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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

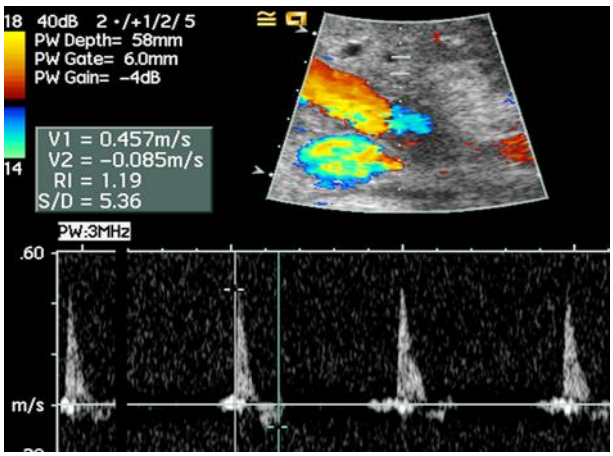
Pre-transplant imaging of transplant candidates has an important role in identifying contraindications to transplantation, anatomical abnormalities and variants that may alter the surgical approach. The technical approach differs in patients with acute liver failure or in patients with chronic liver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



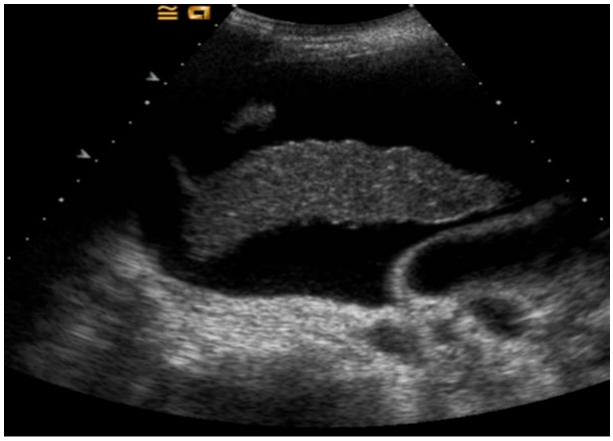
Chronic liver disease

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

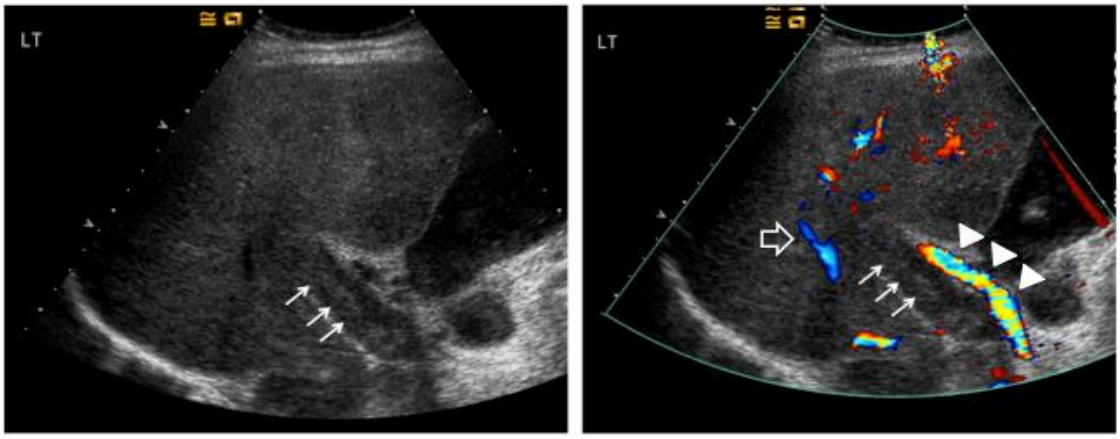
Portal vein

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].

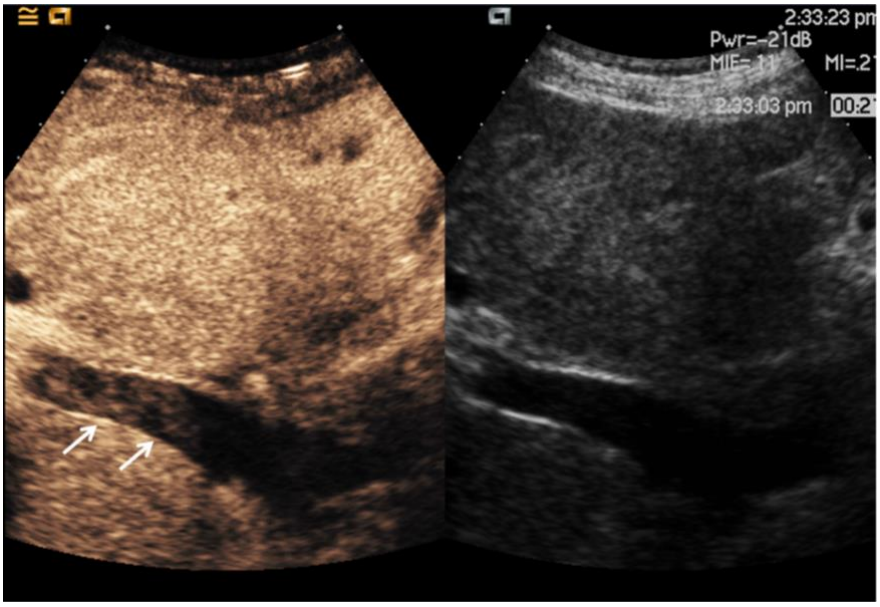
Figure 3 **The right and main portal vein (white arrows), observed through a right intercostal scan, are filled with echogenic material with complete occlusion of the lumen. This is confirmed with a lack of any colour Doppler signal within the vessel. Colour Doppler signals are seen both in hepatic artery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

Figure 4 Contrast enhanced ultrasound shows intraluminal contrast signals during the portal venous phase confirming portal patency even when the portal vein flow is too slow for detection on conventional Doppler techniques. Arrows indicate the portal vein.

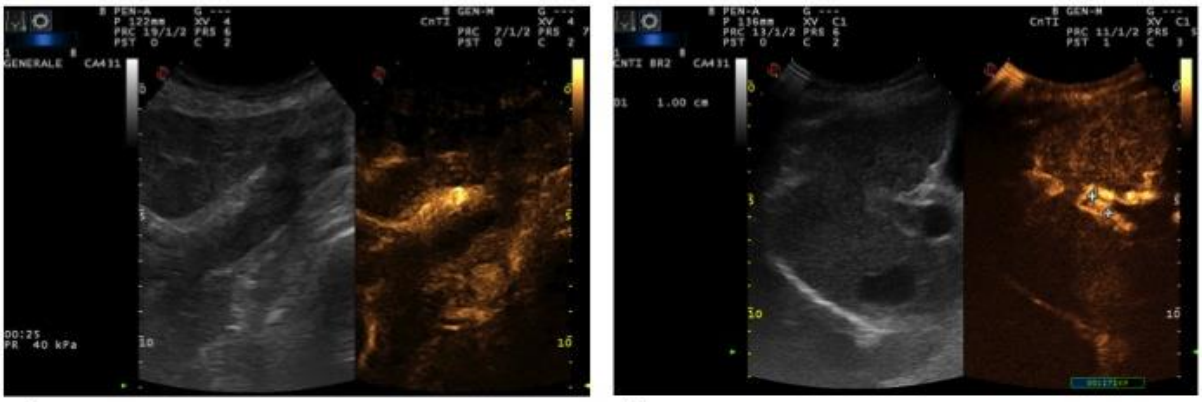


The discussion regarding portal vein thrombus is only valid in the presence of bland, non-neoplastic thrombosis. Tumour portal vein thrombosis (corresponding to direct invasion of the tumour into liver vessels) is an absolute contraindication to liver transplantation because it associated with a very high rate of post-transplant recurrence of tumours. Any portal vein thrombus development in patients with an HCC is likely to be neoplastic. Most centres will exclude patients with simultaneous HCC and portal thrombosis to avoid the risk of transplanting a patient with a high probability of having a contraindication. However, either malignant or benign (fibrin clot or bland) portal vein thrombosis may affect patients with early HCC and liver cirrhosis. A recent prospective study investigated the use of selected diagnostic criteria for benign or malignant portal vein thrombosis for transplantation for HCC, including criteria on the basis of both CEUS and conventional ultrasound [(8)]. Fourteen patients with HCC and cirrhosis who were found with portal thrombosis and an associated HCC, or who developed thrombosis, awaiting transplantation, were considered to be affected by bland thrombosis and therefore finally transplanted with confirmation of non-tumour thrombosis at explant analysis [(8)]. The criteria for establishing the diagnosis of

benign portal vein thrombosis are: lack of vascularization of the thrombus on CEUS, and on CT or MRI; absence of mass-forming features of the thrombus; absence of disruption of the walls of veins (the latter assessed at B-mode ultrasound); and, if uncertainty persisted, ultrasound-guided biopsy of the thrombus for histological examination [(8)]. Patients who did not fulfil the criteria for benign thrombosis were not placed on the transplantation waiting list. Indeed, in patients with HCC, malignant thrombus can be inferred by the presence of enhancement within the thrombus with CEUS [(20, 21)]. CEUS was shown to be more sensitive than CT for the detection and characterization of small thrombosis of peripheral portal branches [(20)].

Briefly, accurate ultrasound investigation, possibly with the support of CEUS [Figure 5], and adequate and extensive reporting of the portal system status is required in any patient awaiting transplantation to enhance the success rate of this complex treatment.

Figure 5 **The two images show the comparison of two different enhancement behaviours of portal thrombosis at CEUS. Extensive thrombosis of portal and splenic veins demonstrates no enhancement with CEUS, confirming non-neoplastic thrombus (A), whereas thrombosis of the right branch of the portal vein (B) demonstrates enhancement (measured by callipers) during the arterial phase in a different patient, indicating a malignant nature.**



A B

Hepatic veins

The main branches of the hepatic vein drain into the IVC. Accessory right hepatic veins often not recognised on ultrasound prior to transplant surgery occur in 6% of people and may be responsible for haemorrhage, if they are not diagnosed.

Occlusion of venous flow occurs in Budd-Chiari syndrome and CDUS is an accurate method of assessing for vein patency [(22)]. Non-visualisation of the veins is not always indicative of occlusion and use of CEUS may improve operator confidence [(13)]. Hepatic venography remains the reference standard used in diagnosis of hepatic vein occlusion demonstrating a spider web appearance due to occlusion of the hepatic veins. With current technologies, such an invasive procedure is usually preceded by contrast-enhanced CT, which often clarifies the circumstances and helps to delineate vascular anatomy. A thorough assessment is required in candidates for transplantation of outflow tract disease (Budd-Chiari syndrome), whereas in all other causes of chronic liver disease, the detection of hepatic vein patency is sufficient.

Hepatic artery

Usually the assessment of the hepatic artery by Doppler ultrasound in potential candidates for liver transplantation is not required. As previously suggested, the only exception is in the case of fulminant hepatic failure, in which the RI of the hepatic artery increases, mirroring the decline in hepatic function, and might be used as a further parameter to indicate the need for transplantation, but only a few centres rely on this parameter [(10)].

