

Review Article

Application of percutaneous liver biopsy in living donor liver transplantation

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Abstract: Percutaneous liver biopsy (PLB) is one of the most important procedures to obtain tissue for assessment of the liver's condition, both for potential donor evaluation and for graft pathological identification in living donor liver transplantation (LDLT). To describe a skillful technique with different situations on LDLT, a series of PLB procedures was developed as a teaching program from clinic to the bench since 1988 to 2012. A total of 2054 episodes of PLB were reviewed in the current series including potential donor evaluation in 8.3% (169), selected liver biopsy in 77.2% (1586), dual graft biopsy in 1.2% (26), pediatric liver biopsy in 8.8% (181), difficult biopsy in 4.2% (87), and intra-abdominal biopsy in 0.24% (5). For infant and pediatric recipients, intravenous general anesthesia or sedation was necessary. The acute rejection rate was 15%, which included 64.6% in mild and 35.4% in moderate degree. The overall complication rate was 0.097%. A satisfactory liver biopsy specimen containing at least six to eight portal triads was necessary, indicating that the ideal biopsy sample should consist of at least a 2-cm length of liver tissue. PLB technique is an important component of the continuing medical education of junior transplant hepatologists and surgeons who want their practice to benefit from a familiarity with new knowledge from clinical practice to the laboratory bench in all its dimensions on living donor liver transplantation.

Keywords: Living donor liver transplantation, Menghini needle, percutaneous liver biopsy, transplant hepatology, ultrasonic guidance

Introduction

Percutaneous liver biopsy (PLB) is a relatively risky invasive procedure because serious complications such as internal bleeding or bile duct damage can occur [1, 2]. To avoid potential legal problems, many doctors are unwilling to perform liver biopsies. However, numerous important issues need evaluation after liver transplantation [3-5]. Day-to-day assessments may be necessary to monitor immunosuppression therapy in recipients to evaluate surgical complications or detect recurrent disease. Despite improvements in diagnostic imaging, liver biopsy remains invaluable in establishing the final clinical diagnosis. We performed a longitudinal observation study using ultrasonic guidance one-man PLB in the liver transplantation program of Kaohsiung Chang Gung Memorial Hospital since 1988 to 2012. There were

enrolled 2054 cases including 169 (8.3%) in potential donor evaluation, 1586 (77.2%) in selected liver biopsy, 26 (1.2%) in dual graft biopsy, 181 (8.8%) in pediatric liver biopsy, 87 (4.2%) in difficult biopsy, and 5 (0.24%) in case of intra/extra-hepatic mass in the current series (**Table 1**). There were not significant differences between the categories in successful biopsy ($P>0.05$). All of the PLB processes were performed by the first author as a transplant hepatologist to avoid personal error for statistical analysis contribution in the technical skill.

Transplant hepatology

In the Western countries, transplant hepatology has postgraduate education programs in surgery (<http://columbiasurgery.org/transplant-hepatology-fellowship/clinical-program-description>). By the definition, the hepatologist is a

Table 1. Percutaneous liver biopsy in Kaohsiung Chang Gung Memorial Hospital liver transplantation program since 1988 to 2012

Category	No (%)
Potential donor evaluation	169 (8.3)
Selective liver biopsy	1586 (77.2)*
Dual graft biopsy	26 (1.2)
Pediatric liver biopsy	181 (8.8)
Difficult liver biopsy	87 (4.2)
Intra-abdominal biopsy	5 (0.24)
Total biopsy	2054 (100)

*: 2 recipients occurred major complication (0.097%, 2/2054) after selective liver.



Figure 1. Ultrasonic guidance one-man percutaneous liver biopsy. Left hand holds the ultrasonic probe, which is picked up by an aseptic plastic bag, then right hand holds the syringe and introduced Menghini needle into the skin, and creating negative pressure with the right ring finger by hocking the end of the suction syringe.

subspecialist from within the specialty of gastroenterology in our center. Most patients that have chronic liver disease such as chronic B or C hepatitis, cirrhosis, or hepatocellular carcinoma are cared for by the hepatologist [6-10]. In addition, performing daily ultrasound examinations of the abdomen is also part of the hepatologist's duties.

An earlier guideline recommended that to document the degree of inflammatory activity and the stage of the disease, as well as for tissue diagnosis of the hepatic malignancy, patients should undergo a PLB, which should be performed by a clinical hepatologist [11, 12], but not by an interventional radiologist. Our training program for transplant hepatologists includes a 2-year course during which all of the liver

biopsies are performed by the fellow and confirmed by the senior hepatologist.

