective protocol at all institutions performing LDLT. Recommendations for handling an orphan liver graft include, (1) before donation, informed consent should be obtained from all donors indicating what the donor would want to have done with the orphan graft, (2) the sequence of steps in the operation should be structured to avoid removal of the donor graft until the recipient hepatectomy has been performed and the recipient's survival is likely, and (3) the orphan graft is allocated according to preestablished institutional guidelines (Siegler J et al., 2004). If the recipient dies intraoperatively and this possibility has not been covered in the preoperative consent discussion, the surgical team must obtain oral and written consent from the donor or the donor's family to reallocate the organ.

5. Evaluation and selection of the potential recipient

5.1 Selection of the potential recipient

Given the potential risks to the living donor, only recipients with a reasonably favorable post-transplant outcome should be considered for LDLT. Thus, before proceeding to work up any potential donor, the recipient candidate should first be deemed suitable for the LDLT operation both medically as well as surgically (Abdullah K et al, 2007).

All potential LDLT recipients must first be listed for DDLT. This ensures the following, (1) the recipient is an appropriate candidate for liver transplant and avoids LDLT being done in futile situations (e.g., inoperable hepatocellular carcinoma), (2) should there be any post-LDLT complications including poor- or nonfunctioning graft, the recipient can be immediately upgraded to a top priority status to obtain a DDLT, and (3) third-party payers may require listing for DDLT before approving a patient for LDLT (Tan et al., 2007).

It has been suggested that a MELD score of 18 may be a reasonably good cutoff level above which LDLT is indicated, because a patient with a MELD score above 18 has a greater than 10% risk of 90-day mortality without transplantation; this exceeds the 1-year mortality after LDLT (10%). On the other hand, for patients with a MELD score below 17, the risk of transplant surgery is said to outweigh the risk of death from liver disease (Li C et al, 2010).

Whether there is an upper limit for the MELD score above which LDLT may not be a viable option is unclear. Poorly decompensated patients have a comparatively poor prognosis and may not tolerate LDLT very well. It is thought that small grafts are unable to meet the needs of patients experiencing severe and prolonged illness. Some experts argue that a MELD score greater than 25 precludes LDLT, since a whole allograft, rather than a partial liver, is required to ensure adequate post-transplant recovery (Li C et al., 2010).

On the other hand, some of the patients with a low MELD score (below 18) may have other medically compelling reasons that prompt to consider LDLT (Li C et al., 2010; Trotter J et al., 2005). These cases may include:

1. Patients with HCC who may benefit from an expeditious LDLT before tumor progression occurs while on the waiting list (see later).
2. Patients with a low MELD score that does not truly reflect their illness e.g. those with cholestatic liver diseases such as primary biliary cirrhosis or primary sclerosing cholangitis. These patients may have significant refractory symptoms or complications, e.g. severe pruritus, intractable ascites, infections, or hepatic encephalopathy.
3. Patients with symptomatic benign hepatic masses, e.g. huge hemangioma, hemangioendothelioma, polycystic liver disease.
4. Patients with metabolic disorders, e.g. familial amyloidosis, hyperoxaluria, tyrosinemia, and glycogen storage disease.
5. Patients where LDLT can help prevent life-threatening complications, e.g. cholangiocarcinoma in primary sclerosing cholangitis.

5.2 Evaluation of the potential recipient

The evaluation of potential recipients for LDLT involves a multidisciplinary team approach which includes transplant surgeons, hepatologists, psychologists/psychiatrists, social workers, nurse coordinators, and other consultants (anesthesiologist, cardiologist, pulmonologist, infectious disease, neurologist, gynecologist, nutritionist, dentist, etc) (Abdullah K et al., 2005). Although the pretransplant workup varies with transplant centers, it should not differ from that of those accepted for DDLT. Most programs require a basic battery of laboratory tests, imaging studies, EKG, upper GI endoscopy and thorough evaluation of the general medical condition and fitness for major surgery (see Table 1).

5.2.1 Psychosocial evaluation of the potential recipient

The pretransplant period can be extremely stressful. Declining health, uncertainty about the possibility of LT, and inability to continue working and participating in daily activities all may increase the risk of depression and/or anxiety for the transplant candidate. Those patients who experience psychological distress prior to transplantation are likely to experience increased distress after transplantation, which may ultimately impact their recovery from transplantation (Walter M et al., 2002). Patients with chronic hepatitis C hepatitis have a greater incidence of depression and anxiety than patients with other forms of liver disease; thus, these patients in particular should be carefully screened and monitored. Patients who experience depression or anxiety are encouraged to seek psychiatric treatment prior to LT to improve their emotional and physical functioning. Some patients experience psychological distress or impairment that interferes with their health behavior to an extent that it may prevent them from adhering to medical directives. These patients should be required to pursue psychiatric services until their functioning is stable enough to be evaluated and satisfactorily listed for LT (Walter M et al., 2002).

5.2.2 Social support

Patients cannot and should not undergo stressful LT without considerable social support. Depending on the severity of the patient's illness at the time of LT evaluation, many family

members and/or close friends may already have assumed care giving duties, including overseeing medication and dietary regimens and coordinating the patient's medical appointments. Specifically, the caregiver's relationship with the patient, current functioning, availability, and willingness to provide perioperative care should be assessed, as patients will rely heavily upon their caregivers during the perioperative period.

Laboratory tests
1. ABO blood grouping.
2. Complete blood count, serum electrolytes, BUN, creatinine, liver biochemistry, alpha-fetoprotein and coagulation panel.
3. Serology (hepatitis markers, RPR, HIV, CMV, EBV, etc).
4. Stool and urine analysis and cultures.
5. Others (serum alfa-1 antitrypsin, ferritin, ceruloplasmin, antinuclear antibody, antismooth muscle antibody etc.)

Imaging studies
1. Chest x-ray.
2. Abdominal ultrasound to assess the patency of hepatic vasculature, presence of ascites, and to exclude focal lesions.
3. Abdominal CT/MRI to exclude HCC, and to clarify abnormalities seen in ultrasound.

EKG

Endoscopy: Upper GI endoscopy to evaluate and treat varices.

For selected patients
1. Mammography, pap smear and pregnancy tests for female patients.
2. Dental and dermatology evaluation.
3. Cardiac stress test if EKG is abnormal.
4. Coronary angiogram if cardiac stress test is positive.
5. Carotid duplex.
6. Pulmonary function tests and arterial blood gas.
7. Bone scan and bone density.
8. Liver biopsy.
9. ERCP.
10. Colonoscopy.
11. PPD skin test.

Table 1. list of investigations required for evaluation of a potential LDLT recipient

5.2.3 Readiness for transplantation

Certain patients may be in denial regarding the severity of their liver disease. It is important to ensure that patients possess a good understanding of the transplant process. When assessing readiness for transplantation, patients are reminded of the importance of continued adherence to all medical directives.

5.3 Contraindications for recipient listing for LDLT

Contraindications to LDLT are becoming fewer. Absolute contraindications for LDLT are similar to those for DDLT and include multisystem organ failure, severe and uncontrolled sepsis, irreversible brain damage, extrahepatic malignancy, advanced cardiopulmonary

disease, active substance abuse, and medical noncompliance. Common relative contraindications include thrombosis of multiple visceral veins, multiple significan abdominal surgeries, morbid obesity, uncontrolled diabetes, HIV, adverse psychosocial factors, and advanced age. Budd-Chiari syndrome and portal vein thrombosis are not usually deemed to be absolute contraindications (Trotter J et al., 2005).

6. Controversial indication for LDLT

6.1 Hepatitis C infection

At present, patients with HCV should not be denied live donor transplants. Large number of studies has been published supporting differing views including that LDLT for patients with hepatitis C yields worse results, equivalent results, and even better results than those of DDLT. The majority of studies, however, have suggested the outcome is not different for HCV-positive recipients undergoing LDLT (Gallegos-Orozco J 2009). The benefits of LDLT in HCV-positive patients include: younger donors, less cold ischemia time, and the possibility of successfully treating patients with antiviral therapy prior to transplantation. It is not certain whether the regeneration of a partial liver graft, particularly in small-for-size grafts may stimulate and increase the rate of reactivation of the latent infection. Previous concerns about a higher frequency of cholestatic hepatitis or more aggressive fibrogenesis with live donors have not turned out to be true (Kuo A; Terrault NA 2009.).

6.2 Hepatocellular carcinoma (HCC)

Success in treating HCC with transplantation has been complicated by the supply and demand issues. LDLT was developed as a solution to this imbalance between cadaveric donor graft availability and the growing number of potential recipients. Changes in organ allocation systems giving priority to specific HCC patients have raised questions to the use of LDLT as a treatment for HCC. From an operative standpoint, the HCC patient is an ideal LDLT recipient, because the MELD priority points assigned to HCC patients mean that they have a much lower calculated MELD score. HCC patients generally have preserved liver function and less portal hypertension, and they are better able to tolerate implantation of a relatively undersized graft (Takada Y et al., 2010).

6.2.1 Indications for LDLT for patients with HCC

6.2.1.1 Long time on the waiting-list for DDLT

A main indication for LDLT in HCC is when the patient will not likely receive a deceased donor organ in a timely fashion with the resulting potential for tumor progression to an untransplantable state. Therefore, in regions where cadaveric donation is limited by religious and cultural beliefs or there is a prolonged waiting time for deceased organs, the use of LDLT to curb tumor progression and increase survival is indicated. Even in areas where the waiting time is moderate, LDLT may still be valuable, if it can be determined that tumor progression is accelerated. Independent predictors of tumor progression may be useful to define aggressive tumors that are more sensitive to waiting list time. Thus, in those patients with large and multiple tumors, and those with high AFP levels, LDLT may still be indicated in those settings with short to moderate waiting time (Bhangui P et al., 2011).

