Editorial

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Recent trends and new developments in liver transplantation

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SUMMARY Liver transplantation (LT) has been an established treatment for end-staged liver disease for acute, chronic, metabolic diseases and liver cancer. Advanced surgical techniques, refined indications and contraindications for LT, improvements of donor selection, prognostic scorings system and immunosuppressive regimens have contributed to the improved outcomes of liver transplantation. The etiologies of cirrhosis have been shifting from viral hepatitis to metabolic associated fatty liver disease. New indications include peripheral or mass forming bile duct cancer, metastases from bowel cancers or neuroendocrine tumors. Resection and partial liver segments 2-3 transplantation with delayed total hepatectomy has been performed to the limited cases, which was the explored technique of auxiliary partial orthotopic LT. Minimally invasive donor hepatectomy (laparoscopic or robotic) has been increasingly done. In this review are described the recent pressing topics in LT.

Keywords liver transplantation, living donor, hepatocellular carcinoma, metabolic associated steatohepatitis, bariatric surgery

Liver transplantation (LT) is the only recognized effective treatment for end-stage liver disease and acute fulminant liver failure. Nowadays, a good survival (of > 90% and > 75% at one year and five years) can be achieved. However, despite recent improvements in donor and recipient selection, perioperative management and organ preservation techniques, there are still several challenges that the transplant community has to face.

1. Metabolic associates steatohepatitis (MASH) for liver transplantation

1.1. Epidemiology

Metabolic syndrome manifest itself in the liver with metabolic dysfunction-associated fatty liver disease. It has affected approximately 25% of the population in the world. And 25% of them will suffer from the progressive inflammatory metabolic dysfunction-associated steatohepatitis (MASH) subtype (*1*). MASH increases to 17–42 million depending on a linear or exponential trendline (*2*). The growing prevalence has led MASH as one of the most common indications for LT (*3*). According to the United Network for Organ Sharing and Organ Procurement and Transplantation Network registry, the number of the patients listing for MASH have approximately three times in ten years (*4*).

A study disclosed that the F0–1 developed in 22–26 years in, F2 in 9 years, F3 in 2 years and F4 in 1 year (*4*). The epidemic of MASH will decrease potential donor pools. It will increase the high-risk recipients. More than 50% of liver transplant patients are obese or morbidly obese (*5*). Obesity will necessitate challenges in the transplantation. The procedure will be technically more demanding with increased operation times and the complications will be expected.

1.2. Bariatric surgery relationship with LT

Bariatric surgery (BS) is a feasible treatment for obesity adjunct in the LT algorithm. BS plus LT will be more reliable procedure for weight loss than LT alone. However, the ideal timing of BS (before, after or simultaneous with LT) remains established (*5*).

The BS procedures include balloon insertion in the stomach, gastric banding, sleeve gastrectomy and gastric/small bowel bypass (*5*). Gastric banding is a less invasive, easy and safe procedure. It will not affect endoscopic access to the biliary tree. The complications will include poor efficacy, foreign body infection and migration of the band (*1*). Sleeve gastrectomy is effective for weight loss and accompanies with a balance between efficacy and safety (*5*). It does not cause malabsorption, affect immunosuppressive drug pharmacokinetics nor prevent access to the bile ducts by the endoscopy. The complication includes bleeding and leakage from the staple-line. Roux-en-Y bypass of small bowel has the largest efficacy for weight loss. However, it is

invasive and takes the longest duration for weight loss. Endoscopic access to the biliary tree is bothered and the immunosuppressive drug pharmacokinetics. The complications include malabsorption and sarcopenia (*5*).

BS before LT is safe and associated with zero-mortality and the reoperation rates ranged 5-17% (*6*). The limitations of the approach included that obesity of LT candidates is less prevalent than that in the general (*7*). One third of transplant recipients develop postoperative metabolic syndrome and/or a de novo obesity. Therefore, it has remained unclear if BS before LT has really had an effect on the obesity natural history of the liver recipients.

BS simultaneous with LT is an attractive idea. It will reduce the number of surgeries (*8,9*). In the selected patients, sleeve gastrectomy and gastric banding will be effective for weight loss However the rates of the surgical complications are higher than those in the general population. A staple line leak rate is 14% and a reoperation rate is 13%. It can be explained by poor nutritional status of these patients and immunosuppressive drugs.

BS after LT will be the last possibility (*10-12*). The advantage of the strategy included that it could select the patients who survived LT and developed obesity after LT. The procedure is technically demanding. An open approach is 45% (*11*). Morbidity remains higher than that in the general. A reoperation rate is 33% (*11*). Totally 14% of the patients died within one year after BS (*11*).