Portal-venous shunts

The creation of a shunt between the portal and hepatic venous systems, a transjugular intra-hepatic port-systemic shunt (TIPSS), is a common procedure in the management of variceal haemorrhage and intractable ascites secondary to portal hypertension. A TIPSS procedure is often a temporary manoeuvre until transplantation can take place. TIPSS stents have a substantial rate of stenosis and occlusion, and there is a need for regular imaging [Figure 6 and 7]. Doppler ultrasound is well-established as a valid tool for assessment, with established criteria for TIPSS dysfunction detailed in the chapter on liver ultrasound. Any

suspected TIPSS stenosis on ultrasound should be referred for further imaging, either with MRI or transjugular venography. Surgical portocaval shunts may be visualized by Doppler ultrasound, but contrast-enhanced CT is required for correct anatomical assessment and planning of transplant surgical strategy.

Figure 6 **TIPSS visualized both in B-mode (A, arrows) and colour Doppler ultrasound examination (B). The aliasing phenomena in panel B(arrow) reflects the rapid blood flow inside the artificial shunt**

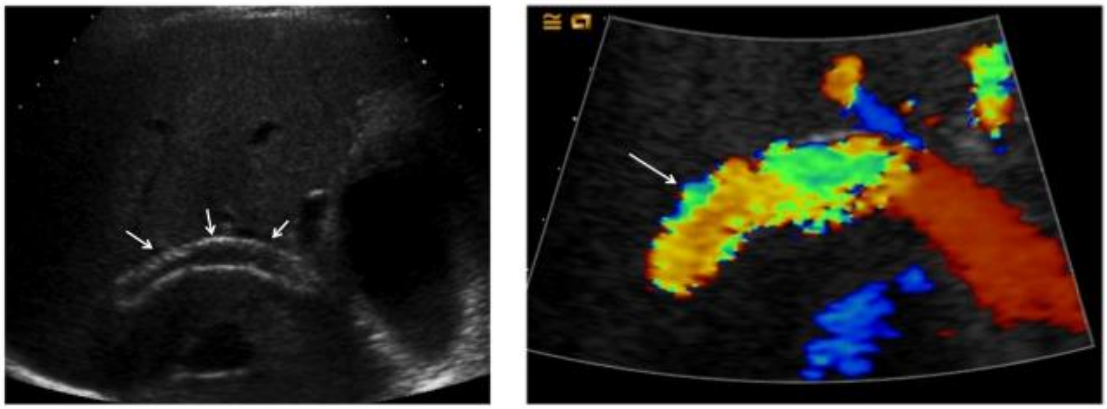
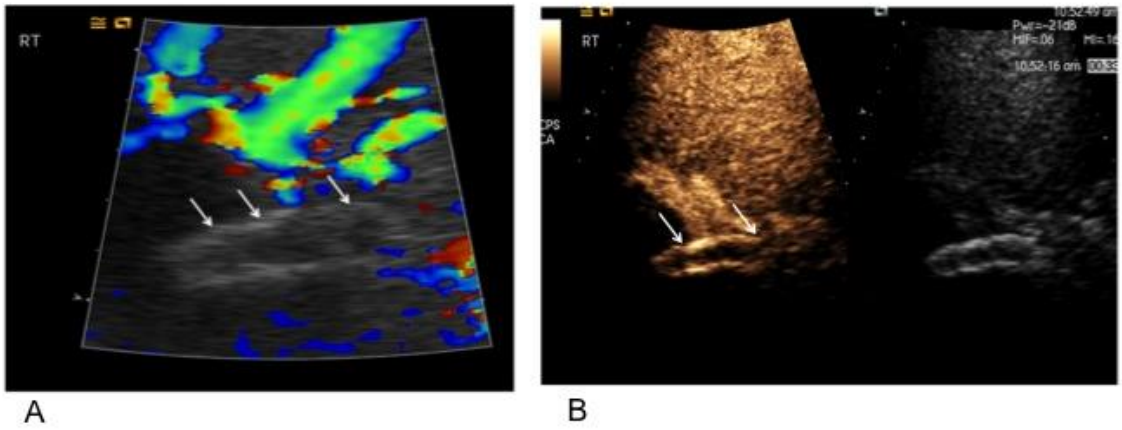


Figure 7 **Another case of TIPSS in which optimized colour Doppler could not show any flow inside the shunt (A, arrows). CEUS examination confirms the diagnosis of thrombosis of the shunt in (B) (arrows).**



Assessment of living, related donors

Although ultrasound of the abdomen is routinely performed as part of the radiological work-up, it does not dictate the surgical approach. Ultrasound will confirm normality, and exclude liver parenchyma changes and unsuspected lesions. The focus of the examination is the hepatic vasculature, with particular attention paid to the anatomy of the artery and hepatic veins, because this influences choice of resection. Normally recipient candidate patients will routinely undergo triple-phase contrast-enhanced CT of the liver (arterial, portal and hepatic venous phases), giving the surgeon the maximum possible information with which to plan the intervention. Early arterial phase with three-dimensional reconstruction is the ideal method to assess the hepatic arterial tree and to decide on the likelihood of obtaining two satisfactory portions of the liver.

Donor liver volume assessment

Determining successful outcome of transplantation, particularly with split-liver grafts in paediatric and living, related donor transplantation, is the size of the graft used. A donor liver should be not less than 50% of the size of the substituted native liver; below this there is a risk of post-transplantation hepatic failure. A graft may be up to 20% larger than the explanted liver, any larger size implies a potential risk of compression of the adjacent vascular structures diminishing the perfusion of the liver. Furthermore, disparities lead to difficulties in the execution of vascular and biliary anastomoses [(23, 24)]. It is possible to determine the volume on ultrasound by measuring the cross-sectional area of the liver on consecutive images in the sagittal plane and adding these together, a technique that has been shown to be accurate and reproducible [(25)]. This is a time consuming technique and is normally undertaken with contrast-enhanced CT, which is accurate and has the additional capability of calculating segmental volumes. Ultrasonography has, therefore, hardly any role in this setting.

Surgical techniques

Surgical techniques and split liver grafts for adult liver transplantation

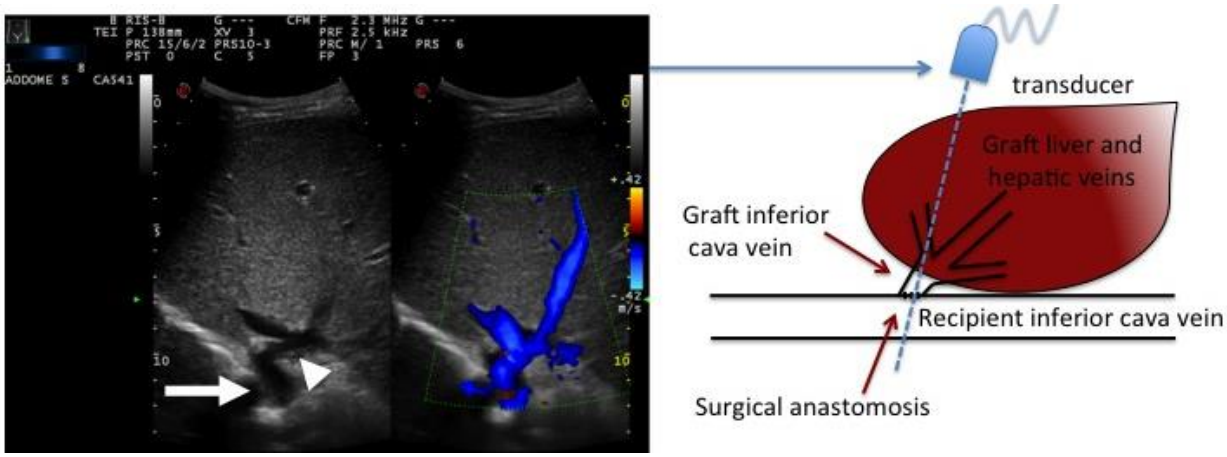
When conducting an ultrasound examination in the post-transplant patient, it is important to know the type of surgical procedure performed, as variations exist, *e.g.* transplant of the whole liver, transplant of a single liver lobe or segmental liver transplantation. After

transplantation of a partial graft (spit liver) the volume increases and reaches a final size over 4 to 8 weeks, but the vascular anatomy does not alter, maintaining the original configuration of the transplanted portion. It is important, therefore, to be aware of the type of graft used. In adults, the normal procedure is to explant the native liver and replace it with a cadaver allograft, termed orthotopic liver transplantation (OLT). Revascularization of the allograft requires anastomoses of the hepatic artery, portal vein and IVC, with biliary tract reconstruction performed to establish bile drainage; the gallbladder is normally removed to avoid ischaemic and infectious complications. Many different anastomoses can be performed according to the preference of the surgeon, the anatomy of the donor and recipient vessels, and the underlying disease. Traditionally, the anastomoses are 'end-to-end' except with the IVC in which a modified technique preserves a stump of the donor IVC and anastomoses is formed with the three hepatic veins (‘piggy-back’ technique). This technique avoids clamping the IVC during surgery [Figure 8].

When discrepancies exist in vessel diameter or length, or the portal vein thrombosis is localized and the thrombus cannot be removed, conduit vessels — prepared with bench reconstruction (either arterial or venous, often iliac vessels, often from donor vessel grafts) — are used, leading to the need of two anastomoses, at the proximal and distal ends of the conduit. When this occurs, the artery is seen to be at increased risk of thrombosis. An older donor (>65 years old) is also a known risk factor for arterial thrombosis [(26)]. In the case of marked arterial size discrepancies, a patch reconstruction at the site of gastroduodenal artery origin is occasionally performed, which may subsequently develop an aneurysmal dilatation. With anatomical variants of the donor graft, right and left hepatic arteries may require separate anastomoses to different vessels. Knowledge of this situation is particularly relevant for ultrasound assessment. Occasionally, if needed, the common hepatic artery may be implanted directly onto the abdominal aorta.

Figure 8 **Following liver transplantation the ultrasound operator is able to appreciate the double lumen of the piggy-back anastomosis in a subcostal panoramic view. The left image shows the conjunction of the hepatic veins (white arrow) plus a minor part of donor inferior vena cava (arrowhead). The schematic**

image represents the piggy-back technique and how the operator must orientate the transducer in a subcostal scan to visualize the anastomosis.



The term liver reduction is used when a liver is cut down to the required size for the recipient and the remaining segments are discarded. The technique of liver splitting is an extension of liver reduction and allows a donor liver to be used to transplant two recipients rather than one. The liver is usually split into an extended right lobe and the left lateral segment, each of them being suitable for selected recipients [(27)]. In case of splitting, the IVC is retained with the right lobe. The main portal trunk and hepatic artery are assigned to one side or the other of the split (not necessarily the same side). This inevitably results in anastomoses, closer to the hilum than usual, on the grafts with a short portal vein or hepatic artery. An exception to this arises if there is an anatomical condition of replaced right or left hepatic artery, in which case both sides of the split liver graft can have a good length of artery.