6.2.1.2 HCC exceeding the Milan criteria

A second potential indication for LDLT in HCC patients is the presence of tumors exceeding the Milan Criteria. There is evidence to suggest, that Milan criteria may be too restrictive, and that there may be patients with potentially curable tumors that go untreated because of their exclusion from DDLT listing. The idea of using LDLT to transplant those patients with HCC exceeding the Milan Criteria requires a reasonable possibility of long-term survival (Shirabe K et al., 2011).

6.2.2 Impact of LDLT on HCC recurrence

Some centers have noted an increase in the recurrence of HCC when examined on a stage-for-stage basis in those patients who have had their transplant waiting time shortened by using expanded donor options (LDLT, split liver transplants, domino liver transplants). In contrast, other centers have described no difference in recurrence rates between LDLT and cadaveric transplant for HCC. The explanations offered by the groups that report a higher rate of recurrence are: (1) the release of growth factors and cytokines that induce hepatic regeneration in LDLT. These factors have tumor-promoting effects (2) the biological aggressiveness of the tumor. Prolonged waiting time allows a tumor to declare its biological aggressiveness. Using LDLT to shorten the time on the waiting list may result in transplanting very aggressive tumors that have already metastasized on a microscopic level but are not yet apparent. A short waitlist time may prevent identification of these aggressive tumors, so that LDLT may result in transplanting those patients that are likely to have recurrent HCC. Preoperative microdissection genotyping of the HCC, with measurements of DCP levels, may identify HCC with a high certainty of recurrence and allow judicious use of LDLT minimizing recurrence attributed to "fast-tracking." (Kaido T et al., 2011)

6.2.3 Ethical concerns

Because the donor safety is the paramount concern in LDLT, it is important to consider ethical issues related to LDLT specific to HCC. The potential risks and complications to the donor mean that LDLT should only take place when there is an acceptable survival. However, some will argue that survival outcomes for LDLT for HCC should be compared to nonsurgical/no-treatment outcomes rather than compared to outcomes from transplanting non-HCC patients (Mazzaferro V et al, 2008).

LDLT is ethically justified in those cases where waiting time is disproportionately long and the prolonged waitlist increases the risk of the HCC progression to a nontransplantable state. The risk to the donor can be justified because acceptable survival results can be expected. On the other hand, when LDLT is performed for HCC that exceeds the Milan Criteria it is ethically less clear, because the LDLT is being done due the recipient's exclusion from a possible cadaveric transplant. It is difficult to justify the potential risks to the donor in such a situation where the society prohibits a transplant because it is unlikely to be of benefit. As stated above, there is accumulating evidence, however, that slightly exceeding the Milan Criteria can still yield acceptable survival and for this situation LDLT may be ethically acceptable. Beyond this, there is poor survival, and it is not acceptable to expose the donor to the risks in this situation. Normally if a graft acutely fails, it requires an urgent retransplant (Shirabe K et al., 2011). If LDLT were used in a situation where a cadaveric

donor is contraindicated, such as exceeding the Milan Criteria, the urgent retransplant would require a cadaveric organ, even though the patient was originally contraindicated. In these situations, the patient should not be retransplanted (Takada Y et al., 2010).

6.3 Acute liver failure

Patients with fulminant hepatic failure (FHF) rarely recover spontaneously, and there is a limited interval between the onset and irreversible complications and death. Despite advances in medical management, including hemodiafiltration and plasma exchange, the survival rate of patients with FHF under these treatments is low. Liver transplantation is the only available effective treatment for this group of patients. Timely access to an organ is paramount, to ensure reversibility of the condition. Although the outcomes of LDLT are fairly acceptable despite severe general conditions and emergent transplant settings, the use of LDLT for patients with FHF is a matter of controversy and raises significant ethical issues. The major advantage of LDLT for FHF is the timely availability of a liver graft. This has beneficial effects on the neurological outcomes (Matsui Y et al., 2008).

But LDLT also has major disadvantages. The donor needs to be selected in a timely fashion, under medical and social pressures. In addition, there is the possibility of acquiring an extra small graft, which cannot support the metabolic demand of a recipient. Some physicians have expressed concern that the expedited evaluation in the setting of acute liver failure potentially could preclude the potential donor from making a careful reasoned decision about donation. Because of these concerns, some centers have elected to exclude acute liver failure as an indication for LDLT (Rudow D et al, 2003).

In countries where DD transplants are limited, LDLT is the only chance to rescue patients suffering from highly urgent conditions like FHF, with satisfactory overall patient and graft survival rates. On the other hand, in countries where DDLT is available, such patients are listed as high priority and thus have a good chance to receive a DDLT in a short time. However, even programs with good access to DDLT, LDLT should be kept as a viable option in emergency situations, when any wait increases the risk to the potential recipient.

6.3.1 Ethical concerns

The emergency nature of FHF could preclude the potential donor from making a careful decision about donation. The process of informed consent by the donor could also be influenced by coercion from family members or from the medical team. Autocoercion is also a strong possibility. In the context of extending elective LDLT to the more urgent situation of FHF, transplant programs must pay special attention to the autonomy of the potential donor and must ensure truly informed consent (Rudow D et al., 2003).

7. Donor evaluation

Donor evaluation consists of comprehensive examinations evaluating medical suitability for major surgery, psychological suitability, and liver-related suitability. The two fundamental purposes of the donor evaluation are to ensure (1) donor safety and (2) that the donor is able to yield a suitable graft for the recipient. Members of the evaluation team should include hepatologist, surgeon, psychologist, social worker, and transplant coordinator (Marcos A et al., 2000).

Guidelines for evaluating potential living liver donors are not standardized. There is a great deal of variability among individual centers regarding components of their living donor evaluation protocols. Variability exists in the performance of some diagnostic studies, such as liver biopsy, hepatic angiography, and cholangiography (Totter J et al., 2002). The most frequently used model is a process that involves phases that are progressively more invasive and expensive (see table 2). In principle, one should try to limit the number of invasive investigations and reserve them for the later part of the evaluation. In an effort to limit the cost, more expensive tests are generally performed later in the evaluation process (Abdullah K et al., 2007). Another advantage of such a process includes several opportunities for the donor candidate to re-evaluate and reaffirm the decision to donate. The entire process usually takes a period of 1 to 2 months. In emergent situations, it can be shortened to less than 24 hours.

The initial phase is designed to determine that the potential donor meets all the appropriate inclusion criteria for donation: appropriate blood type, age, body size, and relationship to the recipient. The initial screening history may be performed by an experienced transplant coordinator, or the donor is asked to fill out an information sheet. Questions regarding age; height; weight; blood type (if known); past and current medical, surgical, or psychosocial problems (including a history of alcohol use); and current medication use are included in the questionnaire (Totter J et al., 2002). The lower limit of age for donation is determined by the ability to give legal consent. The potential donor must be between the ages of 18 and 55 years. However, some extend the upper limit to 60 years. Most centers require that the potential donor should show a significant long-term relationship with the recipient. Body size compatibility between the donor and recipient is an important preliminary consideration in the donor evaluation. The potential donor should have an identical or compatible blood type and no significant medical problems. Surgical history is documented, along with current medications. Serum electrolyte levels, blood count, liver function tests, and hepatitis serological tests are performed. Relative contraindications for donor evaluation are discovered frequently in this phase and include, previous significant abdominal surgery, hypertension, hypercholesterolemia, and obesity (Chen Y et al., 2003).

The next phase, involves a thorough history and physical examination to determine eligibility for the operation. Female potential donors of reproductive age should undergo a pregnancy test. The use of oral contraceptive pills or hormonal devices indicates perioperative deep vein thrombosis prophylaxis by subcutaneous heparin in addition to physical means. This phase involves evaluation of the donor liver. This can be subdivided into three components, which include assessment of the (1) hepatic parenchyma, (2) liver volume, and (3) vascular and biliary anatomy (Bradhagen D, et al., 2003).

7.1 Evaluation of hepatic parenchyma

The presence of chronic liver disease and steatosis could have potential implications for both the donor and recipient. This begins with liver biochemistry tests, including aspartate aminotransferase, alanine aminotransferase, bilirubin, alkaline phosphatase, albumin, and international normalized ratio (Chen Y et al., 2003). Blood tests to exclude chronic liver disease often are performed early in the course of the evaluation. These tests include serum transferrin saturation, ferritin, ceruloplasmin, alfa-1-antitrypsin phenotype, antinuclear antibody, smooth muscle antibody, antimitochondrial antibody, and hepatitis serological

Phase 1

The potential donor should satisfy the following before proceeding to the next phases

1. Clinical evaluation:
   - Age: between 18 and 55 years.
   - Identical or compatible blood type with recipient.
   - Body weight, height and Body mass index.
   - Absence of previous significant abdominal surgery and/or medical problems.
   - Significant long-term relationship with recipient.
2. Normal liver function test results, serum electrolyte levels, complete blood count with differential cell count, and negative hepatitis B surface antigen and hepatitis C antibody results.
3. Informed consent (for testing and surgery).

Phase 2

1. Complete and thorough medical history and physical examination.
2. Laboratory tests:
   - Serology: hepatitis A, B and C (surface antigen, core antibody, surface antibody), rapid plasmin reagin, cytomegalovirus antibody (immunoglobulin G), Epstein-Barr virus antibody (immunoglobulin G), antinuclear antibody, human immunodeficiency antibody, toxicology/substance abuse screen.
   - Serum ferritin, iron, transferrin, ceruloplasmin, alpha-1-antitrypsin, transferring, alpha fetoprotein, carcinoembryonic antigen.
   - Urinalysis.
   - Coagulation profile; protein C; antithrombin III; factor V, VII, and VIII.
   - C-reactive protein.
   - Thyroid function tests .
   - Pregnancy test for female donors.
3. Imaging studies:
   - Chest X-ray.
   - Abdominal ultrasound scan.
   - CT scan and magnetic resonance imaging to assess the liver volume, the biliary system, and vascular anatomy.
4. Electrocardiogram.

