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Ultrasound of liver transplantation

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Introduction

Liver transplantation has become the standard–of-care for end-stage liver disease and for selected liver tumours. From the beginning of the century, more than 85,000 transplantations have been performed in Europe. Between 2005 and 2010, the rate of liver transplantation has been estimated to be approximately 5000 per year (European Liver Transplant Registry, http://www.eltr.org/spip.php?article152). The management of these patients, including ultrasound investigations, might be considered to only be of interest to transplant centres. However, as 10-year survival of patients who have a transplant has stabilized at between 50% and 66% (with survival figures varying according to recipient age), ultrasound practitioners are requested to examine patients, who have had liver transplants, more often. Nonetheless, liver-transplant recipients are still mainly managed in tertiary referral centres in the pre-transplant waiting period and for at least 1 year following transplantation, until clinical conditions have stabilized. Thereafter, patients are managed locally and return to their usual activities.

Following the onset of an unexpected clinical manifestation, which is not infrequent, the patient may only be referred to the transplant centre of origin if conveniently located. However, patients often live some way from the original transplant centre (transplant expertise is centred at only a few sites in most countries) and thus, at least initially, patients need rapid management at the local hospital. The availability of many different modalities at the initial assessment has a strong impact on subsequent outcomes. Ultrasonography is used as the first-line imaging investigation in this setting and a proper and thorough examination is required to avoid misinterpreting relevant abnormalities, which would benefit from timely treatment.

This chapter is aimed at describing the anatomical and technical aspects of liver transplantation, how ultrasound scans should be performed and how to recognize disease conditions, either for expert operators in transplant centres and for operators working in centres not directly connected with transplant units. The chapter is organized according to the chronological clinical approach to transplantation: indications for liver transplantation; assessment of the patient on the waiting list; assessment of the living, related donor, when they become potentially eligible; surgical techniques, including intraoperative ultrasound;

and, most importantly, the post-transplant ultrasound assessment, which is carried out on numerous occasions, not just in transplant centres.

Indications for liver transplantation

Liver transplantation has become the standard-of-care for adults with decompensated or end-stage, medically refractory, cirrhosis or for cirrhosis complicated by early hepatocellular carcinoma (HCC). At the cirrhotic stage, the clinical and ultrasound images are unique, whatever the initial aetiology of chronic liver disease (viral, alcohol, autoimmunity, cholestasis or metabolic). Key elements for establishing the indication for liver transplantation are the presence of complications of cirrhosis, particularly liver failure and portal hypertension, known to be associated with a poor prognosis over the short- to mid-term. The current reference for assessing prognosis and for the decision to "list" the patient for transplantation is the model for end-stage liver disease (MELD) score [(1)]. The MELD score is calculated from serum creatinine, international normalised ratio (INR) and total bilirubin (http://www.mayoclinic.org/meld/mayomodel6.html) and ranges from 6 to 40, accurately predicting 3-month mortality in cirrhotic patients. It is also used for deciding clinical priority in liver graft allocation. Indeed, for patients with a MELD score of <15 the transplant benefit (expected survival with or without transplantation at 1 year) is, in general, uncertain, whereas all patients with a MELD score of >15 have a clear benefit in survival by receiving a liver graft, even over the short-term [(2)]. Clearly, any possible liver transplant candidate must be investigated before being placed on the list to ascertain absence of contraindications to the transplant procedure. Decompensated cirrhosis was the primary indication for liver transplantation in 59% of transplanted patients in Europe between 1988–2009 (www.eltr.org).

Following the 1996 seminal paper of Mazzaferro *et al*. [(3)] it is accepted that liver transplantation is also effective in cirrhotic patients with HCC, provided the tumour stage is early enough. The early tumour stage achieves graft survival equivalent to that observed in patients transplanted for cirrhosis. This limited tumour stage consists of either one single cancer nodule, up to 5cm in diameter, or to 2–3 nodules, the largest not greater than 3cm. These are termed Milan criteria and have been widely accepted worldwide [(3)]. A moderate expansion of these criteria have been proposed and applied in several centres [(4-6)], with

different combinations of number and size of tumours, but without general agreement between centres. Presently, HCC is the second most common reason for liver transplantation, approaching 14% of all indications in Europe between 1988–2009 (www.eltr.org). Ultrasound is the backbone of assessment in these patients, contributing to the characterization of any incidental focal liver lesion in cirrhosis [(7)]. This is an issue of paramount importance especially in patients with multiple nodules, which cannot all be subject to a biopsy. Contrast-enhanced ultrasound (CEUS) provides an added modality to aid characterization of these nodules. Furthermore in cases of concurrent early HCC and portal vein thrombosis, in which it is necessary to demonstrate that thrombosis is not of neoplastic nature, CEUS provides an important contribution [(8)].