Surgical techniques for paediatric liver transplantation

Bismuth first reported on the orthotopic transplantation of a reduced-sized graft from a deceased adult [(28)] in a 5-year-old recipient. Living donor liver transplantation using a left lateral segment (segments 2 and 3) graft may be also used [(29)]. Various techniques have been developed to provide suitable organs for paediatric recipients, including reduced, split and living, related liver transplantation [(28, 30)]. Split-liver transplantation, in cases of paediatric transplantation, results in the liver being shared between an adult (extended right

lobe) and a child (left lateral segment). If a liver is available from a paediatric organ donor and is implanted into a similar-sized recipient then the technical principles of the transplant operation are identical to those of the adult operation. A major difference is that in children the majority of biliary anastomoses are hepatico-jejunostomy rather than duct-to-duct anastomoses. This is because invariably the recipient duct is either absent (in extrahepatic biliary atresia) or too small [(31)].

Auxiliary liver transplantation

Auxiliary liver transplantation is performed on children with acute liver failure and to correct liver-based metabolic disorders. Instead of removing the whole of the diseased liver, only part of it is resected and a donor reduced or split lobe is used to replace the resected lobe. In acute liver failure, once the native right liver recovers and regenerates, withdrawal of immunosuppression will cause the atrophy of the transplanted segments [(32)].

Reduced liver transplantation

When a liver is cut down to the required size of recipient and the remaining segments are discarded, this is termed liver reduction [(33)]. Either the left lobe (segments 1 to 4) can be removed, leaving the right lobe (segments 5 to 8) for transplantation or *vice versa*. The IVC is retained with the transplanted lobe, so either cava replacement or piggy-back techniques can be used. A liver can also be reduced to a left-lateral segment (segments 2 and 3) by removing the extended right lobe (segments 1, and 4 to 8) allowing an adult liver to be used for a small paediatric recipient. In this case, the IVC of the donor liver cannot be retained with the left lateral segment and the piggy-back technique has to be used, joining the left hepatic vein of the donor liver to the confluence of the hepatic veins on the anterior wall of the IVC of the recipient. A left-lateral segment reduction is rarely performed these days as the right lobe can be used for another recipient, resulting in a split-liver transplant in which one organ is used for two recipients. In a reduced graft there is a relatively flat cut-surface, which has the potential to bleed or leak bile.

Post-operative ultrasound

Normal post-operative ultrasound

It is advisable to check previous imaging studies, particularly earlier Doppler ultrasound studies, if available, before starting the examination.

The first ultrasound examination after transplantation will often be carried out in the intensive care unit where the physical conditions might be suboptimal. The lights in the room should be dimmed and curtains used, with the examination conducted, as is conventional, from the patient's right side. Right intercostal access might be the most convenient not only for the presence of surgical wounds, but occasionally owing to a high location of the liver and a fixed supine position. Surgical dressings should be removed if their presence prevents a satisfactory examination. Since the scanning is performed close to the surgical wound, it is preferable to drape the transducer and use sterile gel.

The ultrasound examination consists of two parts: grey-scale examination of the hepatic parenchyma and the bile ducts, and Doppler ultrasound examination of the hepatic vessels.

After transplantation the liver appears with normal smooth homogenous reflectivity. Haemorrhage during the procedure often occurs or pre-operative ascites may still be present. Small perihepatic collections of septated ascites are common and tend to reabsorb in few weeks. The biliary tree is normal, although aerobilia may be seen in patients with a choledochojejunostomy (Roux-en-Y loop).

Vascular Doppler examination

All the vessels (hepatic artery, portal vein, IVC and hepatic veins) should be patent. Colour and spectral Doppler imaging of the vessels should confirm patency. An intercostal approach is preferred using a transducer with a small footprint, with a frequency of 2–3.5MHz. Attention should be paid to optimal adjustment of gain, scale and wall filter parameters.

One of the main objectives of the ultrasound examination of a liver transplant is to document the status of the hepatic artery, so knowledge of the spectrum of appearances of the spectral-Doppler-trace of the post-transplant hepatic artery is important.

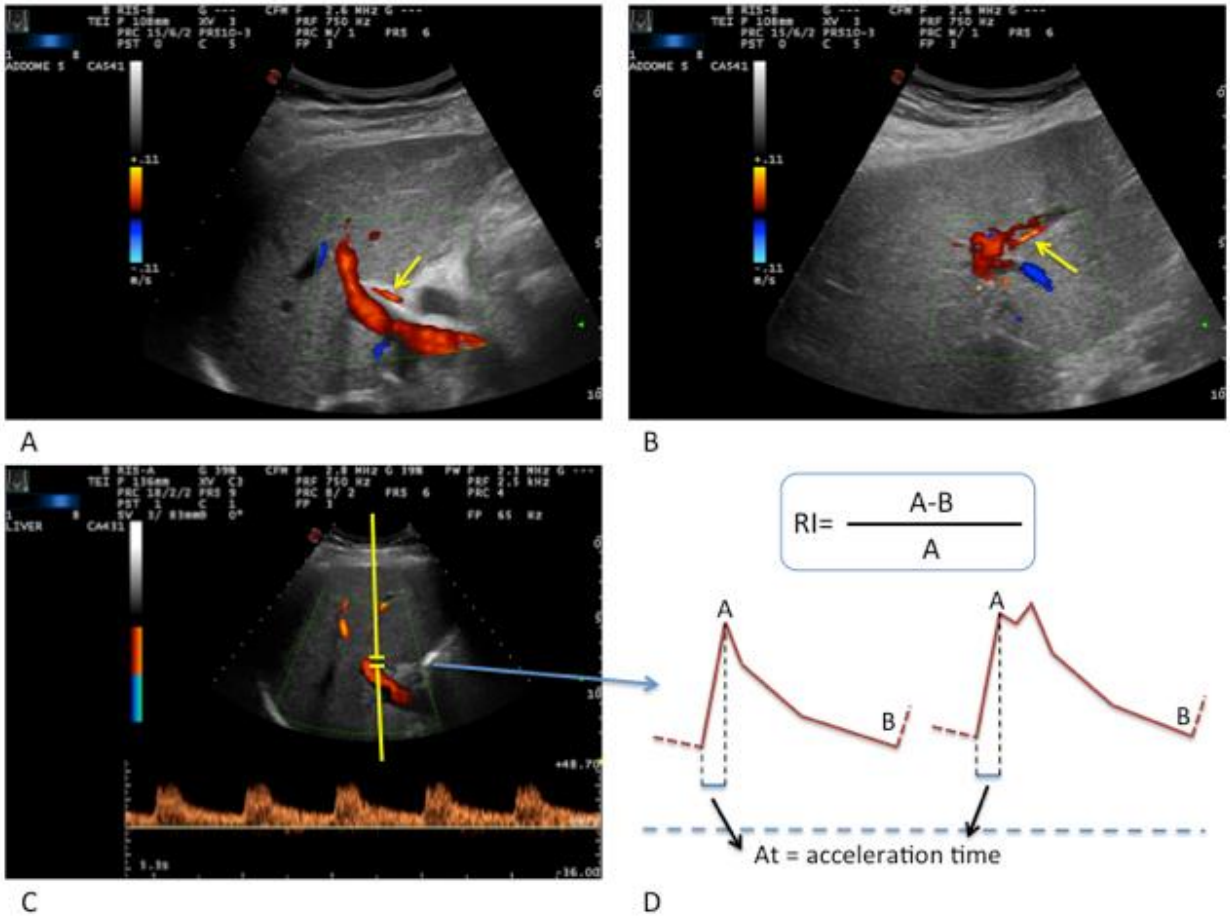
Doppler ultrasound should ideally include the visualisation of the extra- and intrahepatic artery. In most cases there is only one arterial anastomosis; however, this may vary from

patient to patient, and it is therefore important to have a thorough knowledge of the number and localisation of the arterial anastomoses, particularly if there are more than one, as is the case whenever an arterial conduit graft is used. A surgical illustration of the hepatic arterial anatomy including the anastomoses is useful for ultrasound examination, particularly if there are deviations from the standard procedure, but this is rarely available.

The first ultrasound examination is performed at the end of the surgical intervention, the second within 24 hours following transplantation. The main purposes of these first examinations are to confirm the patency of the hepatic vessels and to identify any technical issues. In most cases the artery is readily identified alongside and, more or less, in parallel with the portal vein. It is usually possible to visualize the artery intrahepatically in both lobes as well as in the liver hilum. From the spectral Doppler tracings, obtained from the artery both in the hilum and intrahepatically, the RI, as well as the acceleration time, are measured (Figure 9). The normal hepatic artery should return a low-moderate resistance spectral pattern; the RI of a normal hepatic artery should range between 0.5 and 0.8 and the normal acceleration time (from end diastole to the first systolic peak) should be less than 0.08s [(34)].

The portal vein should be visualised both with B-mode and Doppler, verifying flow velocity and direction; usually it shows a monophasic continuous hepatopedal flow with minor respiratory modulation. Areas of colour aliasing (given a correct colour-scale setting) should be further evaluated with spectral Doppler to rule out or confirm the presence of a stenosis.

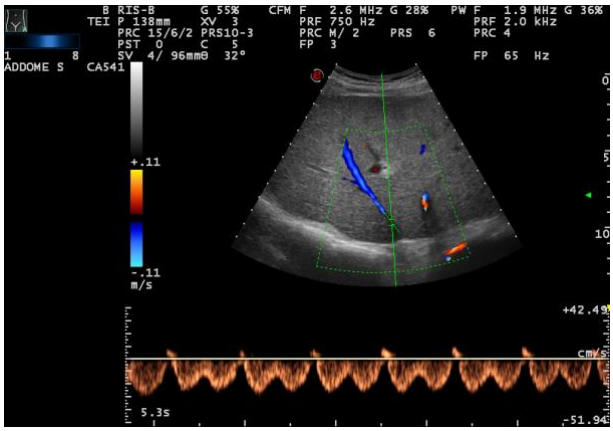
Figure 9 **Colour Doppler appearance of the right (A) and left (B) hepatic artery (arrows), respectively through an intercostal and epigastric approach close to the corresponding portal branch. A normal spectral Doppler tracing of the right hepatic artery is displayed in (C). (D) Shows a normal hepatic artery Doppler spectrum and the calculation of both acceleration time and resistance index. The scheme shows that occasionally there might be one single (trace on the left) or two systolic peaks (trace on the right, one early and one late). The acceleration time must be calculated considering the first (early) peak, whereas the resistance index must be calculated from the highest peak, whichever it is, the early or the late.**



Using a subcostal approach and correct angulation it is often possible to visualize the hepatic veins and their convergence at the site of the piggy-back anastomosis or IVC (seen in Figure 8). All three hepatic veins should ideally be visualised with colour Doppler and spectral

Doppler tracings. The main flow direction of the hepatic veins is towards the IVC with the hepatic waveform demonstrating variation (ideally triphasic) during the cardiac cycle (Figure 10). The IVC is evaluated both with B-mode, colour and spectral Doppler, most often using an intercostal approach. Any stenosis or thrombosis should be noted.

Figure 10 Spectral Doppler trace shows a normal hepatic vein triphasic waveform flow.