Due to the increase in the number of living donor liver transplantations (LDLTs), PLBs are required almost daily, and more than 2000 have been performed in the past 20 years in our liver transplant program. Transplant hepatologists are a bridge between liver transplant and hepatology medicine, providing everything necessary for the liver transplantation because they are particularly knowledgeable about transplant surgery. Cellular grading of hepatocellular carcinoma may require a PLB during the pre-transplantation evaluation because poorly differentiated carcinomas recur more frequently after LDLT. PLB can also help in decision-making for consideration of LDLT regarding whether pre-transplantation portal vein thrombosis is related to the cirrhosis itself or to the tumor thrombi [13]. Despite new advanced diagnostic imaging, the major role of the transplant hepatologist is increasingly necessary in Asian countries [14]. In our center, all of the PLBs are performed by the senior transplant hepatologist.

One-man Menghini needle liver biopsy

Despite blind PLBs having been performed in some countries, ultrasonic-guided PLB is recommended in order to avoid mis-punctures leading to internal bleeding or gallbladder perforation. Real-time ultrasound is the best method of imaging to have good guidance for needle aspiration of the liver [4, 11, 12].

After aseptic preparation with povidone-iodine of the skin, the hepatologist's left hand holds the ultrasonic probe, and the right hand introduces the injection needle. The ultrasonic probe is packed into an aseptic plastic bag that contains the jelly medium. When the Menghini needle is introduced into the skin, the hepatologist creates negative pressure with the right ring finger by hooking the syringe's tail-end. Under ultrasonic guidance, the left hand holds the probe and adjusts the puncture direction along the puncture line on the screen. The Menghini needle is introduced into the liver parenchyma to the depth that is required (**Figure 1**). Generally, the pathologist would like to have a specimen at least 2 cm long that contains 6 to 8 portal triads [15]. When performing PLB with the Menghini needle, a liver core 1 to

Table 2. Details and advantages of different biopsy needles and biopsy techniques

Category	Menghini needle	Tru-cut needle**
Needle puncture	One-man (right hand)	By operator
Ultrasound probe holding	One-man (left hand)	By assistant
Technique required	Experience skill	General practice*
Operation space needed	One-man space	Two-man space
Puncture accuracy	Limited error	Some error
Time adjustment	Less request	Time-wasting
Tissue puncture	Long track cutting	Focal cutting
Tissue length (cm)	2 to 10	1 to 1.5
Tissue thickness (mm)	1	0.5
Puncture success	Negative puncture	Positive puncture*

*Advantage of the Tru-cut (or biopsy gun) needle biopsy; **: Tru-cut needle liver biopsy was performed in 253 non-liver transplantation cases for the diagnosis of hepatic malignancy in our medical clinic [12, 13].

Table 3. Histological diagnosis of percutaneous liver biopsy in our liver transplantation program

Category	No (%)
Acute rejection	308 (15.0)
Mild	199 (64.6)
Moderate	109 (35.4)
Severe	0
Chronic rejection	5 (0.2)
Cholestasis	536 (26.1)
Non-specific pathologic finding	901 (43.9)
Recurrent hepatitis	45 (2.2)
Steatosis*	254 (12.4)
Post-transplant lymphoproliferative disease	5 (0.2)

*: Donor evaluation plus post liver transplantation steatosis.

10 cm long, depending on the clinical requirements, can be obtained. This provides a great advantage over Chiba needle aspiration, biopsy guns, or Tru-cut biopsy needles (Table 2).

Although the Menghini needle biopsy requires more technique, experience, and skill than the Tru-cut needle biopsy, a bigger piece of liver tissue, up to 1 mm in thickness and 10 cm in length can be obtained. This is very important for pathological documentation, and for the molecular biological, proteomic, and genomic studies performed in liver disease research. In our non-transplant patients, we had performed 253 episodes of Tru-cut liver biopsy for the diagnosis of liver tumors [12, 13]. Although Tru-cut biopsies may be less challenging to perform, we had to take into account the size of the liver tissue obtained. For the diagnosis of

the malignancy or not, small biopsy tissue should be enough to get it. In our series, the acute rejection rate was 15% (308/2054) included 64.6% (199/308) in mild degree and 35.4% (109/308) in moderate degree. There was 0.2% in chronic rejection needed to have re-transplantation and also 0.2% recipients developed post-transplant lymphoproliferative disease (Table 3). In the clinical application of PLB on the liver transplantation setting, these are divided into the pre-transplantation evaluation and the post-transplantation investigation.

Potential donor evaluation

For donor evaluation, PLB is the second step in the process, followed by clinical evaluation and hepatitis and blood screening. About 14% of liver transplantation centers perform PLB on all donors before LDLT. In contrast, 26% of liver transplantation centers do not perform PLB on any donors. Similar to the policy of our center, 60% of liver transplantation centers have selected donors for PLB if it is thought necessary [16]. More than 35% of the graft-recipient body weight ratio is very important for the recipient with end-

stage liver disease leading to decompensation. Severe fatty liver of the donor makes it necessary to access an adequate donor liver graft volume for the safety of both the donor and recipient. In our center, PLB is indicated for donor evaluation if the liver images, such as computed tomography (CT) or magnetic resonance imaging (MRI), identify more than 10% fatty liver [17].