Liver transplantation is the treatment for many other liver diseases. The commonest indication, other than cirrhosis and HCC is acute liver failure (9% of transplantations, www.eltr.org), which may be caused by hepatotoxic drugs, acute viral hepatitis and inadvertent poisoning. Non-acute indications in the adult population include metabolic or storage diseases, accounting for 6% of transplantations in Europe over the past 20 years, amyloidosis, some rare tumours (*e.g.* neuroendocrine tumours with unresectable liver metastases or primary liver haemangioendothelioma). In children, the main indications are related to congenital disease, especially bile-tract malformations. In Europe, cholestatic disease accounts for 75% of indications in children between 0 and 2 years of age, and for 42% in patients aged 2–15 years, whereas metabolic disease accounts for 26%, acute liver failure for 16% and cirrhosis for 10%.

The large majority of liver graft recipients are adult, although paediatric transplantation has become an established procedure. Previously, only cadaveric full-size grafts were transplanted, limiting child transplantations to a relatively small-sized graft. The advent of “bench-resizing” allowed to transplant only one lobe or a few segments, thus the waiting list for paediatric transplantation has shortened.

Types of liver graft

A liver transplant is performed with one of the following methods:

- full cadaveric graft,

- living donor graft (corresponding either to the right or the left lobe, resected from the donor and transplanted into the recipient),
- split cadaveric donor grafts (from one single large cadaveric graft, two grafts can be obtained for small-sized recipients, including paediatric recipients),
- reduced grafts (one single cadaveric graft from a large-sized donor needs to be partially resected before transplantation in a small-sized
- domino transplantations (livers of patients affected by metabolic disease caused by the liver, but not affecting the li*ver* itself, *e.g.* amyloidosis, can be explanted and transplanted in a waiting candidate who has, for several reasons, but mainly because they are older, a life expectancy no longer than approximately 10–20 years even with successful transplantation).

Knowing the type of liver graft present is of paramount importance for the ultrasound operator, together with the applied surgical technique, as the anatomical circumstances, including vessel location, varies substantially depending on whether a full graft or a “cut-down” graft has been positioned. Before starting an ultrasound scan, the operator must acquire as much information as possible about the type of graft and the surgical procedure.

Pre-transplant ultrasound

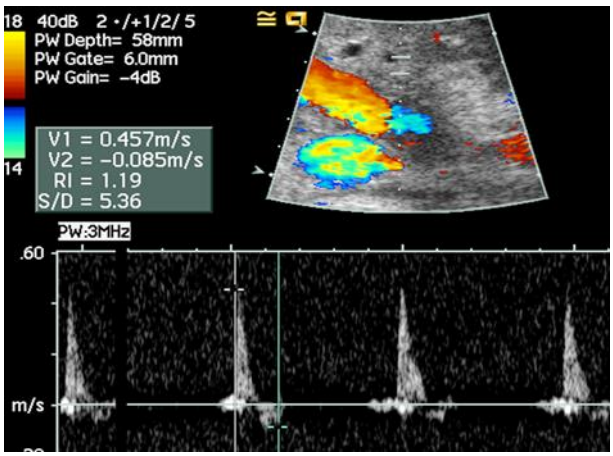
Pre-transplant imaging of transplant candidates has an important role in identifying contraindications to transplantation, anatomical abnormalities and variants that may alter the surgical approach. The technical approach differs in patients with acute liver failure or in patients with chronic liver disease.

Acute liver failure

Patients presenting with acute liver failure often have no chronic underlying liver disease, although patients with chronic liver disease may develop acute-on-chronic liver disease. Patients with acute liver failure are frequently managed in intensive care units and assessed by portable ultrasound. Patients with no previous liver disease may have a normal liver on ultrasound, or may present with a small or a rapidly shrinking liver. Monitoring the size of

the liver by ultrasound is able to guide prognosis; a shrinking liver carries a worse prognosis [(9)]. Patients presenting with acute liver failure will lack the usual features of chronic liver disease and portal hypertension: ascites, coarse liver echo-texture, nodular liver margin and an enlarged spleen. Ultrasound serves as a screening tool to exclude unsuspected disease without contributing to the management of the liver failure, to confirm the patency of the portal vein and to exclude extensive liver malignancy. The assessment of the hepatic artery resistive index (RI) — an indirect measure of liver stiffness — provides evidence for predicting the need for transplantation in acute failure [(10)]. This information may be useful to improve medical management of acute liver failure, avoid or delay the need of transplantation [Figure 1].