Phase 3

1. Psychological evaluation, and informed consent.
2. Other tests or consultations to clarify any potential problems uncovered during evaluation: e.g., endoscopic retrograde cholangiopancreatography, hepatic angiogram, liver biopsy, echocardiogram, and stress echocardiogram (some centers routinely perform some or all of these tests as part of the donor evaluation).

Step 4

1. Planning of OR date and availability of intensive care unit facilities.
2. Blood bank: autologous blood donation.
3. Second informed consent (for blood and surgery).

Table 2. Suggested protocol for living donor evaluation

tests (hepatitis B surface antigen and antibody, hepatitis B core antibody, and hepatitis C antibody). Donors with evidence of underlying chronic liver disease or a positive hepatitis C antibody or, hepatitis B surface antigen result are excluded from further consideration. There is no consensus on the use of donors who are alfa-1-antitrypsin phenotype MZ or hemochromatosis C282Y heterozygotes. (Bradhagen D, et al., 2003)

7.1.1 Steatosis

Hepatic steatosis can be characterized histologically as microvesicular or macrovesicular. In general, macrovesicular steatosis is regarded as a benign lesion and often is asymptomatic, whereas microvesicular steatosis often is more serious. Hepatic steatosis can adversely affect both of the recipient and the donor. Steatotic livers may not function well because they are more susceptible to injury from general anesthesia and ischemia-reperfusion. In addition, steatosis has been shown to increase cold ischemic injury and impair hepatic regeneration. Several studies have shown that the risk for primary allograft nonfunction increases with increasing severity of steatosis. Because steatosis reduces functional hepatic mass, some advocate subtracting the percentage of steatosis from the estimated liver mass before calculating the final mass of the hepatic allograft and remnant (Bradhagen D, et al., 2003).

There is currently no agreed cutoff value on the percentage of steatosis that is safe for performance of LDLT. The maximal acceptable amount of steatosis in the donor liver varies among LDLT programs and ranges from 10% to 30%. Several studies have shown that livers from deceased donors with less than 30% steatosis can be transplanted with results similar to organs without fat. Additional studies are needed to better define the acceptable amount of steatosis in the donor liver that will ensure a safe and successful operation for both the donor and recipient. There are some data to suggest that steatosis identified on a predonation biopsy can be reversed with a program of dieting and exercise, and rebiopsy in this situation may show the potential donor to be suitable (Chen Y et al., 2003).

7.1.1.1 Liver biochemistry tests

Liver biochemistry tests are not sensitive or specific and may even show normal results in those with advanced hepatic fibrosis. Other methods, such as body topography and lipid levels, have shown a weak correlation with hepatic steatosis. Of all biochemical parameters, serum triglyceride level appears to have the strongest correlation.

7.1.1.2 Anthropometric measures

Waist-hip ratio seems to be a good predictor of steatosis. An increased waist-hip ratio, which is present more commonly in men, is associated with a greater risk for hepatic steatosis. Of all noninvasive methods for assessment of hepatic steatosis, body mass index (BMI) may have the greatest utility. Several studies have shown a correlation between hepatic steatosis and increasing BMI. In addition, obese patients are more likely to have comorbid conditions (hypertension, hypercholesterolemia, and diabetes), which could increase the risk for postoperative complications after donor hepatectomy. Studies from the general surgery literature, suggest an increased incidence of surgical complications such as bleeding and wound problems in obese individuals. Obesity is also a risk factor for underlying cardiovascular problems, which could lead to an increased chance for medical complications posttransplant. Because of these risk factors, most obese donors will not be

suitable donors. In general, obese individuals (BMI > 28 kg/m2) are unsuitable for donation. Certainly a BMI of > 35 would be a contraindication. Many centers exclude donors with BMI > 30, but others will selectively evaluate these donors and perform a liver biopsy to rule out the possibility of liver steatosis (Bradhagen D, et al., 2003).

7.1.1.3 Abdominal imaging

Ultrasound, CT, and MRI, may detect the presence of hepatic steatosis. Their sensitivity and specificity are technique and operator dependent and also may vary based on degree of steatosis. The imaging modalities are not able to quantify the amount of steatosis or distinguish between simple steatosis and steatohepatitis. Iwasaki and colleagues (2004) have demonstrated that liver-to-spleen CT alternation values ratios using noncontrast CT scan are useful to detect appreciable hepatic macrovesicular steatosis. Newer imaging modalities, such as dual-echo and gradient-echo MR sequences, may provide increasing accuracy for the detection and quantification of hepatic steatosis. At present, the available abdominal imaging studies do not appear to be sufficiently sensitive or specific to replace liver biopsy in most situations (Iwasaki et al, 2004) .

7.1.1.4 Liver biopsy

Liver biopsy is the gold standard for the assessment of hepatic parenchymal disease, including steatosis. In general, liver biopsy is a safe procedure with a low risk for serious complications. Liver biopsy also is useful in excluding occult chronic liver disease. The appropriate use of liver biopsy in the evaluation of living donor candidates is an area of continuing controversy (Bradhagen D, et al., 2003). The role of liver biopsy in the donor evaluation process varies greatly from center to center. Some centers perform liver biopsy on all potential donors, whereas others perform liver biopsy based only on clinical findings that suggest some degree of concern e.g., significant history of alcohol intake, BMI greater than 28 kg/m2, elevated serum ferritin level, presence of steatosis on imaging studies, and so on. Liver biopsy may be avoided is patients with a BMI less than 25 who do not have diabetes, hypertension, or a history of excess alcohol consumption. In addition, they also should have normal liver test results and lipid levels and undergo tests to exclude chronic liver disease and hepatic imaging studies. Liver biopsy results that would preclude donation include fibrosis, nonalcoholic steatohepatitis (NASH), steatosis > 30% and histologic abnormalities such as inflammatory changes (Nadalin S et al, 2005).

7.2 Volumetric assessment

Donor safety is of primary concern, and the smallest resection that provides adequate actual and functional mass for the recipient is selected. Determination of adequate hepatic mass is critical for successful outcomes for both donor and recipient. Height and weight of the donor and recipient pair can be useful in excluding a very small donor when the intended recipient is large, but is not accurate enough in most other situations. Volumetric assessment of the hepatic segments can be performed using either CT or MRI. In general, hepatic mass estimated by volumetric imaging correlates well with actual hepatic mass determined at the time of hepatectomy. It is helpful for the surgeon to work with the radiologist in making the planned line of liver transection and to provide the most accurate assessment of graft volume (Hill MJ, et al., 2009).

Two formulas are used to assess graft size adequacy: (1) graft-recipient body weight ratio (GRBWR) and (2) graft weight as a percentage of standard liver mass. There is an excellent linear correlation between the two, and either is acceptable. It probably is reasonable to correct the GRBWR for steatosis by subtracting the percentage of steatosis noted on liver biopsy from the functional hepatic mass (Hill MJ, et al., 2009).

Resection should not exceed 70% of the total liver volume; that is, the donor should be left with at least 30% of the measured total liver volume. Liver failure has been reported postdonation, with at least one donor requiring an urgent liver transplant because of liver failure after donation. As a result, LDLT has limited applicability in large patients because of the inability to identify a suitable donor (Nadalin S et al, 2004).

A GRBWR of 1% is approximately equal to 50% of standard liver mass. The consensus is that the GRBWR should be equal or greater than 0.8 % (equivalent to about 40 % of the standard liver volume). It should be stressed, however, that these values are based upon LDLT performed in noncritically ill patients. Patients with significant decompensation of chronic liver disease will have excessive metabolic demands and require the maximum liver volume available. On the other hand, some authorities (Selzner et al, 2009) suggest that, patients with Child's class A cirrhosis or those without portal hypertension could receive an allograft with a GRBWR greater than 0.6%. Marcos A (2000) summarized the issue of hepatic mass by stating, "Neither the minimum transplantable hepatic mass nor the optimal mass have been accurately determined. In all likelihood, these values are dependent on both donor- and recipient-specific characteristics and could never be determined with precision".

For physically large recipients greater than 100 kg, the likelihood of finding a donor physically large enough to yield a sufficiently large graft is small. For a pediatric recipient, the main issue is not usually whether the liver volume may be too small; rather the issue is whether it may be too large; this may lead to problems with closure of the abdomen in the recipient. Usually the GRBWR should not exceed 5%(Bradhagen D, et al., 2003).

7.3 Donor liver anatomy

Variations in vascular and biliary anatomy can be quite common. Preoperative knowledge of the anatomical variations is important for planning the operative procedure and for maximizing the chances of a safe and successful operation for both donor and recipient. Preoperative imaging studies include MR angiography and cholangiography, CT angiography, ERCP, and mesenteric angiography. The choice of the imaging modalities is dependent on institutional experience and expertise. Most centers have abandoned the use of invasive tests such as angiogram, and routinely use CT or MRI with 3-D reconstructions (Tsang Let al, 2008).

Common arterial variations include replaced right and left hepatic arteries with and without the presence of proper, right, and left hepatic arteries. These variations are usually detectable by CT or MR angiography. A replaced left hepatic artery increases donor safety because the artery is away from the surgical field and less prone to injury during right hepatectomy (Takatsuki M et al,2006). A completely replaced right hepatic artery is a favorable situation for both donor and recipient. It is longer than a right hepatic artery, remote from the left liver arterial in-flow, and more amenable to dissection from surrounding tissue. The presence of both replaced and standard right hepatic arteries

introduces more complexity. Reconstruction before implantation is possible with a bifurcated recipient proper hepatic artery graft, or the arteries can be sewn separately to the recipient right and left hepatic arteries. Nevertheless, the presence of two arteries increases the risk for thrombosis. Occasionally, a right hepatic branch may arise from the left hepatic artery or a left hepatic branch may arise from the right hepatic artery; both situations may preclude donation (Sugawara Y, et al. 2003).

The most common portal venous variation is separate right anterior and posterior portal venous trunks which may require reconstruction before implantation (most commonly with a bifurcated venous graft) or separate anastomoses during implantation to the recipient right and left portal veins. A sizable left portal branch arising from the right portal system or a right branch from the left system may preclude donation (Xu M, et al, 2008).