2. LT for cancer except for hepatocellular carcinoma (HCC)

2.1. Peri-hilar cholangiocarcinoma (CCA)

Outcomes of the LT for peri-hilar CCA has been reported. The patients undergo neoadjuvant chemoradiotherapy (with which protocol from Mayo, Toronto, University of Michigan) (*13*). The outcome of the patients who underwent neoadjuvant chemoradiotherapy with Mayo protocol and subsequent LT in 17 centers was analyzed (*14*). The 5-year disease-free survival was 62%.

The United Network of Organ Sharing (UNOS) has now offered a model for end stage liver diseases score exception for peri-hilar CCA. Data from 12 the United States (US) transplantation centers (n = 287) showed post-transplant, recurrence- free survival rates at 5 years being 65% (*15*). Poor prognostic factors included outside the UNOS criteria (the maximum diameter of the tumor more than 3 cm, transperitoneal tumor biopsy or metastatic lesions) or a prior malignancy. The dropout rates from the waiting list is higher than that of HCC; the cumulative incidence rates at 6 and 12 months are 13% and 24% for peri-hilar CCA and 7% and 13% for HCC) (*16*).

2.2. Intrahepatic CCA

Another primary liver malignant diseases indicated for LT has included early stage intrahepatic CCA (single, less than 2 cm in diameter), which is unresectable due to the location or the poor liver functional reserve. According to a multicenter study of the 48 patients (*17*) were found to have intrahepatic CCA on explant pathology, 31% had "early" intrahepatic CCA (single, less than 2 cm in diameter) and 69% had "advanced" intrahepatic CCA (single tumor, more than 2 cm in diameter or multiple). The 1-, 3-, and 5-year recurrence rates in the very early cohort (7%, 18%, and 18%, respectively) were significantly lower than those in the advanced cohort (30%, 47%, and 61%). A median follow-up period was 35 months. The 5- year survival rate was 65% in the very early cohort, which was higher than that in the advanced cohort (45%, p = 0.02).

A more recent multi-center French study (*18*) reported outcomes of the patients with intrahepatic CCA < 5 cm who underwent LT (n = 49) or liver resection (n = 26). It showed that the patients who underwent LT had a higher 5-year recurrent-free survival (75% *vs*. 36%; p = 0.004). Data were shown from a single US center (*19*). The criteria include that unresectable intrahepatic CCA in normal function liver, without the vascular involvement of the tumors, no extrahepatic lesions, treated with gemcitabine-based chemotherapy with a minimum of 6 months and the radiographic response. Six of the 12 patients satisfied the criteria and underwent LT. The overall survival rates were100% and 83% at 1 and 3 years, respectively and the recurrence-free survival was 50% at 3 years.

A follow up report from the group (*20*) revealed that the 18 patients with locally advanced intrahepatic CCA underwent neoadjuvant therapy and LT. The overall survival rates at 1-, 3-, and 5-years were 100%, 71%, and 57%, respectively. Seven of the them (39%) developed the recurrence of CCA.

2.3. Neuro-endocrine tumor (NET)

There are some established selection criteria of LT for NET. Mazzaferro *et al*. (*21*) proposed the Milan NET criteria (Table 1). They reported that a 5-year overall and disease-free survival rates were 97% and 89%, respectively. The 280 patients were referred for LT. Of them 88 patients (31%) were considered to be indicated for LT. And 42 patients (15%) actually underwent LT. The UNOS guidelines for NET (*22*) include no NET recurrence for 3 months and lymph node metastatic lesions, which will turn negative (examined by positron emission tomography scan) at least 6 months before re-enlisting.

According to the European liver transplant registry (ELTR) included the 213 patients who received LT for NET in 27 years. The tumors were synchronous in 119 patients. Prior to LT, 83% patients underwent resection of the tumors. The 76% patients underwent nonoperative treatment (trans-arterial chemoembolization and

Table 1. LT criteria for neuro-endocrine tumor

Milan criteria	
Absolute	
	G1 or G2 grade
	Primary tumor with portal drainage
	Extrahepatic lesions are curatively resected before transplantation
	Tumor involvement < 50% of liver
	Stable disease > 6 months
Relative	
	Age ≤ 60
UNOS guidelines (common with Milan and additionally needed)	
	Unresectable
	Radiographic characteristics of neuro-endocrine tumor
	Metastatic tumors are negative by positron emission tomography scan
	No extrahepatic lesions > 3 months
	If lymph node metastases are detected by positron emission tomography scan, they should become negative < 6 months before re-listing.

LT, liver transplantation; G, graft.

somatostatin analogues). The 1-, 3-, and 5-year overall survival and disease-free survival rates were 81%, 65% and 52%, and 65%, 40% and 30%, respectively.

A UNOS data-based study (*23*) disclosed that the overall survival rates of the patients who underwent LT for NET (n = 184) at 1-, 3-, and 5-years were 80%, 61 % and 49%, respectively. Of them 39% occurred prior to model for end staged liver diseases (MELD) score introduction. The outcome of the was worse than those underwent LT after MELD adaptation. After MELD adaptation, the overall survival rates improve to be 85%, 65%, and 58%, respectively, at 1-,3-, and 5-years.