Figure 1 **Hepatic Doppler arterial tracing in a patient with fulminant hepatitis. Hepatic arterial Doppler spectrum normally has a low resistance, but becomes high resistance, even acquiring early diastolic flow reversal and absent diastolic flow, as demonstrated in the this case. Such Doppler tracing corresponds to a very high resistance index (RI) during acute liver failure, reflecting an increase in arterial impedance in the liver arterial tree. As a consequence, patients who fulfil liver transplantation criteria, showed a much higher RI than patients that do not reach the criteria and even higher compared with healthy participants (RI 0.77 *vs* 0.71 *vs* 0.64, respectively) [(10)].**



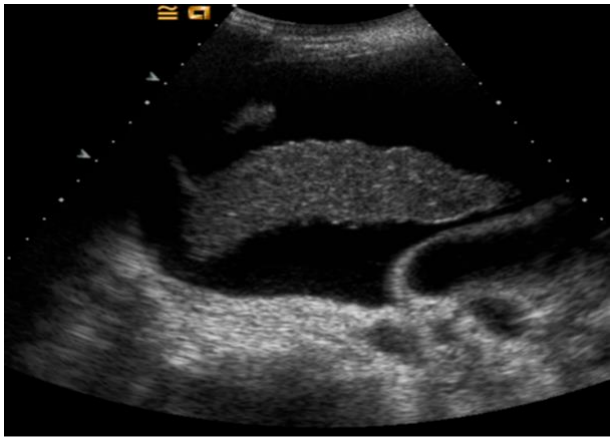
Chronic liver disease

The majority of patients referred for liver transplant assessment, have chronic liver disease, the cause of which has already been established, and the need for transplantation — the final therapeutic option — has been decided by a multidisciplinary team. The importance in continuing to investigate these patients is in recognizing the consequences of chronic liver disease [Figure 2] and to exclude any contraindications to transplantation, which could arise during the waiting list period. The role of ultrasound is vital, but needs to be combined with other imaging modalities. Ultrasound is as an inexpensive, repeatable, bedside examination that accurately assesses the majority of potential complications that could interfere with transplantation. Imaging assessment at 3-month intervals is recommended for waiting list patients with cirrhosis, either with or without HCC. For those without HCC, strict follow up (3-month interval) is aimed at surveillance for the early detection of liver cancer, since presence of HCC may modify transplant priorities or eligibility. However, ultrasound alone is considered sub-optimal as a solitary modality for HCC surveillance in this setting and is combined with CT imaging or MRI every 6 months, providing a more comprehensive overview of the abdominal organs and splanchnic vasculature.

For patients with known HCC, a 3-month follow-up with CT or MRI, often incorporating ultrasound, is recommended, to detect tumour progression beyond transplant criteria, and to detect vascular or lymph node invasion. Any new nodule in a patient with cirrhosis should be considered suspicious for HCC and requires thorough assessment. In this setting, the application of CEUS is recommended.

Briefly, in the preoperative transplant setting ultrasound is aimed at the assessment of the eligibility to transplantation in terms of vascular anatomy (detailed later), presence and exclusion of liver tumours and to rescreen for any unexpected abdominal disease. Once the patient is listed for transplantation, ultrasound can ensure that eligibility is maintained.

Figure 2 The typical features of chronic liver disease, especially in end-stage disease, are a small liver with irregular surface as well as complications such as ascites.