Hepatic venous anatomy is also variable. Most commonly, there are two tributaries to the middle hepatic vein (MHV) within the anterior segments of the right liver, segments V and VIII. The need for reconstruction of these tributaries in the recipient remains controversial. Some centers routinely reconstruct both veins, others reconstruct them when large, and others never do (see later). Large caudate veins also are common. Most centers reimplant caudate veins larger than 0.5 cm. Intraoperative ultrasonography is helpful, as well (Radtke A et al., 2010).

The biliary anatomy may be difficult to evaluate accurately preoperatively. Some centers routinely perform MRCP or ERCP as part of the evaluation process. The latter is an invasive test, whereas the former may not provide the degree of accuracy and clarity required to be of value. As a result many centers choose to perform an intraoperative cholangiogram, rather than preoperative biliary imaging. However, ongoing improvements in imaging modalities may soon allow for preoperative noninvasive imaging that is equivalent to the intraoperative cholangiogram with regards to its detail and clarity. The most common variations are multiple right hepatic ducts that require separate anastomoses in the recipient, but. Occasionally, a left duct arises from the right system, but these ducts usually are small and can be safely divided during right hepatectomy (Limanond P et al, 2004).

7.4 Evaluation for thrombophilia

Deep venous thrombosis with subsequent pulmonary embolism represents a serious postoperative complication to the living donor. Several cases of pulmonary embolism have been reported with at least one donor mortality due to this complication. Known risk factors for thromboembolic complications include obesity, use of oral hormone therapy, old age, smoking, positive family history, and an identified underlying procoagulation disorder. These risk factors should be addressed during the evaluation process, including screening tests to identify a procoagulation disorder. Tests include, protein C and S and alfa-1-antitrypsin deficiency, checking for factor VIII elevation, evaluating for the presence of antiphospholipid or anticardiolipin antibodies, and screening for the factor V Leiden and prothrombin gene mutations (Ogawa H, et al., 2011).

7.5 Psychosocial evaluation

This part of the evaluation assesses the donor's mental fitness and willingness to donate, ensuring that consent is obtained in a voluntary manner with the absence of coercion. A

trained transplant psychiatrist, psychologist, clinical social worker, and psychiatric nurse perform this psychological assessment. The professional(s) responsible for psychological assessment should be part of the transplant team and must be experienced in the assessment of liver transplant recipients, so that they understand the particular context and unique psychological demands of liver transplants (Walter M, et al, 2002).

No strict guidelines exist for psychological assessment of prospective donor. However, most transplant centers have adopted formal psychological assessment as an integral part of their donor evaluation. There are several components to this part of the evaluation, but basically the following issues should be addressed: (1) mental, psychological, emotional, and social stability, (2) motivation for donation including a careful assessment to ensure that there is no coercion or inducement involved and competency to give informed consent, and (3) full understanding of, the donation process, the surgery involved, the potential complications, and the recovery involved (Walter M, et al, 2002).

The presence of underlying mental illness, cognitive impairments, aberrant personality traits, or other factors that may interfere with the potential donor's ability to make a reasoned decision may preclude donation. A history of anxiety, depression, or other concerns are discussed to determine whether donation could exacerbate underlying symptoms. Present and past behaviors are explored because they may be predictors to coping with potential donor outcomes. Donors must understand how donation could impact on their mental health (Noma et al., 2010).

The clinical psychologist makes an independent recommendation as to whether the donor is suitable to undergo donation. Informed consent to proceed with the necessary tests and surgery is discussed in detail with the prospective donor. After all the donor candidate's questions are answered to his or her satisfaction, written consent is obtained, and a copy of the consent form is given to the candidate to keep; this is separate from a second written informed consent, which is obtained prior to the LDLT surgery itself. Upon completion of this step, a decision regarding donor acceptability needs to be made by a multidisciplinary committee, which takes into consideration both the medical and ethical aspects of each case.

8. Hepatitis B virus core antibody positive donors

The presence of antibody to hepatitis B core antigen (anti-HBc) in the absence of hepatitis B surface antigen (HBsAg) signifies past exposure to hepatitis B virus (HBV) and may represent a state of resolved infection with immunity or recent clearance of HbsAg and yet persistent low-grade hepatitis activity. The use of live donors who are anti-HBc positive involves consideration of two factors: risk to the donor and potential risk of transmission to the recipient. With regard to the recipient, the issues are no different from those for a deceased donor who is core positive (Suehiro T et al., 2005).

8.1 Risks to the recipient

Experience with the use of anti-HBc-positive livers from deceased donors indicated that the risk of HBV reactivation varies with the recipient's HBV serology status. A variety of terms such as *de novo* hepatitis B, recurrent hepatitis B, transmission of hepatitis B, or reactivation

of hepatitis B have been used to describe HBV infection in this setting. The presence of anti-HBs in the recipient has been reported to protect against reactivation. Anti-HBc seropositivity has also been shown to be associated with a lower risk of HBV reactivation. On the other hand, the concomitant presence of anti-HBs in the donor's serum does not offer any protective effect. Other factors as the Child-Pugh score and the type of immunosuppressive therapy, have been suggested to affect the rate of HBV reactivation through its effect on the host immune response (Munoz S, 2002).

8.1.1 Strategies to minimize the risks to the recipient

a. **Matching:** In DDLT. anti-HBc-positive liver graft from a deceased donor is usually allocated first to HBsAg-positive recipients who would in any case need prophylaxis against recurrence. Unfortunately, a matching policy has little role in the practice of LDLT. A living donor is evaluated for the possibility of donation to a specific recipient (Fontana R & Merion R, 2003).
b. **Prophylaxis against HBV reactivation:** Strategies including hepatitis- B-immune globulin (HBIG) and/or lamivudine to prevent recurrent hepatitis B in HBsAg-negative recipients have been used (Suehiro T et al., 2005).

8.2 Risks to the donor

Theoretically, the potential problems in anti-HBc-positive donors include, (1) the underlying hepatitis infection may delay the recovery and regeneration of the liver remnant. (2) reactivation of integrated HBV virus in the postoperative period, (3) on the long-term, the occult hepatitis infection may progress to the development of cirrhosis or HCC and the previous hepatic resection for liver donation may compromise the prospects for appropriate treatment (Suehiro T et al., 2005). Whether the risk is significant in patients with biochemically and histologically normal liver is controversial. Transplant centers that accept living donors positive for anti-HBc are obliged to continue lifelong follow-up of these donors in order to assess these potential long-term sequels.

8.3 Recommendations

a. Detailed preoperative assessment is mandatory for both the donor and the recipient.
b. Donors with ongoing chronic hepatitis and viremia as indicated by abnormal liver biochemistry and positive serum HBV DNA should be excluded.
c. A routine preoperative liver biopsy is mandatory in the HB c antibody-positive donor. The presence of hepatic fibrosis would preclude donor hepatectomy.
d. Donors seronegative for anti-HBs should receive HBV vaccination to protect against the risk of future HBV reactivation.
e. For the HBsAg-positive recipients, there is no need for any adjustment to the appropriate prophylaxis against HBV recurrence.
f. All HBsAg-negative recipients should receive prophylactic treatment with lamivudine alone or in combination with HBIG after transplantation.
g. Both the donor and the recipient should receive regular and lifelong follow-up. Any episode of liver dysfunction should be investigated for HBV reactivation with serological and virological testing. (Suehiro T et al., 2005; Fontana R; Merion R, 2003)

9. Technical aspects of LDLT

Timing of the donor procedure in relation to the recipient procedure is very important. Recipients with nonmalignant disorders are usually brought to the operating room after the anatomy in the donor has been assessed and found to be suitable for donation. Recipients with potentially malignant lesions should be explored through a relatively small right subcostal incision before the donor is anesthetized. If enlarged lymph nodes are found, biopsies are sent for frozen section (Henrik P et al., 2009; Polak W et al., 2009).

9.1 Recipient hepatectomy

A generous bilateral subcostal incision and upward midline extension is made. Native hepatectomy with caval flow preservation is performed in a standard fashion except for vascular and biliary management. Hilar dissection is made to free the right and left hepatic artery, the common hepatic duct, the right and left portal vein and its main trunk. The tissue around the common hepatic duct is preserved as far as possible in order to retain its blood supply (Soejima Y, et al., 2008). It is then divided close to the liver hilum so as to retain enough length for subsequent duct-to-duct anastomosis. The left and right portal veins must be free for the full length (Kim B et al., 2009). The portal vein is not divided until the liver graft is available. Then, the main portal vein is clamped and the right and left portal veins are divided close to the liver hilum. The hepatic veins are clamped and divided. The hepatic vein stump intended for venous outflow reconstruction is slit open to fashion a triangular venotomy opening that matches in size and shape with the hepatic vein opening of the liver graft (Henrik P et al., 2009; Polak W et al., 2009).

9.2 Donor right hepatectomy

9.2.1 Access

Access is gained through a bilateral subcostal incision with upper midline extension. The ligamentum teres is ligated and divided, and the falciform ligament severed toward the suprahepatic vena cava to reveal the border between the RHV and the MHV. The right liver is then mobilized by dissection of the triangular ligament (Cipe G, et al., 2011).

9.2.2 Intraoperative cholangiogram and Doppler ultrasound

Cholecystectomy is performed and a tube for cholangiogram is inserted through the cystic duct. Cholangiogram can be postponed until the right hepatic duct is roughly dissected and marked with a clip. Intraoperative Doppler ultrasound is performed to map the position and direction of the MHV. The route of the MHV can be drawn on the anterior surface of the liver with electrocautery (Haberal M et al,2011).