Both left and right lobe PLB is recommended for fatty liver evaluation of the potential donor. After transplantation, the first priority is ensuring the remnant liver volume is secure. On the other hand, LDLT should be avoided for small-for-size syndrome, which is frequently associated with adverse outcomes, especially for high-urgency recipients with a Model for End-Stage Liver Disease score >30 [18].

Table 4. Percutaneous one-man Menghini needle liver biopsy in different clinical setting of living donor liver transplantation

Clinical setting	Graft biopsy priority	Anesthesia type	Tissue request (cm)	Difficulty and time involved*
<i>Pre-transplantation evaluation</i>				
Potential donor evaluation	Left then right	Local	>2, for each side	Moderate
<i>Post-transplantation investigation</i>				
Selected liver biopsy	Left or right	Local	>2	Mild/much [#]
Dual grafts liver transplantation	Left then right	Local	>2, for each graft	Much
Pediatric liver transplantation	Left	General ^{***}	>2	Much
Difficult biopsy ^{**}	Left	Local	>2	Moderate
Other (intra-/extra-hepatic mass)	By the mass location	Local/General	>2	Mild to moderate

*: Biopsy performed is much difficult and risky at the intensive care units. The process difficulty is needs time wasting more.

** : In cases of thrombocytopenia and/or ascites formation, it is more difficult and risky intervention after living donor liver transplantation. ***: Intravenous general anesthesia. #: 2 major complications on selected liver biopsy at the intensive care units after liver transplantation.

Obtaining sufficient core liver tissue is important in order to reduce the calculated error of the fatty liver as a potential donation. In order to perform a good pathological interpretation of the severity of fatty liver, the optimal sample of PLB should be at least 2 to 4 cm in length.

Selected liver biopsy

In some liver transplantation centers, a protocol for liver biopsy after liver transplantation has been established [19], but there is no consensus on how to select patients for liver biopsy [20]. Early PLB is performed 7 days after transplantation. All liver interventional approaches are more difficult and risky during the early period after transplantation.

To ensure hepatic artery and portal vein patency, and to prevent hepatic veno-occlusive disease, low dose heparin infusion is commonly administered after transplantation. Hence, the recipient should have the heparin infusion discontinued the night before performing PLB. Too many drainage tubes for monitoring intra-abdominal bleeding, bile leakage, ascites, and drainage tubes for pleural effusion in the abdominal wall can disturb the approach field for performing PLB. We have experienced two cases of complicated hemothorax after right liver graft PLB. The possibility of this complication is therefore approximately 0.097% (2/2054) in our institute. Both of them completely recovered after conservative treatment, including drainage and blood transfusion. In our center, clinicians select candidates for PLB depending on the clinical requirements, not on a scheduled protocol.

Dual grafts liver biopsy

In cases of insufficient graft volume donation, dual grafts liver transplantation should be considered. This depends not only on the graft volume to avoid small-for-size syndrome, but also on the intrahepatic structure, such as the number of portal veins, the right lobe liver associated with the right inferior hepatic vein, and/or necessary biliary re-construction before the grafts implantation. When there is evidence of acute rejection or unexplained abnormal liver function, jaundice, unexplained fever, or a steatotic liver evaluation, PLB is indicated, and both grafts should be biopsied at the same time [21].

The procedure of dual grafts PLB is similar to that of the living donor evaluation, but difficulty and long process time involved is much different in dual grafts PLB (Table 4). In our experience, PLB is very difficult to perform in cases of the left lobe implanted in the right graft position. This is because the relatively small left lobe graft is rotated and adheres to the abdominal wall in the right flank area, which is a difficult area to perform ultrasonic-guided PLB. No mortality or severe adverse experiences have occurred in our series [22].