The study of University of Göteborg (*24*) showed that the 15 patients undergoing LT (n = 10) or multi-visceral transplantation (n = 5). The 5-year overall survival rate was of 90%. The recurrence-free survival rate was 70% at 1-year. The age, hepatic involvement, or Ki-67 was not associated with the outcome. The tumors of the 12 patients were greater than 50% of the total liver. The tumor proliferation rates were less than 10%.

Lim *et al*. (*25*) reported that the 5-year overall survival rate of the LT patients with NET and liver metastasis ranged from 41% to 71% which was comparable with that for the other indications. However the recurrence rate was higher (31-57%).

2.4. Colorectal liver metastasis (CRLM)

2.4.1. SECA study

The experience of LT for CRLM is still limited. The SECA-I study (*26*) was undertaken in Norway. The surgical outcome of the 21 patients who underwent LT was compared with that of the 47 patients treated with chemotherapy. The 5- year survival was higher in the LT recipients than that of the patients who were treated only by chemotherapy (56% *vs*. 9%; $p < 0.001$). There was no significant difference between the groups in median disease-free survival (10 months and 8 months). In the LT patients, better prognostic factors included the small tumor (diameter less than 5.5 cm), time interval between the diagnosis of the primary therapy and the LT was more than 2 years, serum carcinoembryonic antigen level less than 80 mg/L and regression or stability of the CRLM lesions to neoadjuvant therapy.

2.4.2. Living donor liver transplantation (LDLT) for CRLM

A multi-center series (*27*) in North America included the 10 patients who underwent LDLT for CRLM. Of these, the 9 had synchronous lesions and the other developed metachronous disease. Three patients with poor differentiation were included. The median period from the diagnosis and LDLT was 2 years. Proceeding treatments to LDLT included liver resection (n = 4), trans hepatic arterial chemotherapy (n = 3) and tumor ablation (n = 3). The overall and recurrence-free survival was 100% and 62%, respectively.

Rajendran *et al*. (*28*) disclosed a LDLT experience for CRLM (n = 7). The prior treatment included chemotherapy (a median of 20–60 cycles) (n = 6) and partial liver resection (n = 2). The period between the assessment to LDLT was 15 months. The Oslo score was 0–2. Two patients developed recurrence 3 months after LDLT. The duration of the assessment to follow-up was 30 months (median). The overall 3-year survival rate from time of initial assessment was 100%. The 1- and 3-year recurrence-free survival rates were 86% and 69%, respectively.

To maximize the successful rates, a good timing of LT is mandatory. From the point of the view, LDLT will be advantageous. So far, the recurrence rates with LT for CRLM are higher than those of the other malignancies. Larger studies comparing LT with chemotherapy or locoregional therapy may be necessitated.

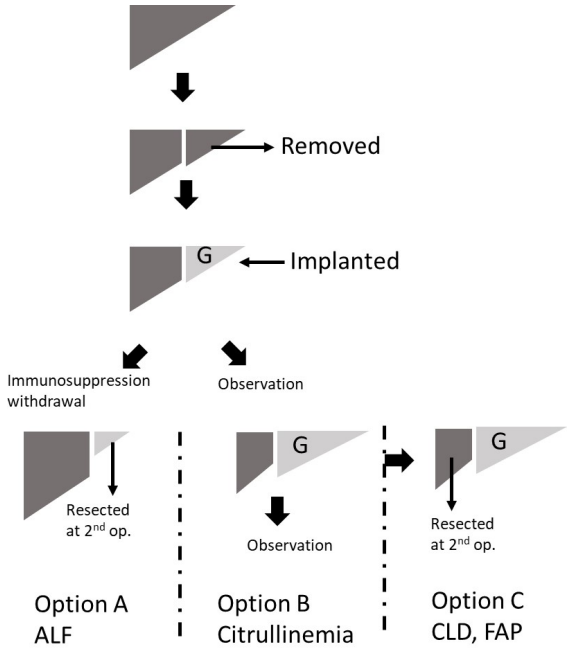

Figure 1. Schematic view of APOLT and RAPID. When indicated for acute liver failure patients, waiting recovering of the native liver, immunosuppressive drugs will be stopped. The graft will be atrophy, which will and be removed **(A)**. Indicated for metabolic diseases which will cause an enzyme deficiency, the graft will be regenerated and observed **(B)**. Indicated for chronic liver disease, HCC in the left liver, or familial amyloid polyneuropathy, the resection of native liver (usually left liver) is resected and a left liver graft is implanted. After the graft regeneration, the remained diseased liver will be removed **(C)**. *Abbreviations*: APOLT, auxiliary partial orthotopic liver transplantation; RAPID, Resection and partial liver segments 2-3 transplantation with delayed total hepatectomy; ALF, acute liver failure, CLD, chronic liver diseases, FAP, familial amyloid polyneuropathy; G, graft.