Preoperative vascular assessment

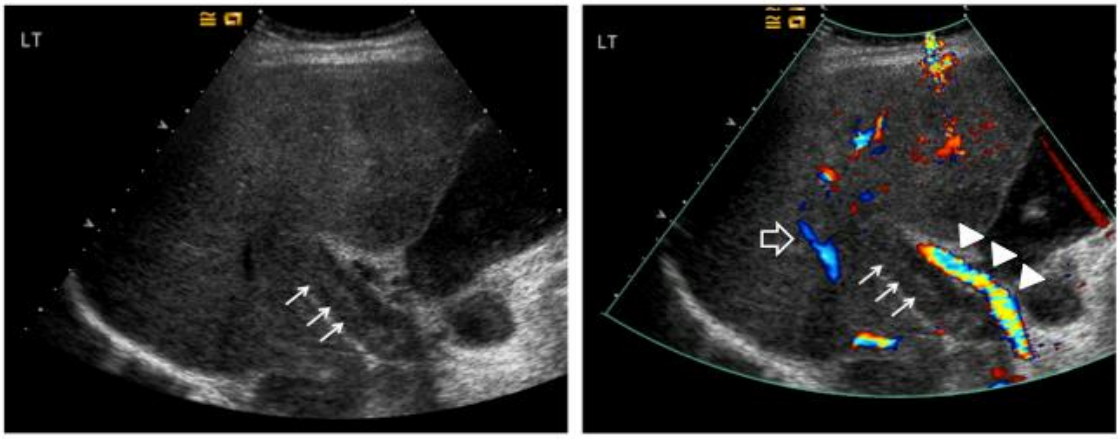
Portal vein

The main portal vein typically divides into the right and left portal veins, and can be readily appreciated on ultrasound with colour Doppler imaging. There are some variations to this pattern, mainly the trifurcation of the portal vein with an early branching pattern in the right hepatic lobe. However, ultrasound is not reliable in the demarcation of more complex anatomy of the portal vein. The assessment of the portal venous flow is not a direct requirement for transplant enlistment, but rather a contribution to the general and prognostic assessment of the cirrhotic patient. However, the assessment of the patency of the portal system is relevant in the evaluation of transplant candidates, especially in patients with HCC, and should be meticulously performed. Portal vein patency should not only be performed at the time of initial assessment, but repeatedly while the patient is on the waiting list. Portal vein thrombosis, either complete or mural, may occur at any time and may only manifest as a worsening of the decompensating liver failure already present.

Portal venous thrombosis is a complication of chronic liver disease, arising in 5–10% of patients with end-stage cirrhosis [(11, 12)]. Although this is not an outright contraindication to transplantation [(13)], preoperative recognition is important to allow assessment of the

extent of thrombus, which is necessary for optimal surgical planning [(14)]. In these patients with end-stage cirrhosis, the thrombus may be hyper-reflective and be seen as completely occluding the vein or with partial occlusion with some surrounding colour Doppler flow [Figure 3].

Figure 3 **The right and main portal vein (white arrows), observed through a right intercostal scan, are filled with echogenic material with complete occlusion of the lumen. This is confirmed with a lack of any colour Doppler signal within the vessel. Colour Doppler signals are seen both in hepatic artery (arrowheads) and in the middle hepatic vein (empty arrow) in the image on the right.**



After the onset of portal vein thrombosis, usually within the first 24–48 hours, thrombus are echo-poor and difficult to detect on B-mode ultrasound. The integration of grey-scale imaging with colour Doppler ultrasound (CDUS) as well as spectral Doppler is used to distinguish patent from occluded portal vessels. Thrombus limited to the portal trunk requires a venous conduit to be created from the patent superior mesenteric vein (SMV) to the donor graft. Thus, the demonstration of SMV patency is also a requirement but may be difficult even with the use of CEUS or with conventional angiographic indirect portography. CT or MRI should be performed in conjunction with ultrasound in the presence of thrombosis. Total thrombosis of the portal venous system (splenic, mesenteric and portal vein) occurs more rarely. Many transplant centres do not regard extensive portal thrombosis an absolute contraindication to liver transplantation, but do require a different surgical

approach, often requiring a portocaval hemitransposition. The inferior vena cava (IVC) is anastomosed to the recipient portal vein, directing blood flow from the lower half of the body through the liver. This requires considerably higher surgical technical skill and is associated with delayed graft recovery and higher risk of complications. Therefore, surgeons must be aware of the existence of extensive thrombosis to adequately select the candidate and the graft (since suboptimal grafts may not recover fully with this approach). Ultrasound is accurate in the detection of portal venous thrombosis, with a small proportion of erroneous, false-positive investigations attributed to a diminished flow rate: the sluggish or ‘static’ flow of portal hypertension [(15, 16)]. Portal vein CDUS has a reported sensitivity of 94.0% compared with indirect portography and the use of CEUS significantly improves visualization in challenging cases [(17, 18)] [Figure 4]. CEUS may be used to enhance weak Doppler signals [(19)] — even in the late phase (more than 3–4 min after injection) — when contrast signals become too weak for conventional low mechanical index CEUS, but are still satisfactorily seen on conventional CDUS. A switch from CEUS to CDUS should always be kept in mind during difficult investigations, but only after completion of CEUS assessment, since CDUS, working at higher mechanical index, disrupts the circulating contrast microbubbles.