The importance of a full colour and spectral Doppler ultrasound examination cannot be over-emphasized. A study by Kok *et al.* [(35)], investigating early routine use of ultrasound following transplantation, reported that detection of vascular complications was possible prior to any symptoms developing (with the potential for rapid correction): 64% of complications of the hepatic artery, 30% of the portal vein, 33% of the IVC and more than 90% of hepatic veins. A further study [(36)] demonstrated that the routine use of Doppler ultrasound in the early post-transplant period compared with Doppler ultrasound based on clinical indication reduced the need for retransplantation. Therefore, Doppler ultrasound should be performed on a routine basis and not on the basis of the development of clinical signs and symptoms, particularly in the early post-operative period when complications often occur. Doppler ultrasound assessment should be performed initially at 24–48 hours after transplantation and then, if normal findings are reported, every 3–5 days for the first 2 weeks. One additional assessment at 4 weeks could be considered, but no randomised controlled trials have investigated the optimal frequency and number of Doppler ultrasound investigations. Each centre should, therefore, decide its own policy depending on local

resources, quality of donor grafts and rate of complications. Individualised protocols, with more frequent examinations, are recommended in patients at higher risk of vascular complications owing to anatomical variants, in the presence of major risk factors or in case of detection of pathological findings (residual portal vein thrombosis, elevated RI of hepatic artery). Moreover, Doppler ultrasound investigation should be repeated in case of clinical issues (fever, persistent ascites) or laboratory alterations.

Post- transplant adverse events

Vascular complications are the most frequent adverse events after liver transplantation. Split, reduced-sized or living donor livers are at increased risk of vascular and biliary complications — which also occur in full-liver grafts — since one or both parts of the liver are usually anastomosed with lobar vessels or lobar bile ducts (not main liver vessels). Consequently their size is smaller, and the anatomical course within the abdomen might be suboptimal making the risk of obstruction, stenosis or kinking significantly higher. Most vascular complications occur within the first few weeks after transplantation. Indeed, 43% of vascular anastomotic complications were observed in a series of 268 liver transplantations within the first 2 weeks [(35)]. Moreover, early (<30 days) hepatic artery thrombosis occurred in 4.7% of patients, representing around two-thirds of total arterial thrombosis in a series from the Bologna Transplant Centre [(26)]. It is important to point out the discrepancy between the mild, early clinical and laboratory signs of ischaemic hepatic arterial damage and the potentially severe later consequences; the presence of hepatic artery complications are a serious development.

Since the early correction of hepatic vascular complications could permit a complete recovery (or occasionally may save the graft), timely detection is important.

Thus, it is important to define a tool able to identify, rapidly, the disturbances and complications of all vascular anastomoses. Ultrasound is the most appropriate methodology to screen and survey patients for vascular complications, because it is non-invasive, lacks most contrast agent related hazards (especially important in patients with impaired renal function), implies no exposition to ionising radiation, is all-around applicable (particularly relevant in intubated patients) and easily repeatable, even more than once a day, whenever required, and has a satisfactory accuracy.

Hepatic artery

The pathological conditions that may affect the hepatic artery include stenosis, thrombosis and pseudoaneurysm formation. There is no specific clinical indicator of hepatic artery dysfunction. The transplanted liver is more sensitive to hepatic flow disturbances than the healthy liver. The native liver tolerates a hepatic artery occlusion well, owing to an arterial and portal dual blood flow supply, respectively, of about 25–30% and 70–75% of total liver blood flow volume,. In fact, occlusion— which is a rare occurrence seen with tumour infiltration or with repeated intra-arterial procedures, such as trans-arterial chemoembolization for HCC — often goes undetected.

Conversely, the transplanted liver is extremely sensitive to arterial ischaemic disturbances, potentially resulting in hepatic failure and occurring rapidly. When arterial dysfunction occurs very early, liver failure becomes usually apparent as primary liver non-function. The consequence is the development of intrahepatic infection and hepatic abscesses and marked damage of biliary ducts. Biliary duct ischaemia is seen as a duct lumen filled with biliary casts of necrotic material, or with the development of biliary stenosis with peritoneal bile spillage. Bile-duct stenosis might be diffuse and involve all intrahepatic biliary branches or may, more often, involve only the biliary surgical anastomosis. This site, if following the surgical section of the common biliary duct and accompanying arterial plexus, is more prone to ischaemic damage. Acute ischaemic necrosis of the biliary tree and diffuse intrahepatic bile duct stenosis are, invariably, irreversible events, often owing to the absence of timely diagnosis, and despite late revascularization can result in retransplantation. Even in the case of early revascularization (within hours), the bile ducts may still develop progressive fibrotic stenosis.

The clinical manifestations of biliary ischemia occur late, and the ability to conserve the biliary tree through timely revascularization of the artery (by radiological or surgical interventions) is lost at this point. Early clinical or laboratory signs of arterial dysfunction are, in fact, non-specific and are primarily an elevation of liver enzymes (particularly gamma-gluthamil transferase and alkaline phosphatase) and signs of liver failure (increase in bilirubin, persistent elevation of pre-existing bilirubin, prolonged prothrombin time). Ideally, routine surveillance in the first weeks by Doppler ultrasound, could detect arterial dysfunction before signs and symptoms occur. In rare instances the patient may report

clinical symptoms of general malaise, a sense of “fullness” or fever. Pain is not usually a symptom, as the transplanted liver is denervated.

Thrombosis

The most severe complications occur in complete arterial thrombosis, especially when this occurs abruptly and is not preceded by progressive stenosis over several months or years, which occasionally allows for the development of collaterals. Collaterals develop only rarely in adult recipients (more often in paediatric patients) and only occasionally are sufficient to avoid clinical manifestations. Hepatic artery thrombosis is reported to occur in 2–12% of adult recipients, with figures in large, experienced centres of around 2–6% [(26)]. Up to 60% of patients will ultimately need retransplantation following hepatic artery thrombosis. In a meta-analysis study the mean incidence of early hepatic artery thrombosis was 4.4% (2.9% in adults and 8.3% in children) with a peak incidence on the seventh day following transplantation and substantial mortality of 33% [(37)]. Doppler ultrasound may correctly identify up to 92% of cases with hepatic artery thrombosis [(38)].

Stenosis

Hepatic artery stenosis (HAS) usually has a milder impact than thrombosis, but may lead to bile duct complications over the longer term, given the high sensitivity of the transplanted bile duct system to even moderate ischaemic insults. Hepatic artery stenosis occurs in up to 11% of patients, most often at the site of the anastomosis [(39)], or as a consequence of arterial kinking when there is artery redundancy. Hepatic artery stenosis may also lead to biliary ischaemia with resulting bile duct strictures.

Pseudoaneurysm

A further arterial complication is the development of a hepatic artery pseudoaneurysm [(40)], which is a rare complication with a reported incidence of less than 1% [(41)]. HAP is usually asymptomatic, but is life-threatening if rupture occurs with the development of a haemoperitoneum. The detection of an extrahepatic pseudoaneurysm, usually a complication at surgical anastomosis, is managed as a surgical urgency. The underlying cause may be infection (mycotic pseudoaneurysm) or a defective vascular reconstruction.

Intrahepatic pseudoaneurysms may be caused by percutaneous interventions, usually a liver biopsy, or arise from a focal infection of the hepatic parenchyma. Ultrasound diagnosis is difficult because a pseudoaneurysm will often remain asymptomatic until a rupture occurs, further strengthening the need for regular surveillance ultrasound examinations in the post-transplant patient who has no clinical symptoms or signs. Any new hypoechoic collection adjacent to the site of the arterial anastomosis should be evaluated with colour Doppler ultrasound and, if necessary, with CEUS [(42, 43)].

Figure 11 **Bile duct dilatation due to severe hepatic artery stenosis (A) and post-stenosis tardus-parvus flow as detected in left (B) or in right (C) hepatic artery branches in two different patients. Resistance index calculation is 0.35 in the right branch and 0.47 in the left branch, lower than the normal threshold of 0.5 (C). Tardus-parvus characteristics (consisting in prolonged systolic acceleration time -At- in this case 115 ms, and low resistance index -RI- in this case 0.35) are depicted by the scheme in the lower right panel (D).**

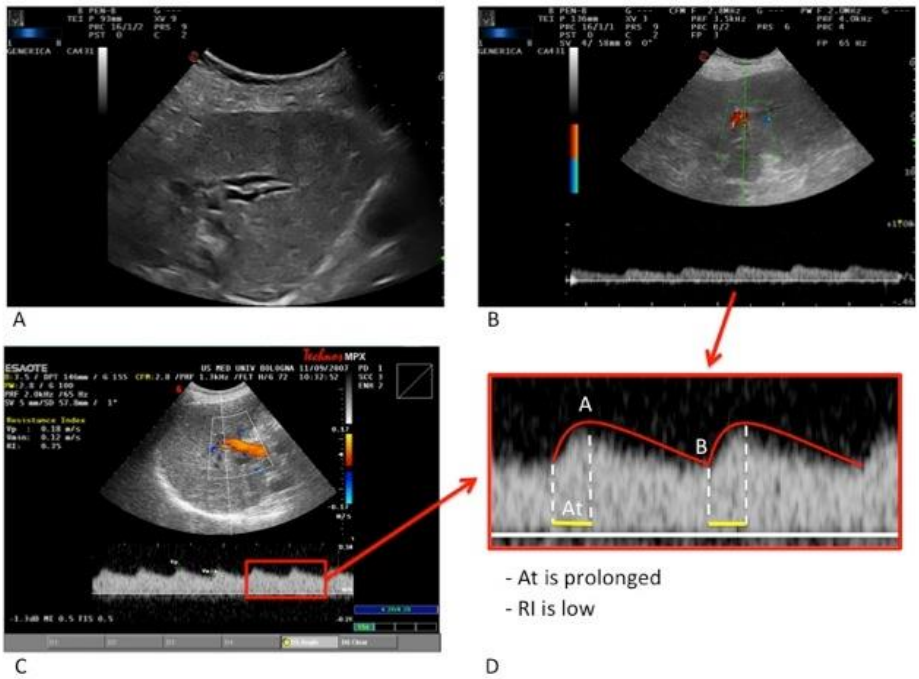
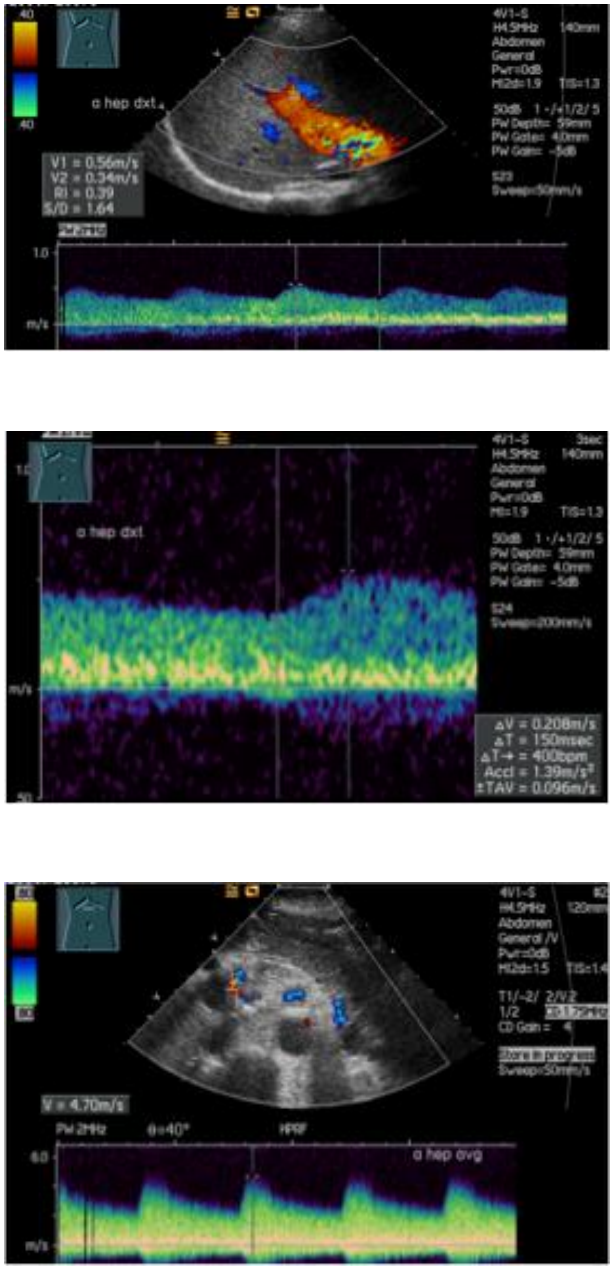
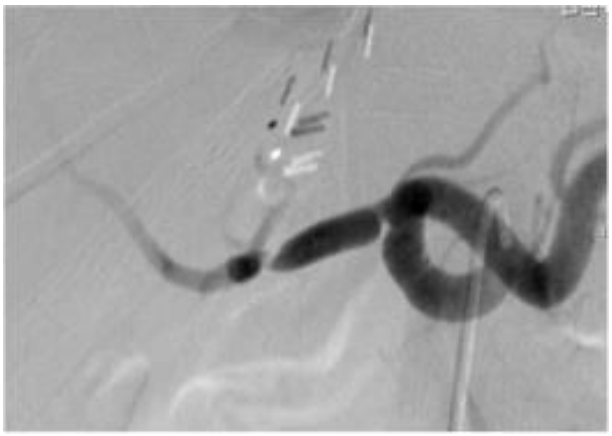