9.2.3 Mobilization

The liver is rotated to expose the retrohepatic cava. Tiny, short hepatic veins are meticulously divided. Posterior hepatic veins with a diameter larger than 0.5 cm should be eventually reanastomosed to the cava of the recipient. The caval side of the vein is oversewn, and the venous stump is temporarily clipped. The IVC ligament just below the RHV usually contains vessels of significant caliber and should be oversewn after

transection. The RHV is fully exposed and encircled. The extent of the dissection of the retrohepatic-cava plane can be pictured as a longitudinal line drawn from the space between RHV and MHV to the midportion of the process of the caudate lobe. It usually corresponds to half to two thirds of the anterior surface of the IVC (Cipe G, et al., 2011).

9.2.4 Hilar time

Hilar dissection is started from the right side of the CBD. The RHA is identified first, followed by the portal vein. The RHA is dissected from its origin to the liver parenchyma. All large branches to segment IV should be spared. The posterior aspect of the RPV is then exposed with division of caudate lobe branches, if necessary. The RPV and RHA are temporarily clamped, with a noncrushing vascular clip, to visualize the demarcation line of the liver. The space between the right hepatic artery and the right hepatic duct should not be disrupted in order to preserve the blood supply of the latter (Soejima Y, et al., 2008).

9.2.5 Parenchymal transection

No matter whether CUSA, Water Jet Dissector, Monopolar and Bipolar Coagulator, Tissue Link or Staple Devices are used, the ultimate goal is to transect the parenchyma with the minimal blood loss possible, respecting the anatomical structures vital to the graft and to the donor. Individual preferences dictate the level of comfort in relying on the aforementioned devices (Cipe G, et al., 2011). Under a low central venous pressure and complete muscle relaxation, bleeding during liver transection would not be excessive. The plane of transection is dictated by the position of the MHV and whether it will be taken with the graft or not. (Humar A et al., 2006; Tanaka K et al., 2010; Belghiti J; R Kianmanesh 2003).

The control and transection of the posterior plane above the vena cava can be facilitated by passing the umbilical tape between the hilar structures and the space between the RHV and MHV and pulling it by both ends *"the hanging maneuver"*. In this way the liver is lifted upward and the resection is greatly facilitated.. To include the MHV in the graft during the hanging maneuver, the origin of the MHV is rounded and a tape is passed to the space between the LHV and MHV (Ogata S, 2007; Cipe G, et al., 2011).

Some surgeons routinely give heparin before vascular clamping. The RHA, RPV, and RHV in sequence are separately clamped and divided, and the liver segment is immediately removed. The vascular stumps are oversewn with Prolene sutures. The donor side of the bile duct is closed after the graft is removed and the vascular stumps are oversewn (Henrik P et al., 2009; Polak W et al., 2009; Humar A et al., 2006).

To shorten the cold ischemic time, the graft is not delivered until the recipient is almost ready for graft implantation. Precise communication between the two teams is vital in this regard (Cipe G, et al., 2011).

9.2.6 Back-table procedure

Once delivered, the graft is flushed with cold preservative solution either, University of Wisconsin (UW) (Via Span, Duramed Pharmaceuticals) or histidine-tryptophane-ketoglutarate (HTK; Custodial, Odyssey Pharmaceuticals). The flushing is continued through the portal vein until the effluent from the hepatic vein is completely clear. This

usually requires 3 mL/g of liver weight (Henrik P et al., 2009; Polak W et al., 2009; Humar A et al., 2006; Tanaka K et al., 2010).

Back-table reconstruction may be required as follows:

a. Tributaries of the donor MHV may require extensions with an autologous vein grafts.
b. The RHV may require a venoplasty using an autologous (portal) vein graft. If two right hepatic veins are present, and if they are not too far apart, they can be sewn together.
c. If two portal vein orifices are present, and are not too far apart, they can be sewn together; alternatively, a venous Y-graft (of autologous portal vein branches from the recipient's resected native liver) can be used.
d. The orifices of the bile duct(s), if they are not too far apart, are sewn together; they can also be incised to create a larger anastomosis.
e. The liver's cut surface is inspected. Leaks identified during flushing are oversewn.

9.3 Right liver implantation

The liver graft is placed in a natural position. The implantation starts with *the hepatic vein anastomosis* performed in a triangular fashion using 5-0 Prolene. Attention should be paid to prevent inversion, especially of the posterior wall. There should be no tension on the suture (Polak W et al., 2009; Humar A et al., 2006; Tan H et al., 2007; Tanaka K et al., 2010).

Portal vein anastomosis is completed using running 6-0 sutures to the RPV, portal bifurcation, or portal trunk of the recipient, depending on its diameter and distance. The running sutures are taken on the anterior wall from the medial to the lateral aspects of the recipient and donor portal veins. The suture is tied at the lateral side with incorporation of a "growth factor." to prevent portal vein narrowing at the anastomotic site itself (Starzl TE et al., 1984; Xu MQ et al., 2008).

The vascular clamp is removed from the recipient portal vein and the liver is reperfused. About 500 mL of blood are vented through the (untied) medial aspect of the vena cava anastomosis. The portal vein is clamped again, and the running suture of the medial aspect of the caval anastomosis is tied to the corner stitch. The clamps on the vena cava and the portal vein are now removed, and the liver graft is reperfused (Humar A et al., 2006; Tan H et al., 2007; Tanaka K et al., 2010). The surgeon assesses the quality of liver perfusion and stops any significant bleeding with suture ligation. Usually, the liver pinks up immediately. If the MHV was not included in the graft or if venous tributaries were not reconstructed, the medial aspects of segments 5 and 8 (right anterior or paramedian segments) may be dusky-blue and are frequently swollen. The cut surface is assessed for bleeding and hemostasis is obtained (Henrik P et al., 2009; Polak W et al., 2009; Tan H 2007; Tanaka K et al., 2010).

The arterial anastomosis is usually tedious because of its small size. The arterial anastomosis is usually performed end-to-end with 7-0 or 8-0 nonabsorbable sutures in interrupted fashion and the use of surgical loop magnification. Alternatively, an operating microscope can be used. After revascularization is complete, flow velocity and signal patterns are checked by Doppler ultrasonography (Henrik P et al., 2009; Polak W et al., 2009).

Biliary reconstruction is technically demanding because of the small diameter and short length. More frequently, multiple small ducts are cut flush in the donor's hilar plate are present. As a consequence, the incidence of technical complications, such as leaks and

strictures, is significantly higher with LDDT (vs. DDLT). The requirements are a tension-free anastomosis and preserving periductal connective tissue to maintain the bile ducts' ascending axial vascular circulation (which originates from the RHA and the superior posterior pancreaticoduodenal artery). Biliary reconstruction is by direct anastomosis or hepaticojejunostomy (Kim B et al., 2009). Direct duct-to-duct anastomosis is now increasingly performed. In general, a duct-to-duct anastomosis is advantageous because it reduces operative time, represents a simpler biliary anastomosis, preserves physiologic bilioenteric and bowel continuity, preserves the physiologic sphincter mechanism with a decreased risk of ascending or reflux cholangitis, eliminates the need for bowel manipulation with a decreased risk of intraabdominal contamination and of postoperative ileus, results in earlier return of gastrointestinal function, allows easy radiologic access to the biliary tract. The decision to stent the biliary anastomosis is controversia (Kim B et al., 2009).

Possible options if more than one duct orifice is encountered (Haberal M et al., 2011):

a. If the ducts are in close proximity or share a common wall, they can be joined together and only 1 anastomosis needs to be done.
b. If the distance between the bile ducts is > 1 cm, two enterotomies may need to be made.
c. Multiple orifices can be anastomosed to RHD, LHD, or the cystic duct of the recipient.
d. If only one recipient bile duct is available for anastomosis, the remaining ducts require construction of a Roux-en-Y loop.
e. Very small (< 1mm), distant biliary orifices are sometimes sacrificed and oversewn.

9.4 Donor left hepatectomy

Donor left hepatectomy consists of either full left, or left lateral hepatectomy depending on the relative donor–recipient size ratio(Humar A et al., 2006; Tanaka K et al., 2010).

9.4.1 Exposure

The abdomen is entered through a bilateral subcostal incision and a midline extension. After division of the round and falciform ligament, the LHV and MHV are exposed to their insertion to the IVC. The left triangular and coronary ligaments are excised to reveal the left surface of the LHV. Any accessory or replaced left hepatic artery from the left gastric artery is carefully preserved as the gastrohepatic ligament is divided (Humar A et al., 2006).

9.4.2 Intraoperative cholangiography and Doppler ultrasound

Intraoperative ultrasonography is performed to study the anatomy of the MHV and the LHV. Doppler study is also performed to locate the site of hepatic artery. Cholecystectomy is then performed and the cystic duct cannulated for operative cholangiography. The location of the proposed division of the left hepatic duct is marked by a large size metal clip (Henrik P et al., 2009; Polak W et al., 2009; Humar A et al., 2006).

9.4.3 Mobilization

The retrohepatic cava is defined after incising the overlying peritoneum along its lateral aspect, exposing the cava up to the LHV junction. Smaller draining veins are ligated or

clipped as the entire left lobe and caudate lobe are retracted to the LHV, MHV and RHV are isolated as they drain into the cava (Humar A et al., 2006; Tanaka K et al., 2010).

9.4.4 Hilar time

Hilar dissection is confined to the left side to free the LHA and LPV. Attention should be paid to the caudate branches of the LPV when moved back to its origin. The LPV is usually longer than the right, and a reasonable segment is isolated and looped. Some surgeons advocate preserving the caudate lobe and its dominant vein draining into the vena cava. If a large branch of the LHA arising from the left gastric artery is encountered, it must be preserved for subsequent reconstruction if needed (Soejima Y, et al., 2008).