Pediatric liver biopsy

Pediatric liver transplantation is a very demanding surgery and usually requires the use of micro-surgical techniques for biliary or hepatic artery construction in the small liver volume. The mean age is around 3.9 years (range 0.25 to 17) in our program [23]. In pediatric LDLT, an

isolated left lateral segment or part of the left liver lobe from an adult donor is a standard selection. Hence, the epigastric approach is the only choice in pediatric PLB. Because of the co-operation and small liver volume considerations of infants and children, PLB should be performed under general anesthesia plus ultrasonic guidance. In the small left liver graft, the hepatic artery and biliary tree definitely needs to be protected during the procedure. Despite blind PLB having been performed on infants and young children, it is not suitable for pediatric LDLT [24]. In our center, if the patient presents with unexplained jaundice after LDLT, the pediatric recipient undergoes CT, MRI, or a CT angiography study. During the PLB, the patient should be provided with optimal sedation and analgesia at the same time. An empty puncture or insufficient liver tissue for evaluation is not acceptable. The satisfactory size of a biopsy specimen containing at least six to eight portal triads is recommended in British guidelines [15]. Menghini needle PLB is the best choice and is satisfactory for this difficult procedure. Sedation using propofol with an oxygen mask is provided for the short time (about 5 to 10 min) it takes to perform PLB [25]. A dose of intravenous sedation with propofol infusion starting at 300 µg/kg/min with oxygen via a nasal cannula is commonly used [26].

Difficult liver biopsy (thrombocytopenia and ascites)

Based on the British guidelines on liver biopsy, patients with platelet counts $<60 \times 10^9/L$ or a prothrombin time >3 seconds compared with the normal control are contraindicated for PLB [15]. However, in patients with end-stage liver disease, the platelet count is usually lower than that. During the early stage after liver transplantation in the intensive care unit, a low dose heparin infusion may be administered. If evidence of acute rejection of the liver graft is suspected, PLB was considered immediately. It has been reported that more than 50% of recipients had a platelet count $<70 \times 10^9/L$ [27].

In our experience, recipients can undergo a successful PLB with a platelet count around $26 \times 10^9/L$. The mean platelet count of our patients is around $58 \times 10^9/L$ (range $15 \times 10^9/L$ to $460 \times 10^9/L$). If the heparin infusion is

stopped overnight, PLB may be performed the next day. No additional blood transfusion with platelets or plasmas in our liver intensive care unit has ever been necessary in association with PLBs.

Ascites is another challenging issue after liver transplantation. In cases of veno-occlusive disease with fever, jaundice, and ascites, sinusoid congestion is a very important diagnostic finding on histopathology. In general, ascites is said to be a contraindication for PLB. Intra-abdominal adhesion formation can form as quickly as 1 week after the surgery [28]. At least a small part of the graft surface should be found adhered to the abdominal wall. Using ultrasonography, the site of the adhesion could be detected. It should be an ideal puncture point for PLB under ultrasonic guidance. We never avoid a PLB for the reason of massive ascites in our pediatric or adult LDLT patients. Although a low platelet count may be a predictor of severe complications after liver transplantation [29, 30], thrombocytopenia and ascites formation are not absolute contraindications for PLB in our center.

Intra-abdominal biopsy

Disease recurrence and new growth development can occur following LDLT. Due to the immunosuppression for organ rejection prevention, post-transplant lymphoproliferative disease can develop [31]. Marked elevation of serum alpha-fetal protein is not a reason for performing PLB. If the imaging studies have not documented the problem, PLB with a conventional Tru-cut or Menghini needle liver biopsy should be considered. It is unnecessary to insist on a particular biopsy method except for avoiding fine needle aspiration (FNA), because FNA cytological findings mean nothing in the context of liver transplantation.

Both intra- and extra-hepatic, sonographic guided Menghini needle biopsy have been performed safely in our program. At least five (0.2%) cases of post-transplant lymphoproliferative disease with retroperitoneal mass presentation were identified by Menghini needle biopsy in our series. One of them was a pediatric recipient who underwent LDLT. The procedures for performing Menghini needle abdominal mass biopsy are similar to that of intra-hepatic PLB. The major concept that

should be emphasized here is that color Doppler sonography must be used to prevent large vessel damage during extra-hepatic mass needle biopsy. Another important consideration is to carefully avoid the hollow organs and to not perform the biopsy if the surface of the mass is not clear.

Tissue bank (from the clinic to the laboratory bench)

After LDLT, the liver tissue is very worth researching. All remaining tissue from the liver biopsy should be sent to a tissue bank and stored in the freezer at -70°C. New advances need the support of basic research. Peripheral blood can provide information, but with genomic and proteomic study of liver tissue, a better understanding of the differences between different individuals after liver transplantation can be achieved. Many transplantation centers would like to know how much influence the new liver graft exercises. In particular, in regards to the drug-metabolizing P450 system, they want to know what impact the metabolism of the anti-rejection drugs between the new liver grafts and their own individual changes in blood flow in the liver has on liver function. Genomic and proteomic research needs liver tissue rather than the peripheral blood cells. The size of a satisfactory liver specimen for research varies between 1 and 2 cm in length [32-34].

In conclusion, the one-man PLB technique is a safe procedure for liver transplantation and it should be taught as a part of training programs in transplant hepatology. In Asian countries, it has not setting up of transplant hepatology training program yet. We hope so the current report could encourage creation of a transplant hepatology program also in these Asian countries.

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