Figure 12 **Hepatic artery stenosis 3 months after liver transplantation. Intrahepatically, the hepatic artery flow has a tardus-parvus pattern with low resistance index and long acceleration time (0.15 s). At the site of stenosis, an elevated peak systolic velocity (4.7 m/s) with turbulent flow could be detected. Angiogram confirms a high degree stenosis, which was subject to the placement of an arterial stent at the time of the angiogram.**





Ultrasound examination

The ultrasound examination of the hepatic artery should answer some basic questions: is the artery patent or occluded? Is there evidence of a stenosis or a pseudoaneruysm? As previously indicated, an intercostal scanning approach is preferred to visualize the hepatic artery both at the liver hilum and intrahepatically within the right lobe using a transducer with a small footprint. We use a low colour Doppler frequency of 1.5–2 MHz to ensure sufficient tissue penetration. Normally, the hepatic artery is seen as a pulsating tubular structure running more or less in parallel with the portal vein. It is mandatory to obtain a spectral Doppler waveform from the artery and to measure both the RI and the acceleration time. The normal hepatic artery RI should ideally be between 0.5 and 0.8 and the acceleration time should be less than 0.08s [Figure 11].

In the immediate post-operative period (within hours) the hepatic artery resistance might be lower than usual (below 0.5) due to vasodilation induced by agents released as a consequence of the ischaemia-reperfusion damage. A definite judgement on the level of arterial impedance is reliably made at least 24 hours after surgery. However, the low impedance should not prolong the systolic acceleration time. In the first few post-operative days it is also common to find an elevated RI due to a temporarily increased intrahepatic arterial resistance, probably caused by a buffer mechanism-balancing portal over flow, by hepatic oedema or both [(44)]. The transplanted liver maintains the buffer vascular mechanism [(45)], so that an increase in portal flow is accompanied by arterial vasoconstriction, a consequence of the adenosine wash-out mechanism, to maintain a stable

total liver blood flow. Replacement of the diseased liver with a normal liver abruptly drops intrahepatic portal resistance, which, in the presence of splenomegaly, found in portal hypertension in the pre-transplant cirrhotic patient, will lead to splenoportal overflow and consequently hepatic arterial constriction. This buffer vasoconstriction to splenoportal over flow is similar to the mechanism observed following ingestion of food, responsible for an increased flow in the mesoportal system and hepatic and splenic arterial vasoconstriction. The arterial buffer vasoconstriction may cause difficulties in visualisation of the hepatic artery as the weak arterial signals may be obscured by the strong portal venous signal. This is an important reason to examine transplant recipients after they have fasted. If the artery is not seen with colour Doppler it may sometimes be helpful to adjust the colour scale. If the artery is still not seen, searching with the spectral Doppler gate near the portal vein can help, or attempting to make the spectral Doppler gate wider than usual, including parts of the portal vein (even without the support of colour Doppler). Using this method it is sometimes possible to find arterial spikes within the portal venous signal (since the sample volumes has included both portal and arterial vessels; however, such spikes are not to be confounded with arterial wall thump, which could also be present in case of thrombosis, and in which the signal derives from movements of the arterial wall and not from blood flow). The left hepatic artery is visualised with subcostal scanning, and it is often easy to see it in parallel with the ascending branch of the left portal vein running anteriorly in the left inter-segmental fissure. This part of the left hepatic artery normally has a ventral course and will yield strong Doppler signals (unless obscured by bowel gas). If the surgical wound prevents left-lobe subcostal exploration, an angulated intercostal approach may be attempted. The artery should ideally be visualized both in the hilum and intrahepatically in both lobes. If the artery is not seen with Doppler ultrasound, one should consider further investigations such as CEUS, contrast-enhanced CT or intra-arterial angiography.

If it is not possible to find the artery after several minutes of searching, CEUS should be used. In some cases CEUS will prove that the artery is patent, despite the fact that it is not identified with Doppler ultrasound. 1.2–2.4ml of SonoVue is injected intravenously, and using a contrast-specific modality with low mechanical index, the examination is performed predominantly from the intercostal position. Just prior to the arrival of the contrast bolus it is advisable to use colour Doppler to ensure scanning in the correct anatomical location (along the right portal vein toward the liver hilum), and then switch to contrast mode. The

artery is normally seen as an enhancing tubular structure parallel to the portal vein. When the artery is seen with contrast, spectral Doppler should be used to obtain a spectral curve, and measurement of RI and acceleration time is performed. The CEUS visualisation of intrahepatic arteries alone does not exclude either stenosis or proximal obstruction, as arterial collaterals may have developed, and Doppler tracing is required. Thrombosis cannot be ruled out until a normal Doppler tracing is documented. However, if the artery is not seen with CEUS as well, arterial occlusion is likely to be present. Studies have shown increased sensitivity of CEUS compared with colour and spectral Doppler in the diagnosis of hepatic artery thrombosis [(46, 47)]. Doppler tracing suggestive of thrombosis (as for stenosis) are indicated by either low RI, less than 0.50, or prolonged acceleration time, more than 0.08s, [Figure 11] prompting the need for further investigation such as CT angiography. The concurrent positively of both these parameters has a higher specificity for diagnosing thrombosis in comparison to positively of either one or the other parameter, but sensitivity drops to below 70%, therefore, the identification of just one parameter is usually considered enough to prompt rapid further investigations.

Doppler ultrasound diagnosis of a haemodynamically significant HAS relies on finding an increased peak systolic velocity (>2m/s) in the hepatic artery at the site of the stenosis. Post-stenosis flux is tardus-parvus with a RI <0.5 and an acceleration time >0.08s [Figure 11], reflecting a decrease in systolic peak flow velocity and the simultaneous downstream vasodilation, which tends to increase diastolic flow [Figure 11D] especially in the intrahepatic arterial branches. HAS seen on a subcostal scanning technique in a transverse plane along the hepatic artery, should be examined from the coeliac trunk towards the liver. Using conventional colour scale settings, aliasing is present at the site of a stenosis. To obtain reliable spectral Doppler tracings from the stenotic area it is advisable to angulate the transducer either laterally or medially to reduce the Doppler insonation angle. Occasionally it may be difficult to visualize the site of the stenosis owing to bowel gas or obesity. However, the isolated finding of a tardus-parvus waveform [Figure 12] should lead to further investigations (CT or magnetic resonance angiography) to confirm or rule out a significant stenosis. The clinical consequences of a stenosis depend on the severity; a high degree of stenosis may, in the same way as hepatic artery thrombosis, lead to biliary ischaemia. Stenosis could be corrected either by radiology intervention or surgery.

Hepatic vein and ICV

Complications of the hepatic vascular outflow tract are either thrombosis or stenosis of the hepatic or cava vein, arising from narrowing of the anastomosis, kinking of the vessels or torsion of the entire transplant organ in case of organ size mismatch. Hepatic outflow compromise may impact significantly on liver function. With hepatic outflow compromise, there is no specific concern of the biliary system developing ischaemic change, but there are non-specific signs of liver failure and the development of portal hypertension. If there is complete thrombosis of the hepatic veins or of the cava vein, a rare event, this is a clinical emergency, as irreversible general liver failure may occur within hours or days if unrecognised. The clinical manifestations consist of an increase in liver enzymes, bilirubin and ammonia, impairment of hepatic synthetic activities (low albumin, low coagulation factors resulting in clotting disturbances and low cholinesterases) and usually ascites and a pleural effusion. Necrosis of the liver lobules is observed at pathological analysis, more marked in the perivenular area. Liver function and portal hypertension may recover following interventional radiology or surgical correction of the outflow abnormality, normally located at the anastomosis.

The incidence of hepatic vein stenosis is unknown, but is reported at approximately 1.8% in adults and 2.5% in children. The hepatic venous spectral Doppler waveform is influenced by several factors including steatosis, obesity, cirrhosis, respiratory cycle and cardiac status, and the presence of hepatic vein stenosis. Importantly, a stenosis or thrombosis does not always affect all three veins, but may be isolated to one or two hepatic veins. With a significant hepatic venous outflow stenosis, a clinical scenario similar to Budd-Chiari syndrome with ascites may be observed. If there is a significant stenosis of the IVC both ascites and leg swelling may be observed.

Ultrasound examination

Ultrasound examination is usually carried out through a right intercostal approach, looking for the right and median hepatic veins, which are followed up to the vena cava, with visualization of the caval surgical anastomosis, especially if piggy-back type. Study of the left hepatic vein and a more extended view of the IVC are usually obtained through a subcostal

epigastric approach. A normal triphasic spectral Doppler waveform is reported to virtually exclude the presence of both obstruction and significant stenosis.