9.4.5 Parenchymal transection

The Cantlie line is marked at the anterior surface of the liver by diathermy at a plane demarcated after temporary occlusion of the LHA and LPV. At the inferior surface of the liver, the division plane deviates to the left side of gallbladder fossa to meet the proposed dividing line of the LHD. The transection plane is angled to the left after identification of tributaries to the MHV. The LHD is cut sharply and the donor side is oversewn (Tan H et al., 2007 & Tanaka K et al., 2010). Further transection of the parenchyma is performed along the plane of the ligamentum venosus. Once parenchymal transection is complete, hemostasis and absence of bile leak are confirmed on both surfaces. The LHA, LPV, and LHV in sequence are separately clamped and divided, and the liver segment is immediately removed. Some surgeons routinely give heparin before vascular clamping. The vascular stumps are oversewn with Prolene sutures and the donor side of the bile duct is closed (Henrik P et al., 2009; Polak W et al., 2009).

9.4.6 Left-sided liver implantation

The implantation starts with the hepatic vein anastomosis performed in a triangular fashion using 5-0 Prolene. Attention should be paid to prevent inversion, especially of the posterior wall. There should be no tension on the suture. Depending on its length and diameter, the graft portal vein is anastomosed with the LPV, the portal bifurcation, or the portal trunk of the recipient, using running 6-0 sutures. At this point, the hepatic vein and portal vein are declamped. Arterial anastomosis is performed using interrupted 8-0 sutures . Sharp edges, adequate removal of surrounding tissue, and absence of tension or kinks in the anastomosis contribute to the success of this procedure. When two significant arteries are present within the graft, a good back flow in the second one after the reperfusion of the major one can be a good reason to ligate the second one. After revascularization is complete, flow velocity and signal patterns are checked by Doppler ultrasonography. Biliary reconstruction is by duct-to-duct anastomosis or hepaticojejunostomy. Previously, hepatico-jejunostomy was thought to be the only reconstruction method for left-liver graft. Recently, more and more surgeons perform duct-to-duct anastomosis (Kim B et al., 2009).

The liver graft is fixed by suturing the falciform ligament to the anterior abdominal wall to prevent rotation into the right subphrenic cavity. The latter may lead to graft congestion (as a result of MHV kinking) or poor vascular inflow (as a result of folding of the portal vein) and ultimately graft failure (Henrik P et al., 2009; Humar A et al., 2006).

10. The middle hepatic vein controversy

The construction of an optimal venous outflow determines the outcome of LDLT. The routine anastomosis of the accessory inferior hepatic veins with a diameter larger than 0.5 cm was accepted by almost all centers. However, there are no defined standards for the reconstruction of MHV or its tributaries (Chan SC et al, 2011).

The MHV is responsible for the drainage segment 4 together with variable part of the anterior sector of the right liver (segments 5 and 8) in the great majority of the cases. Transection of the drainage territory of the MHV at the time of procurement leads to venous congestion of "marginal zones" in both graft and donor remnant (Radtke A et al., 2010).

Poor venous outflow has been associated with increased sinusoidal pressure, disruption of sinusoidal epithelium, hepatic artery thrombosis, impaired liver regeneration, and dismal outcome. Such physiologic harm can be particularly detrimental in recipients with relatively small grafts and significant portal hypertension, in whom an underlying SFSS situation can turn into graft failure or at least lead to severe biliary and/or vascular complications. A triangular interrelationship between inflow, outflow, and GRBW ratio has been proposed to determine the fate of the graft (Humar A et al., 2006; Tan H et al., 2007).

When the MHV is not taken with the graft, a variable portion of the anterior sector of the right liver remains congested. The relief of the congestion may occur either through intraparenchymal communication between the venous outflow of the anterior sector and the posterior sector drained by the RHV or by reversal of flow in the anterior branch of the portal vein into the posterior branch. The percentage of the congested portion relative to the overall volume of the graft, the GRBWR, the presence and the degree of portal hypertension, and the compliance of the liver determine the magnitude of graft malfunction after transplantation. If the functional mass of the right-lobe graft is adequate without the MHV (high GRWR), some degree of congestion may be tolerated early posttransplant, until the graft has regenerated or the anterior sector drainage is rerouted (Chan SC et al, 2011).

10.1 Available options for the surgical management of the MHV

(1) Exclusion of the MHV from the graft: The rationale is that not all right grafts present with congestion after reperfusion, and simple RHV anastomosis is sufficient in many cases. Obviously, if venous drainage from segments 5 and 8 is predominately via the RHV, including the MHV with the right-lobe graft is unnecessary. With the donor MHV clamped and reversal of flow in the anterior branch of the portal vein detected by Doppler, the temporary occlusion of the right hepatic artery will determine the portion of right liver affected by congestion (Chan SC et al, 2011).

(2) Inclusion of the MHV with the right-lobe graft: This guarantees the most complete drainage of the anterior sector of the right graft. Contraindications are a small predicted residual liver volume (< 30%) in the donor as this may pose the donor at a higher risk of postoperative complications because the regeneration of segment 4 is stunned by the lack of adequate venous drainage (Radtke A et al., 2010).

(3) Inclusion of the distal part of the MHV with the right-lobe graft (leaving the proximal remnant in the donor): This technique preserves large segment 4a venous tributaries into the

MHV in its most proximal portion. Inclusion of the distal MHV improves segment V drainage but not that of segment VIII (Chan SC et al, 2011).

(4) Anastomosing the major tributaries draining the anterior sector of the right liver into the MHV to the vena cava leaving the MHV with the donor rest liver. Doppler waveform characteristics may identify tributaries that could benefit from separate anastomosis. Reversed flow in the MHV tributaries may indicate that reconstruction is not required. Reconstructing MHV tributaries according to diameter (> 5 mm) has also been recommended. The tributaries from segments 5 and 8 are anastomosed to venous conduits of various origins that serve as jump grafts. This has been accomplished with the donor inferior mesenteric vein, iliac vein, ovarian vein, cryopreserved iliac vein, recipient saphenous vein, umbilical vein, LPV, superficial femoral vein, and internal jugular vein. Reconstruction of interposition grafts is, preferably, done on the back table; it can also be done after restoration of portal flow, in order to first assess the degree of venous congestion.

Reconstruction of these branches with interposition grafts results in a more complex operation, longer operating time, and longer warm ischemia time. Also, a relatively long segment of interposition graft makes it more prone to thrombosis (Radtke A et al., 2010).

Whether one technical approach is sounder than the other is probably not possible to decide. Thus, individualized planning is mandatory for the optimal outcome of both donors and recipients in the setting of the high degree of variability of MHV, RHV, and IHV drainage. A selective approach based on GRBWR, greater or less than 1; graft/recipient standard liver, greater or less than 50%; and size of the MHV tributaries, greater or less than 5 mm in diameter; is used by the some groups to decide whether the graft will be harvested with or without the middle hepatic vein (Chan SC et al, 2011).

11. Double liver transplant

If the donor has a large right lobe (> 70% of total liver volume), the remaining left lobe will be small (< 30% of total liver volume) and thus will threaten donor safety. An alternative is to simultaneously transplant two small liver grafts (left lobe or left lateral segment) from two different donors; that is, a double or dual-graft transplant, to solve graft-size insufficiency and provide donor safety. The recipient and two donor operations are started simultaneously. The first graft is orthotopically positioned in the original left position. The second graft is heterotopically positioned to the right-upper-quadrant fossa, rotating it 180°, so that the graft's hilar structures are at the same level as the recipient's right hilar structures (Lu Q, et al., 2010).

12. Retransplantation

The only therapeutic option for failing hepatic allograft is a liver retransplant. The most common causes are chronic rejection, chronic cholangitis, and vascular complications, small for size graft and primary nonfunction. In Re-LDLTs, ethical problems and the timing of the retransplant are controversial. Furthermore, availability of LDLT and DDLT for retransplants differs in each country or region. Donor selection for Re-LDLTs is difficult. The probability of retransplants (with either DDLT or LDLT) is low because of the lack of donors. Thus, serious posttransplant complications after LDLT often lead to death, with no chance of a retransplant. During the procedure, surgeons encounter difficulty in dissecting

surrounding tissues and identifying the important vessels due to the relatively small size and short length of vessels in LDLT grafts (Lerner S et al., 2005).

13. Recipient outcomes and complications of LDLT

The spectrum of posttransplant complications is not different for LDLT versus DDLT. However, the incidence of biliary, and vascular complications may be more common and severe in nature than in DDLT. In addition, new problems such as small-for-size syndrome have been introduced (Soin A et al., 2010).

13.1 Hepatic artery complications

13.1.1 Hepatic artery thrombosis (HAT)

Risk Factors include, recipients body weight < 10 kg or age < 3 years, reconstructing arteries with diameters < 3 mm, ABO incompatibility, excessive intraoperative fresh frozen plasma transfusion, and elevated hematocrite levels. Doppler ultrasonography has high sensitivity for the diagnosis of HAT. By performing serial examinations at frequent intervals during the first 1 to 2 weeks posttransplant, HAT can be detected before it becomes clinically obvious. Early diagnosis permits immediate thrombectomy and revascularization before the patient deteriorates. If there is suspicion for HAT, one can choose to delineate the anatomy with angiography or proceed urgent re-exploration. Angiography offers nonoperative method to diagnose and potentially treat with balloon angioplasty (Steinbrück K, et al., 2011).

Management depends on the timing and the clinical condition . Early HAT, once diagnosed by ultrasound, the patient is immediately taken to the operating room. The anastomosis is taken down. The vessel is cleared of all clot, inspected for intimal injury, and assessed for adequate inflow. If good inflow is present, a primary anastomosis is attempted. If adequate inflow is not provided, an arterial conduit is anastomosed to the aorta. Postoperatively, the patient is closely watched with frequent Doppler. Systemic heparinization is used according to coagulation parameters (Steinbrück K, et al., 2011).

If there is a delay in the diagnosis, or if ultrasound is questionable, selective arteriography may be employed to diagnose the site of thrombosis and to begin therapeutic thrombolysis. Decisions on retransplantation are made based on the clinical condition, patency of the vessels, and appearance of late complications as biliary stricture (Steinbrück K et al., 2011).