2.5. Resection and partial liver segments 2-3 transplantation with delayed total hepatectomy (RAPID) procedure or auxiliary partial orthotopic liver transplantation (APOLT)

RAPID is a newly advocated concept, which is an extrapolation of auxiliary partial orthotopic liver transplantation (APOLT), which has been a long-used procedure. APOLT is a heterotopic implantation of a partial liver graft. When indicated for acute liver failure patients, the graft supports the liver function until the functional recovery of the native liver. Recovering of the native liver, immunosuppressive drugs will be stopped. The graft will be atrophy, which will be surgically removed (Figure 1A). When indicated for metabolic diseases which will cause an enzyme deficiency for example citrullinemia, the graft will be regenerated and observed (Figure 1B).

On the other hand, indicated for chronic liver disease, HCC in the left liver, the resection of native liver (usually left liver) with the transplantation of a left liver graft as a first step to secure a space for a graft. After the graft being regenerated, the diseased native liver will be removed in a second stage operation (Figure 1C). Familial amyloid polyneuropathy is a good indication. This procedure is now called RAPID (*29*). A recent report (*30*) indicated that patients with a MELD score ≤ 27 and moderate portal hypertension (*31*) can be indicated for RAPID.

3. Minimum invasive procedures for donor hepatectomy

3.1. Laparoscopic donor hepatectomy (right liver) (*32*)

The donor is placed in the reverse Trendelenburg and lithotomy position. The 5 trocars are used: the 12-mm trocar in the umbilicus for a flexible laparoscope, another 12-mm trocar below the right costal margin and at the mid-clavicular line, both the 5-mm port and the 10-mm trocar below the xiphoid process for retraction of the liver and the 5-mm trocar in the left costal margin of the mid-clavicular line. Intra-operative cholangiography is not performed.

Liver dissection was done with a Cavitron ultrasonic surgical aspirator and a laparoscopic bipolar coagulator without inflow occlusion. The parenchymal transection line was determined by the branching pattern of middle hepatic vein (MHV) under ultrasound observation. The hepatic artery and portal vein were divided using Hem-o-lok. The right hepatic vein is closed with vascular stapler. The graft is resected, put in a retrieval bag and extracted through a 10-cm sized supra-pubic transverse incision.

3.2. Robotic Procedure (*33*)

The donors is in a 20-30 degrees reverse Trendelenburg position. The right shoulder will be upward (*34*). The 12-mm port is placed in the umbilicus. Four 8-mm trocars are placed on the right and left flank.

First, the inferior vena cava (IVC) ligaments are mobilized and the window between the right hepatic vein (RHV) and IVC was exposed. The liver is rotated to the left using the third arm. The short and right inferior hepatic veins are divided and ligated. The right l liver was caudally to cranially mobilized until the root of the RHV is clearly identified.

Next, with the S4b segment lifted, the right hepatic artery and right portal vein are dissected and taped with a vascular loop. The right hepatic duct along Glisson's sheath were dissected. The fluorescent cholangiography was done for identifying the bile duct anatomy.

To expose the parenchyma 4-directional retraction is performed without inflow control. The hanging procedure is done using a Nelaton tube for lateral retraction. Liver parenchyma is transected with a Harmonic scalpel. Hemostasis was achieved with bipolar coagulation. V5 and V8 branches were clipped with Hemo-lok. Hepatic hilum and hepatic vein are divided.

3.3. Comparison between Minimum invasive and open for donor hepatectomy

The meta-analysis (*35*) showed the postoperative outcome of the donors who underwent right liver resection by a robotic or laparoscopic liver resection and conventional open approach. There were no statistical difference between the two groups in the complications ≥ Dindo-Clavien classification IIIa, the estimated blood loss, or the length of postoperative hospital stay.

In 6 centers, totally 1194 donors underwent a right liver resection by a robotic (n = 92), laparoscopic (n = 306) and open approach (n = 796) (*36*). Conversions to open approach were in 1 (1%) robotic and 2 (2%) laparoscopic approach, respectively. Robotic approach had a longer operative time but reduced volume of donor blood loss ($p < 0.001$). There was no significant difference between the two arms in overall and Dindo-Clavien classification ≥ IIIa complications. The donors by robotic hepatectomy had significantly less pain ($p < 0.001$).

4. Conclusions

The perioperative care and surgical techniques advancement have allowed the surgeons to use grafts with extended criteria. TIn the new era of transplant oncology (*37*) and constant innovation of surgical techniques, the field of LT may have continued to evolve progress also from now on.

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