Hepatic vein outflow (hepatic veins, vena cava or both) thrombotic obstruction is a rare complication that can be identified by greyscale and CDUS usually as echoic material in the lumen and absence of any flow signals, even after optimisation of the equipment for very slow flow. However, occasionally colour Doppler ultrasound may not be able to distinguish low flow from occlusion. Then CEUS may be helpful to differentiate between slow flow and thrombosis, particularly if the thrombosis is fresh with few internal echoes present.

The accepted criteria for the diagnosis of hepatic vein stenosis is a threefold to fourfold increase in the venous flow velocity at the stenosis site compared with a segment a few centimetres upstream of the stenosis. The stenosis site, to be sampled with Doppler spectral ultrasound, is identified by greyscale B-mode scanning as a narrowing of the lumen vessel (usually at the anastomotic site, either of piggy-back or end-to-end type) with associated aliasing at colour Doppler ultrasound. A persistent monophasic waveform [(48)] associated with a peak velocity measurement of <15–20 cm/s in the upstream hepatic vein or veins suggests the presence of a downstream significant stenosis, in our experience. However a monophasic waveform is occasionally observed in the absence of a significant stenosis. When a monophasic dampened spectral Doppler waveform is seen in inspiration, a spectral Doppler analysis during free breathing or expiration can show a normal phasic pattern, avoiding the false positive suspicion on hepatic vein stenosis [(49)] [Figure 13 and 14]. Flat spectral waveform profiles in the absence of significant stenosis are more commonly observed in piggy-back anastomosis.

Our experience suggests that serial examinations are most valuable, comparing changes in the spectral Doppler waveform. The *de novo* appearance of a monophasic waveform in a hepatic vein in which the waveform previously showed a normal triphasic pattern should prompt the investigator to perform spectral Doppler velocity measurements at the site of the venous anastomosis.

Stenosis of the IVC may occur at the level of the diaphragm, and if significant may cause flow reversal in the IVC. The clinical presentation will vary according to the level of stenosis; if the stenosis is above the level of the hepatic veins, an IVC stenosis may cause an outflow obstruction and a Budd-Chiari-like clinical appearance.

Figure 13 **Dysfunction of liver transplant 1 week post-operatively. Stenosis of the hepatic veins at the level of the piggyback anastomosis is visible on the CT scan in (A) indicated by the yellow circle and is confirmed with contrast-enhanced ultrasound in (B)**

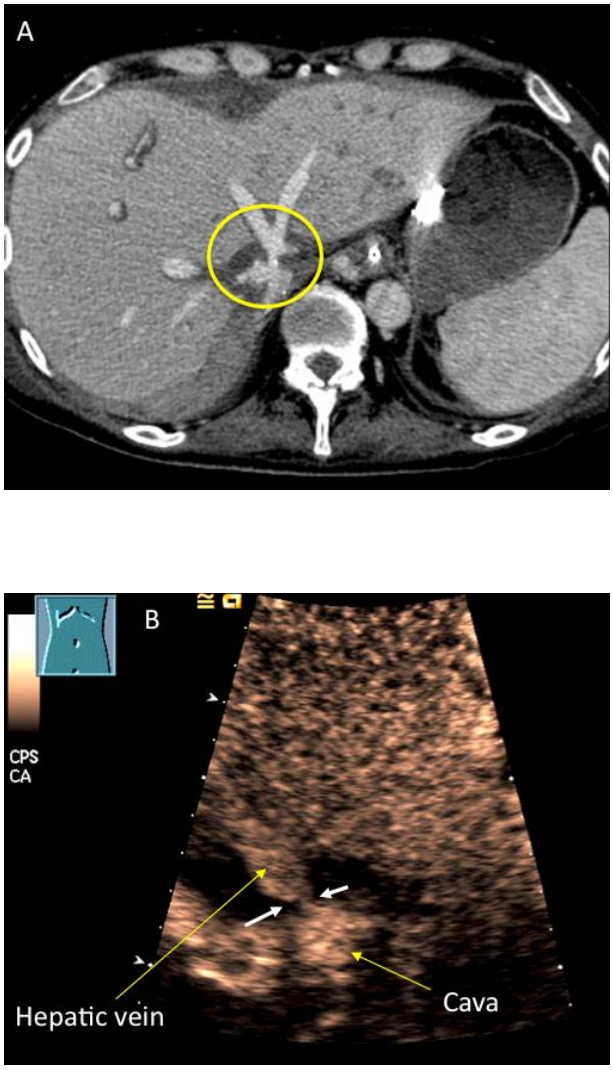
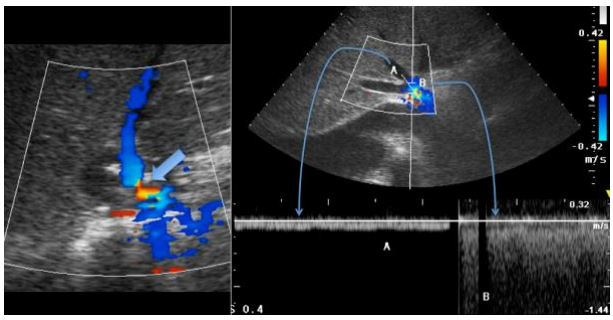


Figure 14 **Hepatic veins stenosis at the piggyback site: colour Doppler shows narrowing of the hepatic vein lumen with aliasing (arrow, image on the left). In another similar case analysis of Doppler spectral tracing shows flattened slow (14cm/s) flow upstream from the anastomosis (sampling site A, image on the right) and accelerated (approximately 100cm/s) turbulent flow within the piggyback**

anastomosis (sampling site B), also suggested by the presence of aliasing at colour Doppler.



Portal vein

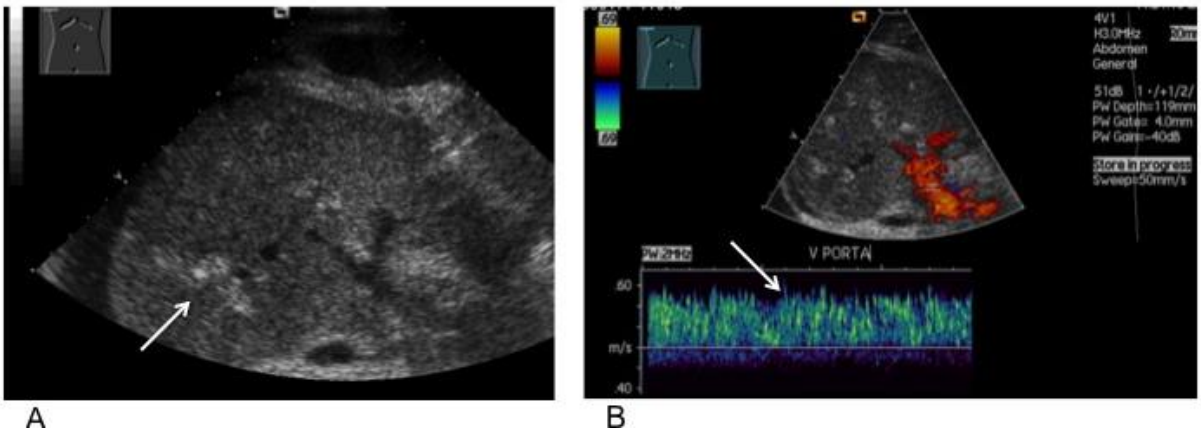
The pathological conditions that can affect the portal vein include stenosis, kinking and thrombosis. These complications are rare and occur in approximately 1–2% of patients and do not usually lead to liver failure or graft loss. The clinical picture may include portal hypertension, hepatic failure, splenomegaly, ascites or all of these [(50)]. Stenosis of the portal vein usually occurs at the site of the anastomosis and may sometimes be suspected from the B-mode ultrasound image. Kinking is also observed by B-mode ultrasound, but assumes importance only when responsible for significant increase in flow velocity. The diagnosis of a portal vein stenosis relies on spectral Doppler measurement of an increased velocity at the site of the stenosis compared with a segment approximately 2cm proximal (upstream). If the ratio between these two velocities exceeds three or four (or in children, 2.4) or if the peak velocity is greater than 1 m/s, a significant stenosis is probably present [(51, 52)].

Portal vein thrombosis is uncommon following liver transplantation. Ultrasound examination will, in most cases, show internal echoes within the portal vein, whereas colour Doppler will reveal either no flow at all or flow around the thrombus. A fresh thrombus with few internal echoes may be quite difficult to distinguish from a state of very slow flow. CEUS may be of assistance in differentiating between these two entities, and distinguish between a “normal”, pure clot thrombus and a tumour thrombus. The former will show no enhancement whereas the latter will show enhancement in the arterial phase [(8)].

Portal venous gas

Ultrasound is a useful method for the detection of portal venous gas, which may be an incidental finding without clinical significance in a small group of transplant patients. However, the presence of gas in the portal vein may indicate serious infection or necrotic bowel [Figure 15] [(53, 54)].

Figure 15 Gas bubbles both in the portal vein and in the hepatic parenchyma 10 days after liver transplantation. Note the bright spikes in the spectral Doppler trace caused by the bubbles (B). Also, note bright areas in the liver parenchyma due to the accumulation of gas bubbles (A). On the same day laparotomy revealed a large bowel perforation.



Rejection

Despite some reports on the use of the splenic pulsatility index and portal venous velocity [(55)], it is widely accepted that the Doppler indices are unreliable for the diagnosis of rejection. Furthermore the presence of parenchymal texture irregularities is not specific in this respect as their presence may have several causes other than rejection. For the diagnosis of rejection a biopsy of the transplanted liver is required.

Small for size Syndrome

The small for size syndrome (SFSS) occurs when a small graft exhibits primary dysfunction in the absence of other diagnoses, even if the name is misleading because the graft could not necessarily be small if it is a marginal or steatotic and if the recipient has risk factors such as severe portal hypertension or severe hepatic impairment. Generally it is related to partial liver transplantation. There is no consensus about the definition of this clinical entity. The main clinical manifestations are ascites, coagulopathy and hyperbilirubinemia. Doppler examination reveals portal hyperperfusion with significant increase in flow velocity and venous congestion. Changes in portal flow induce reciprocal effects on arterial flow by the so-called hepatic arterial buffer response; consequently, the peak systolic velocity in the hepatic artery is reduced with high RI. Splenic artery modulation (ligation or embolisation), porto-caval shunts or less commonly splenectomy are some of the strategies to prevent SFSS [(56)].

Biliary system

Biliary complications occur in 25–35% of patients with a liver transplants. Early complications occur within a few weeks after transplantation and are mainly represented by bile leakage. Late complications, which become evident from 3 months to years after transplantation, include strictures, stones, intraductal debris or sludge formation, kinking and ampulla dysfunction [(56)]. Strictures occurring at the site at the anastomosis (secondary to the formation of scar tissue) will often cause dilatation of the intrahepatic bile duct and can be readily demonstrated on ultrasound. Strictures at non-anastomotic sites are most frequently caused by ischaemia secondary to either thrombosis or severe stenosis of the hepatic artery. At the ultrasound examination, focal segmental intrahepatic or hilum duct dilatation without any stone or obstructing mass may be seen. Careful examination of the hepatic artery should be performed to rule out the presence of stenosis or thrombosis.