Late HAT is often asymptomatic because of the development of a rich collateral network. Attempts at operative revision should not be undertaken, as a large majority survive with normal allograft function, and any operative procedure carries the risk of destroying the graft-sustaining collaterals. Significant late allograft dysfunction needs careful monitoring for septic complications, biloma and cholangitis. Attempts at graft salvage in this population are universally unsuccessful (Henrik P et al., 2009; Polak W et al., 2009).

13.1.2 Hepatic Artery Stenosis (HAS)

HAS, although usually asymptomatic, will eventually progress to HAT. Frequently, patients develop biliary strictures and bile leaks. HAS may be detected on surveillance Doppler. Dampened waveforms with decreased resistive indices (RI) and slow peak velocities suggest HAS. Stenosis should be suspected when the RI is <0.5 or the systolic ascending

time (SAT) is >10 msec. The diagnosis should be confirmed by angiography. If diagnosed in the immediate postoperative period, planned exploration and revision of the arterial anastomosis should be undertaken. Although conventional treatment is either surgical repair or a retransplant, percutaneous transluminal angioplasty (PTA) or stent placement is becoming predominant (Polak W et al., 2009; Humar A et al., 2006; Tanaka K et al., 2010).

13.2 Biliary complications

Biliary complications remain the most common cause of postoperative morbidity and the most challenging complications in LDLT recipients, and occasionally graft loss and death. Risk factors include, small size or multiple bile duct anastomoses, delayed arterial revascularization, HAT, extensive periductal dissection and biliary leaks from the cut-surface of liver tissue., cytomegalovirus infection, and rejection (Yuan Y & Gotoh M, 2010).

13.2.1 Biliary leaks

The sources of biliary leaks could be from (1) The cut surface of the liver, (2) The site of the biliary anastomosis, (3) The site of the intestinal anastomosis, and (4) The exit site of a T tube (or other types of external stents). Anastomotic leaks are caused either by ischemic necrosis of the end of the bile duct or by a technically unsatisfactory anastomosis. Leaks can manifest as sudden onset of biliary drainage from the abdominal drain, or they may present by intraabdominal collection, referred to as "biloma". Biloma can be detected by ultrasonography or CT scan before the recipient becomes symptomatic (Khalaf H et al., 2011).

Leaks from the cut-surface can be managed expectantly as long as it is adequately drained. Leaks from the anastomosis also can be successfully managed with nonsurgical treatment if they are small and localized. Stenting with percutaneous transhepatic cholangiography (PTC) or ERCP at the anastomotic site can resolve minor leaks. If the anastomosis is seriously disrupted, surgical revision is the safest approach (Kohler S et al. 2009).

For bilomas, percutaneous drainage is performed. Once the patient is stabilized, ERCP or PTC is performed, and a stent is placed to bypass the flow of bile through the leak. If excessive leak is diagnosed in the immediate post operative period, operative exploration, drainage, and revision of the anastomosis may be warranted (Khalaf H et al., 2011).

13.2.2 Biliary strictures

Risk factors include, CMV infection, hepatic artery complications, ABO incompatible transplantation, and prior anastomotic leak. The patient may present with asymptomatic elevation of cholestatic liver enzymes or may present with manifestations of cholangitis: fever, jaundice abdominal pain. Ultrasound scan is the initial imaging technique, however, ductal dilatation is often late. Direct cholangiogram is the gold-standard for diagnosing biliary strictures. Any patient with biliary stenosis, especially with multiple strictures, should be evaluated for HAT (Kohler S et al. 2009). Early strictures are often amenable to endoscopic or transhepatic intervention with good long-term results. Operative treatment is indicated for complications of percutaneous therapies and intractable strictures. Patients with strictures associated with HAT should continue to undergo percutaneous treatment. Operative exploration should be avoided, as it disrupts the arterial collaterals supplying the

graft. Evaluation for retransplantation should occur if the strictures affect graft function, associated with bilomas and frequent bouts of cholangitis (Yuan Y and Gotoh M, 2010).

13.3 Portal vein thrombosis (PVT)

Risk factors include, native PVT, the use of interposition grafts, extensive collaterals, portosystemic shunts and splenectomy. The patient may present with ascites, elevated LFTs, and splenomegaly, and gastrointestinal hemorrhage. Diagnosis is made with Doppler and confirmed by venography. Early PVT is treated with surgical thrombectomy and revision of the anastomosis. Late PVT may require surgical shunting to decompress the portal system as treatment of the complications of portal hypertension (Kyoden Y, et al., 2008).

13.4 Hepatic venous outflow block (HVOB)

Risk factors include, technical causes, graft rotation and kinking of the anastomosis and graft regeneration with subsequent rotation. HVOB is occasionally diagnosed during transplant surgery on the basis of swelling and congestion of the graft. The diagnosis is confirmed if intraoperative ultrasonography detects a flat waveform in the hepatic vein. Postoperatively, the clinical presentation includes ascites, elevated liver function test results, splenomegaly, variceal bleeding, lower-extremity edema, and kidney dysfunction. A persistent monophasic wave pattern from the hepatic vein on Doppler ultrasonography suggests substantial stenosis. Subsequent angiography with direct contrast can confirm the diagnosis; the pressure gradient across the stenosis is typically > 3 to 10 mm Hg. Management is by percutaneous balloon venoplasty. Multiple procedures are often required. Stent placement may be required for cases that do not respond to simple dilatation. In severe cases, HVOB may cause graft dysfunction or failure, requiring a retransplantion (Ikeda O, et al., 2010).

13.5 Abdominal compartment syndrome

Causes include, oversized allograft as in adult to pediatric LDLT, closure with considerable intra-abdominal tension, and intestinal edema due to prolonged portal vein clamping. The patient presents with, respiratory compromise, renal insufficiency, hemodynamic instability, and allograft thrombosis because of excessive pressure and positional kinking of the graft.

13.6 The 'small for size' liver graft syndrome (SFSS)

SFSS is a clinical syndrome, which occurs in the presence of a reduced mass of liver insufficient to maintain normal liver function. It is characterized by a combination of early postoperative progressive cholestasis, persistent portal hypertension, ascites, kidney failure, and coagulopathy. Microscopic features include cholestasis with hepatocyte ballooning, vacuolar degeneration, sinusoidal disruption, steatosis, and centrilobular necrosis. SFSS reduces the graft survival rate and increases the mortality rate (Selvaggi G& Tzakis A, 2009).

13.6.1 Pathophysiology

A partial liver graft transplanted into an adult recipient is, by definition, a small-for-size graft. Such a graft is, however, well tolerated when it is not under a critical size. The pathogenesis of the syndrome is primarily tied to graft volume, but three other factors have

been proved to contribute to its occurrence, (1) functional liver mass (graft volume, steatosis, donor age), (2) recipient status and the severity of hepatic disease at the time of the transplant, and (3) graft perfusion (portal hypertension, impaired venous outflow, and immune-mediated cellular infiltration) (Dahm F et al., 2005).

Reduced intrahepatic vascular bed with higher portal flow per gram of remnant liver results in increased portal pressure. Following reperfusion, portal vein flow (PVF) is inversely related to graft size, while hepatic artery flow is reduced proportionately to graft size. Impaired HA flow is results from increased PVF. Enhanced PVF induces shear stress and endothelial injury with progressive alterations of hepatic microcirculation. Shear stress is responsible for up-and-down regulation of vasoregulatory genes, alteration of tissue repair mechanisms, and imbalance of intracellular homeostasis. Liver regeneration may be hindered by increased hepatic portal resistance (Selvaggi G & Tzakis A, 2009).

13.6.2 Prevention and treatment

Different strategies have been proposed (Selvaggi G& Tzakis A, 2009; Dahm F et al., 2005):

a. Pharmacologic approach aiming to reduce the portal pressure.
b. Ischemic preconditioning of the liver to protect the parenchyma against prolonged ischemic periods.
c. Extracorporeal liver support to enhance of liver regeneration.
d. Surgical techniques to control high PVF and PVP after graft reperfusion:
   - Splenic artery ligation (SAL) with or without splenectomy.
   - Meso-caval shunt with downstream ligation of the superior mesenteric vein.
   - Graded porto-caval shunt, portal vein band, or porto-mesenteric disconnection.
e. Retransplantation

14. Donor outcomes and complications

14.1 Recovery of the liver function after donor hepatectomy

Early aminotransferase elevation is common after donor hepatectomy. Liver enzymes peak early, in the first 48 hours, whereas bilirubin tends to peak later, approximately postoperative day 3. Exaggerated enzyme leak in the absence of synthetic dysfunction suggests focal ischemia, which can occur for example with a devascularized segment 4 following lateral segmentectomy. Prolonged or exaggerated cholestasis in the absence of a biliary complication suggests ischemia or a small residual volume. Unusual clinical patterns of liver function should be investigated with ultrasound scanning, duplex sonography and/or computed tomography (Dindo D et al., 2004).

14.2 Donor complications

In worldwide reports donor morbidity ranged between 0% and 67%, depending on the individual definition and recognition of morbidity. Donor morbidity is influenced by variables including center experience, extent and technique of hepatic resection, anatomic factors, and general health of the donor (Fernandes R, et al., 2010). The lack of a standardized assessment of perioperative complications is a limitation to the analysis of donor-related morbidity. A universally accepted classification system for living donor complications would be ideal. This would allow accurate comparisons and help establish trends in the

assessment of morbidity. In this regard, modifications of the Clavien scale for LDLT is gaining acceptance as the standard for reporting surgical morbidity. This system consists of four grades of severity (Clavien P et al. 1994; Dindo D et al., 2004).

Grade I consists of complications that are not life threatening and do not result in any significant morbidity, such as superficial wound infections or transient bile leaks.

Grade II includes complications that have the potential to be life threatening or those requiring drug therapy or <1 foreign blood unit, but does not require therapeutic invasive therapy and does not result in residual disability. An example is any infectious sequelae requiring antimicrobial treatment, postoperative bleeding without requiring relaparotomy and local controlled deep venous thrombosis without thrombembolic complications.