Fluid accumulations

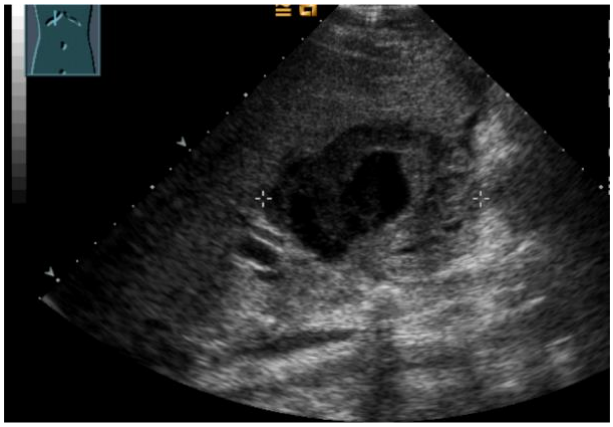
In the early post-operative phase it is quite common to find haematomas adjacent to the liver, most commonly in the subphrenic and subhepatic space [Figure 16]. Haematomas are

recognized as complex fluid collections of mixed echogenicity, and with time they will gradually decrease and eventually disappear. Using CEUS it may be possible to visualize active, on-going bleeding into a haematoma. Normally it is not possible or necessary to drain haematomas with ultrasound guidance.

The development of new fluid accumulations in the late post-operative period should raise the suspicion of bile leakage or loculated ascites. Although ultrasound is highly sensitive in detection of fluid collections, it is not specific and it is often not possible to discriminate between particulate ascites, pus, blood and lymphatic fluid [(55)].

Abscesses occur post-operatively in approximately 10% of liver transplants, most often in the subphrenic or subhepatic space, most are amenable to drainage under ultrasound guidance.

Figure 16 8 cm haematoma in liver hilum 1 week after liver transplantation (between cursors).



Role of ultrasound in long term follow-up

Ultrasound has a vital role in the long-term follow-up of liver transplant patients, because it may explore the long-term complications of immunosuppression. Non-vascular complications are common, particularly disease recurrence, which requires imaging attentiveness.

Similarly, vascular complications may be present although are less common than in the short term after surgery. Hepatic artery thrombosis may be unexpected and will carry a poor long-term prognosis. Ultrasound findings are the same as in the short-term post-surgical setting.

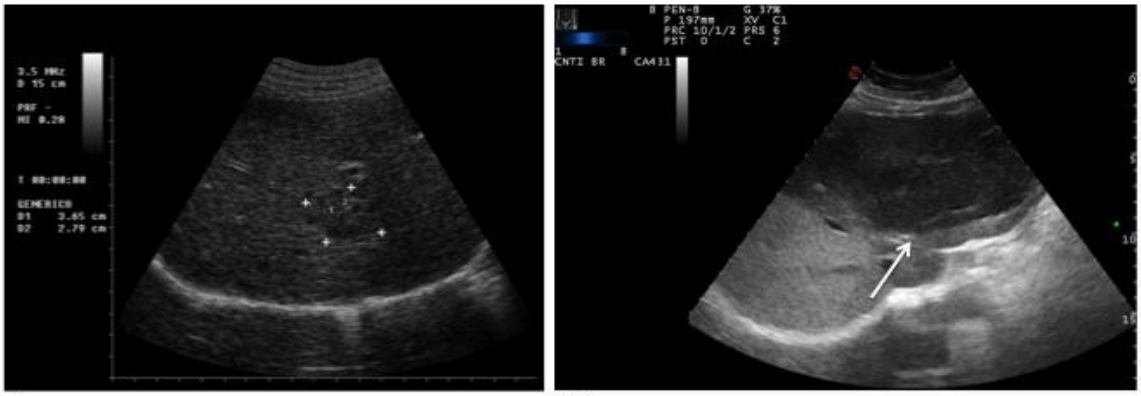
Non-vascular complications

Post-transplant lymphoproliferative disease

Post-transplant lymphoproliferative disease (PTLD) is a B-cell proliferation in lymph nodes and solid organs associated with the Epstein-Barr virus, typically developing within the first year after solid-organ transplantation especially in the younger population [(56)] as a consequence of immunosuppression agent therapy [(57)] and depending on the transplanted organ [59]. The incidence is higher in paediatric patients ranging from 2.9% to 18.9% [(56)], whereas in adult it is estimated to be 2–10% [(58)]. This data was confirmed in a recent cohort study in liver-transplant patients [(59)]. Clinical presentation varies from an infectious mononucleosis-like syndrome to full-blown lymphoma [(60)]. About half of patients present with isolated abdominal disease [(61)]. Abdominal extranodal disease is frequent and affects the liver and spleen especially [(62)]. Contrast-enhanced CT is necessary to stage the disease and for follow-up during treatment, but ultrasound often establishes the diagnosis and guides biopsy. The commonest liver ultrasound features are:

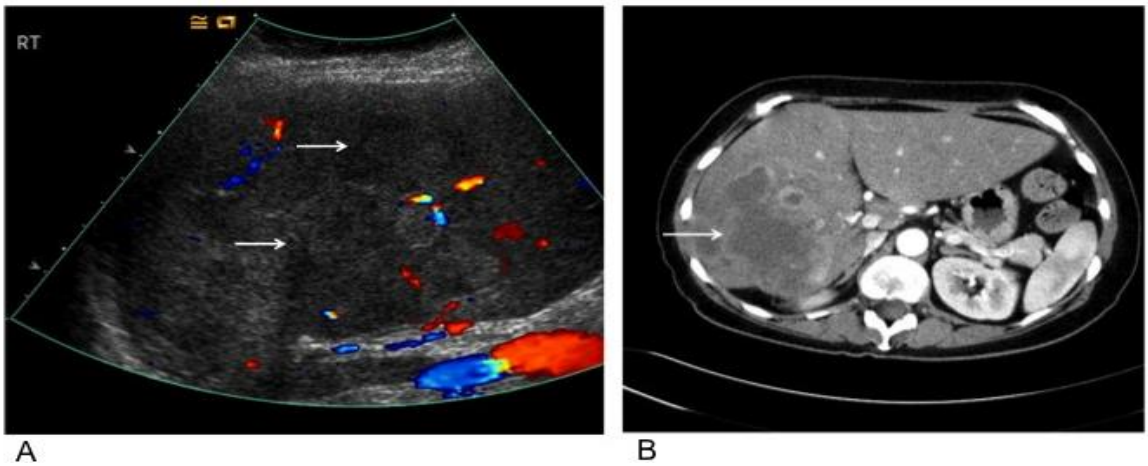
- Hepatomegaly.
- Solitary or multiple well-defined and low-attenuating nodular lesions that are often confused with hepatic abscess [(61)] [Figure 17].
- Diffuse infiltrating parenchymal involvement is depicted with low-attenuating and poorly margined areas, sometimes mimicking fatty infiltration [Figure 18].

Figure 17 **Two examples of liver lymphoproliferative disease. (A) The image demonstrates a small liver focal lesion with undefined margins, irregular shape and smooth echogenicity (between cursors) that may be mistaken for an abscess. (B) The image demonstrates a large hypoechoic mass (arrow) in the anterior aspect of the right lobe of the liver.**



A B

Figure 18 **(A) The colour Doppler image demonstrates multiple areas of low reflectivity (arrows) in the right lobe of the transplanted liver, possibly an area of focal fatty sparing. (B) A CT image demonstrates a low attenuation area (arrow) with rim enhancement in the right lobe of the liver, with histology confirming post-transplant lymphoproliferative disease.**



A B

PTLD hilar masses are rare but can lead to an involvement of the porta hepatis [(63)] or biliary obstruction [(64)]. Rarely, acute liver failure may present as a consequence of PTLD causing extensive graft necrosis [(65)]. Splenic involvement could manifest as splenomegaly or focal low reflectivity lesions or both [(66)]. Other abdominal PTLD localisations include the gastrointestinal tract and kidneys. Unlike renal lymphoma that arises in the non-transplant patient, PTLD kidney involvement tends to be unilateral and unifocal. Lymph nodes localisation appears as non-specific nodal enlargement, typically 2–3 cm in diameter but can coalesce to form larger masses with central low attenuating areas from necrosis [(61)]. Any combination of peritoneal, retroperitoneal and extra-peritoneal lymph nodes may be enlarged.

Renal complications

Acute renal failure after liver transplantation is correlated with a poor prognosis often connected to immunosuppressive therapy in the immediate post-operative period [(67)]. Renal insufficiency from the nephrotoxic effects of immunosuppressive therapy is a common problem in long-term survival paediatric patients [(68)].

Ultrasound may be used to exclude pelvicalyceal obstruction and vascular diseases in patients with deteriorating renal function, especially in the older patient or in patients with vascular risk factors. Ultrasound examination should give information regarding bipolar size and cortical thickness of the kidneys. Doppler ultrasound should be performed, sampling resistance index and acceleration time during systole in intraparenchymal arteries and to look for signs of stenosis in principal renal arteries.

Graft vs host disease and rejection

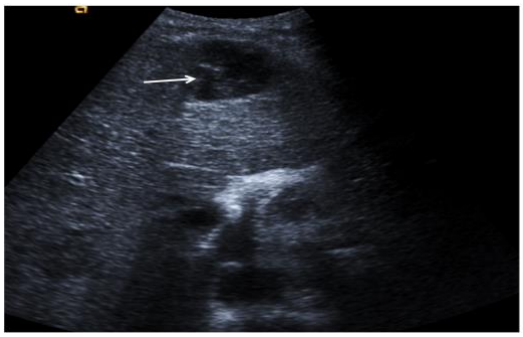
Graft *vs* host disease is a common complication following bone marrow transplantation but is increasingly documented in solid-organ transplantation with an increased mortality rate [(69)]. Its incidence has been reported to exceed 0.1% of liver transplant recipients [(70)] and has been reported in up to 1% in a clinical trial [(71)]. Imaging has no role in the assessment of graft *vs* host disease other than to exclude structural abnormalities of the graft [(72)].

Similarly, imaging is neither sensitive nor specific for rejection [(73)]. Ultrasound is again used to exclude structural abnormalities that may clinically simulate rejection; diagnosis is histological, based on a liver biopsy sample.

Infection

Immunosuppressive therapy is responsible for an increased risk of infections, and liver transplanted patients are no an exception [(74)]. When there is a structural abnormality of the graft, such as hepatic artery thrombosis or a biliary stricture, infection may be localized to the graft. A rapid diagnosis of an abscess is essential to commence the appropriate therapy. Abscesses may be readily visualized as areas of either increased or decreased reflectivity with ultrasound and subject to therapy by image-guided drainage [Figure 19].

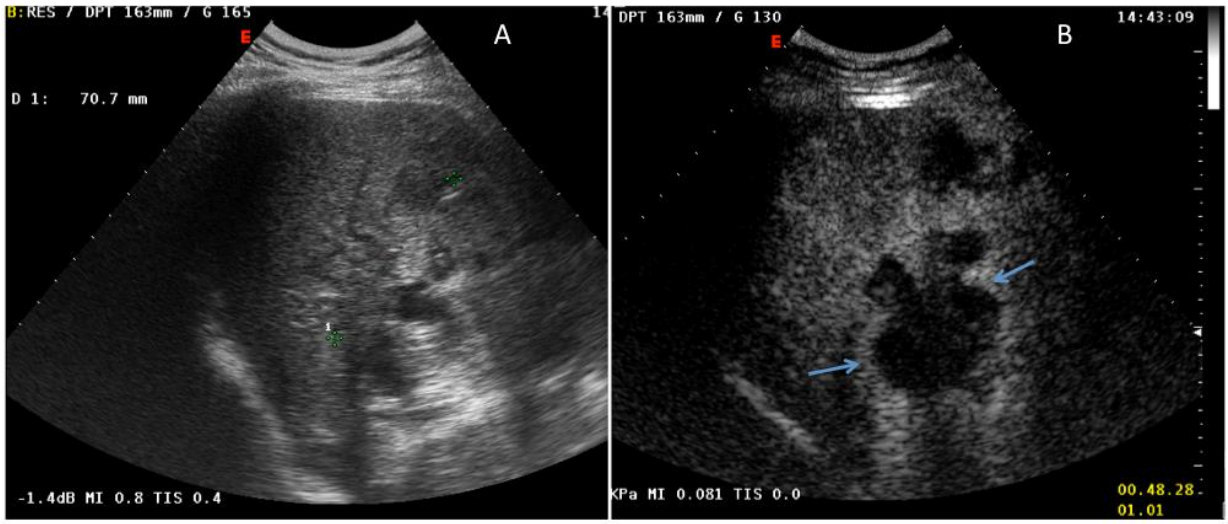
Figure 19 The B-mode ultrasound demonstrates the echogenic needle tip (arrow) within the low reflective abscess within the anterior aspect of the liver, prior to drainage.



The addition of CEUS to the examination can aid in the differential diagnosis of the focal liver lesion in the transplant. CEUS will define a central anechoic area during all vascular phases corresponding to the necrotized tissue. There is often a hyper-enhancing ring-like appearance surrounding the anechoic area that corresponds to the inflammatory reaction at the infective area [(75)] [Figure 20]. Liver abscess are often a complication of hepatic artery thrombosis. The development of an abscess in the transplant liver in the presence of HAT is

higher than in the native liver, for reasons that are poorly understood. Therefore, whenever an abscess is suspected, a careful examination of the hepatic arterial tree is mandatory.

Figure 20 **Abscesses are usually irregular and poorly defined with inhomogeneous echo-structure. CEUS improves definition at the limits of the necrotized tissue. (a) Inhomogeneous area of approximately 7cm seen at the liver hilum through a right intercostal scan in a transplant patient with recent onset of malaise, mild fever and detection of abnormalities of liver enzymes. (b) CEUS shows a large necrotic (avascular area) at the liver hilum surrounded by a hyperechoic (hyperaemic) halo in the portal phase (48s after injection), confirming the inhomogeneous area seen on conventional ultrasound to be an abscess. A late hepatic artery stenosis was then documented, which had favoured the development of intrahepatic abscess.**



Budd-Chiari syndrome

There is a favourable long-term survival following liver transplantation in Budd-Chiari syndrome [(76, 77)]. However the syndrome may recur not only in the hepatic veins, but also may cause thrombosis in the portal vein and hepatic artery, contributing significantly to the post-operative morbidity and mortality [(77, 78)] particularly when adequate anticoagulant

treatment is not started promptly. Patients should be placed on long-term full anticoagulation to prevent recurrent thrombosis, with serial colour Doppler examinations of all hepatic vessels at follow-up to exclude recurrent disease.

Disease recurrence

Surveillance ultrasound is performed in the post-transplant phase to monitor the possibility of disease recurrence.

Viral Infection

Biopsy evidence of recurrence of hepatitis C occured in 87% of transplant patients and tended to occur within 2 years of transplantation [(80)]. Early recurrence was associated with a higher incidence of rejection and cirrhosis, leading to eventual graft loss. The progression to cirrhosis was faster in the transplanted graft than in the native liver. Currently, recurrence hepatitis C is rare after the advent of direct-acting antivirals (DAAs). Most patients are treated before liver transplantation. Anyway, DAAs are safe and effective even in the early post-transplant setting [(81)].

In case of of recurrence of hepatitis C, ultrasound is necessary to exclude other complications when the biochemical parameters become abnormal, and is useful to monitor complications of recurrent infection such as cirrhosis and portal hypertension, and for the surveillance of the development of focal liver lesions.

Recurrence hepatitis B virus (HBV) has become rare when appropriate prophylaxis (a combination of oral antivirals and parenteral immunoglobulins) are administered, whereas it may be as high as 90% [(82)], when it is not. Recurrent HBV infection in a transplant patient is also more aggressive than in the pre-transplant patient; furthermore, patients who have a transplant for chronic HBV may develop end-stage liver disease in a number of months [(83)].

Alcoholic liver disease

Survival after transplantation for alcoholic liver disease is similar to that of other forms of chronic liver disease [(82)]. Long-term survival analysis suggests that the cause of this common survival rate are mostly related to concomitant diseases such as cerebrovascular

accident, respiratory disease and myocardial infarction, and the survival rate at 7 years is around 63% [(83)]. A strict control of alcohol assumption recurrence is essential to avoid the risk of graft complication and loss.

Autoimmune diseases (PBC, PSC and autoimmune hepatitis)

The most accurate method of determining the possibility of recurrence of PBC after transplantation is histological assessment. The presence of pruritus, antimitochondral antibodies and an elevated immunoglobulin M in the post-transplant patient are non-specific. The rate of recurrence increases with time, so that, by 10 years, recurrence may be seen in 30–50% of liver biopsy specimens [(84)]. In the medium term recurrence of PBC has little clinical impact and ultrasound has no role in the detection of recurrence, but can exclude structural abnormalities.

Ultrasound has limited use in the assessment of PSC recurrence, and, as with the pre-transplant condition, ultrasound may be entirely normal [(40)]. However, also in this setting ultrasound is necessary to exclude other complications when the biochemical parameters have become abnormal. The presence of bile-duct dilatation in the transplant graft invariably indicates a newly developed biliary abnormality for which recurrence of PSC must be considered. Most patients transplanted for PSC will have a choledochojejunostomy as a consequence of abnormal recipient extrahepatic ducts, which is prone to a higher incidence of cholangitis and biliary strictures leading to a cholangiopathy. This presents a difficulty in determining PSC recurrence. Furthermore, patients transplanted for PSC are known to have a higher incidence of biliary complications, again reflecting the use of a choledochojejunostomy reconstruction. However, in any case of biliary complication it is mandatory to explore the hepatic arterial tree to rule out stenosis or thrombosis.

Liver transplantation in patients affected by autoimmune hepatitis is usually successful, leading to 80–90% survival at 5 years with an excellent quality of life [(85)]. Of note is the high percentage of acute graft rejection in autoimmune patients compared with other chronic hepatitis aetiology. Some series demonstrated a 61% graft-loss occurrence, higher than the 42% in alcohol-related hepatitis [(86)], but comparable with other autoimmune liver disease such as PBC or PSC. Moreover the experience of the last 20 years reports a 20–30% rate of recurrence of autoimmune hepatitis on the new graft. The reasons of the

relapse are still debated and seem to be related to many factors (graft characteristics, steroid therapy and autoimmune disease severity). The relationship between the autoimmune relapse and the rejection rate is still controversial [(87)]. Recent developments in immunosuppresive drugs are significantly reducing the rate of graft loss for rejection or recurrent autoimmune hepatitis.

After liver transplantation, all patients at risk of hepatitis and cirrhosis recurrence usually undergo a surveillance programme for up to 5 years and then on a yearly basis. At least a clinic and ultrasound examination should be performed every 3 months during the year after liver transplantation, and every 6 months in the following period, but there is no evidence-based study to demonstrate a better cost:benefit ratio in comparison with other time periods. B-mode and Doppler ultrasound should be performed to identify the modification of liver dimensions, margin and echogenicity. In addition, the operator should measure the portal vein calibre and portal flow velocity, spleen dimensions, splenic and hepatic arteries RI and search for the new development of portosystemic collaterals, demonstrating the occurrence of portal hypertension.

A newer technique, transient elastography may be a useful tool to follow-up patients to monitor fibrosis associated with chronic hepatitis relapse after liver transplantation. Transient elastography can produce a mechanical compression of liver parenchyma, generating an elastic wave, allowing a measurement of the wave velocity, which estimates the liver stiffness (a parameter strictly correlated to the hardness or softness of liver tissue). Transient elastography can exclude the presence of significant fibrosis and has also been used to assess the progression of fibrosis after liver transplantation [(88)].

Recent research shows that there is a considerable variation in the development of fibrosis in the transplant patient; some patients have rapid fibrotic deposition and some have slow deposition, leading to a high or low risk of recurrent end-stage disease over the mid-term, respectively. In the first year after transplant transient elastography can accurately distinguish rapid from slow fibrosis [(89)].

Hepatocellular carcinoma

Liver transplantation has been demonstrated to be effective in a well-selected population. The Milan criteria represent the accepted standard to stratify the patients who could benefit

from liver transplantation. According to these criteria, three HCCs less than 3cm or one HCC up to 5cm are eligible for liver transplantation. A 5-year survival of 70%, and a 15% recurrence rate has been reported with the application of the Milan criteria in cohort of patient transplanted for HCC [(3)]. The lowest recurrence rates (7%) occur in small tumours (<5cms) without evidence of disease spread [(90)], whereas a tumour recurrence rate of 62% was seen in large tumours (more than 5cm) [(91)]. Either infiltration of regional lymph nodes or the presence of gross vascular invasion at the time of transplantation could influence the prognosis [(92)]. Children who have received a liver transplant for primary hepatic malignancy have a better prognosis than adults; ten-year survival rate is 21% in adults and 50% in children [(93)].

Currently there is no rational surveillance protocol to screen the HCC population following liver transplant [(92)]. A screening policy based on periodical ultrasound examinations could be helpful to detect early HCC recurrences similar to that in patients with cirrhosis, but this is unclear whether this offers a beneficial outcome. Moreover ultrasound must be combined with a more comprehensive imaging technique to avoid the risk of missing distant recurrence such as lung and bone metastasis [(94)]. The final combination of contrast techniques (CEUS, contrast-enhanced CT and MRI) and alfaphetoprotein monitoring should allow the final diagnosis. HCC features in post-transplant liver are similar to those in the pre-transplant liver.

Fibrolamellar hepatocellular carcinoma

Fibrolamellar HCC is an aggressive neoplasm affecting young adults. The surgical option is the preferred approach, but this is contraindicated in resection, liver transplantation is an alternative choice. Unfortunately, recurrence rate after transplantation is high, which affects patient survival [(95)] . This may be related to the frequently late presentation of the tumour. The survival rate following transplantation ranges between 35% and 50% at 5 years [(95, 96)].

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