Grade III complications are potentially life threatening, requiring invasive intervention, blood transfusions and/or leads to readmission into the ICU, but does not lead to residual disability. For example, postoperative bleeding requiring relaparotomy, bile leak requiring endoscopic or surgical procedures, deep wound infections requiring relaparotomy or interventional drainage and deep venous thrombosis with pulmonary embolism

Grade IV includes any complication with residual or lasting disability or that leads to death. Examples include liver failure requiring liver transplantation.

The majority of donor morbidity are Grades I and II, with Grade III complications less frequent. The most commonly reported complications are listed in Table 3.

Medical complications

1. Transient cholestasis
2. Pulmonary complications: atelectasis, pneumonia, pleural effusion, and pneumothorax
3. Hypophosphatemia
4. Thrombocytopenia
5. Psychiatric complications
6. Urinary infection

General Surgical complications

1. Wound infection
2. Postoperative bleeding
3. Deep vein thrombosis and pulmonary embolism
4. Incisional hernia
5. Nerve palsy
6. Bowel obstruction, ileus

Hepatectomy related complications

1. Aborted donation
2. Portal vein thrombosis
3. Biliary tract complications: leaks, biloma, strictures
4. Liver failure, hepatic encephalopathy

Table 3. The most commonly reported complications in living donors

14.2.1 Biliary complications

Biliary leaks after left lateral segment donation range from 5% to 10%, with a higher rate (up to 13%) in right hepatectomy. The source of leaks are typically the cut surface of the liver, however, the stump of the bile duct could be the source. Most leaks are diagnosed in the early postoperative period during the initial hospitalization by assessment of postoperative drain fluid, though late leaks are also reported. For most cases, observation and simple external drainage of the otherwise asymptomatic patient will be sufficient to avoid sepsis until the leak spontaneously resolves. More severe leaks require an interventional radiology procedure, endoscopic biliary, or reoperation (Yuan Y & Gotoh M. 2010).

Strictures are reported less commonly but will more likely require invasive intervention. Bile duct strictures result from injury to the right, left or common hepatic duct during hepatectomy. Bile duct strictures may increase the lifetime risk of the donor for developing secondary biliary cirrhosis (Yuan Y, & Gotoh M. 2010).

14.2.2 Acute liver failure

Early postoperative acute liver failure suggests a vascular event like portal vein or arterial thrombosis, or acute outflow obstruction. Although acute vascular events can be reversible with immediate intervention (usually surgical), the patient should be listed for transplantation because survival in acute liver failure is directly related to the timing of liver replacement before the development of multiorgan failure or neurological injury (Fernandes R, et al, 2010; Dindo D et al., 2004).

14.2.3 Small-for-size remnant liver

Liver failure in the absence of an early technical complication like arterial or portal venous thrombosis is likely to be caused by a small-for-size remnant liver. Remnant liver volumes less than 30%, especially if there is underlying steatosis have been associated with prolonged cholestasis, portal hypertension, and normal or near enzymes and synthetic function after hepatectomy ("small-for size-syndrome"), especially in the presence of moderate steatosis. Outcome data for small for size syndrome in donors are sparse. The presence of a concomitant complication like bile leak, infection, or bleeding may exacerbate the poor recovery in a small-for-size liver. Treatment of small-for-size syndrome is supportive care and avoidance of further injury to the remnant (Fernandes R et al., 2010).

15. Living donor mortality

Liver donation puts the donor at risk of medical and surgical complications and even death. Unfortunately, the actual risk of death after a donor hepatectomy is unknown, because of the absence of sufficient database to allow an accurate determination of this infrequent but devastating outcome. When death occurs in a healthy donor, there are exceptional consequences. A donor death will have a devastating effect not only on the families and friends of the donor and recipient but also on all the clinical staff involved in the procedure. The impact of death may spread to other potential donors and recipients, and brings negative publicity and potential economic damage to the transplant center (Trotter J, 2006; Hashikura Y et al., 2009).

Placing a healthy individual at risk of death for a procedure that does not directly benefit him or her needs to be balanced by the autonomy and the psychological benefit to the donor. If a donor gives informed consent and if the transplant team is prepared to undertake the procedure, where is the problem?(Akabayashi A et al., 2004; B Ringe & R Strong 2008)

The estimated donor mortality rate is 0.5%. The causes of death include, pulmonary embolism, pulmonary infection due to uncommon pathogen, emphysematous gastritis, liver failure due to congenital lipodystrophy and non-alcoholic steatohepatitis, acute pancreatitis and cerebral hemorrhage. Donor suicide was also reported. The exact number of live liver donor mortality in the world is not available because no central reporting agency exists. Current estimates of donor death rates are derived from either survey data or single-center reports. The use of survey data (in which transplant programs are retrospectively queried regarding clinical outcomes) is inexact because of incomplete follow-up of all donor outcomes and bias toward reporting favorable results (Trotter, J. et al., 2006). Single-center reports are likely to provide more complete follow-up data but, may be biased and are limited by the relatively small numbers of cases. In the absence of a definitive means to record all donor deaths, the medical literature has included reports of deaths that in many cases are based on verbal communications, circular references, or frankly unsubstantiated outcomes. As a result, the actual number of donor deaths after LDLT is difficult to ascertain and is a subject of considerable speculation (Trotter J 2006; Akabayashi A et al., 2004)

The first donor death reported in the world was related to a fatal pulmonary embolus occurring in an adult-to-child living donor liver transplantation and was reported in the literature in detail. The first reported death in the United States was related to anaphylaxis secondary to medication, also in a left lateral segment donor (Trotter J 2006 B Ringe &R Strong 2008). The first death reported from Asia occurred in Kyoto, Japan (Akabayashi A et al., 2004). The donor was a mother in her late forties donated the right lobe of her liver to her daughter with biliary atresia. The mother fell into liver failure and underwent an unsuccessful domino liver transplant from a donor with a metabolic disease. Histological examination of the donor liver revealed that she had nonalcoholic steatohepatitis (NASH).

In Egypt, the number of LDLT procedures performed annually has increased rapidly in the past few years (Abdeldayem H et al., 2008 & 2009). In January, 2010, the number of LDLT procedures performed in Egypt topped out to more than one thousand procedures, done in 11 centers. The case number 1000 had been performed at the National Liver Institute in Menoufeyia. Although the author is aware of at least 6 deaths among living donors in Egypt. the reported deaths were only two. While one case has apparently been fully reported in the literature, the second death was reported in brief in the proceedings of the international congress of organ transplantation, in November 2008 (Abdeldayem H et al., 2008) The first death was a 45 year-old male who donated the right hepatic lobe to his brother and died of sepsis from bile leak 1 month after donation (El-Meteini M et al., 2010). The second donor was a 22 year-old male who donated his right lobe to his father, suffered from massive intraoperative bleeding from the stump of the portal vein and died of multisystem organ failure after 10 days (Abdeldayem H et al., 2009).

15.1 What is the acceptable risk of mortality to the donor?

The main issue is what the acceptable risk of mortality to the donor is and, who should determine if this risk is acceptable? ? Donors may be willing to accept high rates of mortality

if the life of a loved one is in jeopardy. But what mortality rate is acceptable when the donor understands the risks and coercion has been excluded? There has to be a balance between the risk incurred by the donor and what is acceptable to the recipient, the society, and. the medical community (Trotter J 2006; Hashikura Y et al., 2009; Akabayashi A et al., 2004; B Ringe & R Strong 2008; Abdeldayem H et al., 2008 & 2010, Abdullah K et al., 2005, 2007)

16. Transparency and LDLT

Many, including the author, believe that, the true death, and complication rates among both the donors and the recipients in LDLT are underestimated. As clinicians involved in the evaluation of LDLT, we strive to present accurate information on the risks of the procedure. Because of the discrepancy found between published and unpublished data, the dilemma between reporting rumor vs. reporting facts currently prevails. The reluctance to publish any death or serious complication, although understandable in a fraught medicolegal environment, is not good for patient care or the procedure of LDLT itself. Potential liver transplant donors and recipients are best served by accurate information derived from *genuine transparency*. To maintain truly informed consent, it is imperative that all serious complications and deaths be reported. Transplant centers must be fully aware of their own responsibility: being *honest to themselves and their patients. Secrecy is unacceptable,* as it leads to gossip and speculation by others. If the mortality of this surgery is truly as high as reported by some editorialists, a very different message needs to be conveyed to the patients (Ringe & R Strong 2008; Abdeldayem H et al., 2008, 2009 &2010; Abdullah K et al., 2005& 2007). *To be "transparent" or not to be?* That's the question!, … and the answer is clear.

17. Conclusions

LDLT will continue to play an important role for many patients who have no chance of receiving an organ from a deceased donor in timely fashion. This procedure demands technical expertise in both hepatobiliary surgery and whole-liver transplantation and hard work of multidisciplinary medical team. Every step requires attention and should be planned and performed meticulously. The main drawback with LDLT is the potential for donor morbidity and mortality. In order to promote living donation, absolute transparency about the risks and benefits of this procedure is mandatory.

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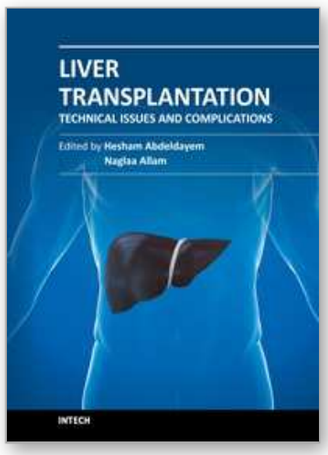

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This book covers a wide spectrum of topics including, but not limited to, the technical issues in living and deceased donor liver transplant procedures, cell and experimental liver transplantation, and the complications of liver transplantation. Some of the very important topics, such as the arterial reconstruction in living donor liver transplantation, biliary complications, and the post-transplant-lymphoprolifrative disorders (PTLD), have been covered in more than one chapter.

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