Liver biopsy: past, present and future

Liver biopsy is an integral part of evaluation of liver disease. Indications and techniques have developed to allow functional and prognostic liver assessment, along with biochemistry and dynamic imaging, in both diffuse and focal liver disease. However, non-invasive techniques are changing the way clinicians use liver biopsy.

The first aspiration of liver parenchyma was performed by Erlich in 1883 and 40 years later, Bingel reported the first percutaneous biopsy for diagnostic yield in 1923 (Grant et al, 2004). This technique was adapted when Menghini developed a suction needle, leading to expansion of the use of liver biopsy (Menghini, 1958). Over this time there has been a significant change in how liver disease is assessed and managed. Within the past two decades there has been a shift to a more standardized approach to liver biopsy. The British Society of Gastroenterology (Grant et al, 2004) and the American Association for the Study of Liver Disease (Rockey et al, 2009) have published guidelines to this effect. This review highlights current practice, areas of debate and changes to liver biopsy moving forward.

Indications for liver biopsy

The need for liver biopsy and histological assessment has changed since its introduction. In the past, virtually all forms of liver disease were diagnosed using this technique. Recently the advent of non-invasive assessment has changed the way clinicians use liver biopsy.

Diffuse liver disease

Simple clinical and biochemical features can lead to the diagnosis of diffuse hepatic disease including viral hepatitis, genetic haemochromatosis, Wilson's disease and autoimmune conditions including primary biliary cirrhosis and autoimmune hepatitis (Grant et al, 2004). Liver biopsy may be useful in patients with atypical presentations or non-diagnostic first-line tests in order to differentiate between conditions that have specific histological features.

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In viral hepatitis, liver biopsy has historically been crucial in diagnosis and staging. Originally it was necessary before commencing therapy; however, non-invasive assessment has become more widespread and this has reduced the need for biopsy. This is the case for patients with hepatitis C with the most recent European Association for the Study of the Liver (2015) guidelines stating that liver biopsy is now reserved for cases of uncertainty or where there may be additional aetiology. The role of biopsy in patients with hepatitis B is not as clear-cut. The European Association for the Study of the Liver (2012) recommends its use to identify patients with necroinflammation and fibrosis and to assist the decision to treat.

Despite the shift in use of liver biopsy to specific situations, its role has significantly expanded particularly in patients with liver transplants. Most centres now advocate the use of liver biopsy to assess post-transplant patients. Histology can ascertain changes associated with rejection, viral illness, reperfusion injury, drug-induced liver injury and bile duct damage (Grant et al, 2004; Rockey et al, 2009). There remain discussions about its use as a screening tool to identify early disease in post-transplant patients. Some argue that liver function tests are poor markers of underlying disease and that biopsy may be useful in detecting early disease, in fact some centres advocate biopsies as early as a year after transplant (Carbone and Neuberger, 2011). However, the potential complications and costs need to be carefully considered.

Focal liver disease

The indications for biopsy of focal lesions vary in the literature. The majority of interest centres around hepatocellular carcinoma, specifically in the context of liver cirrhosis. Larger lesions can now be confidently diagnosed and staged based on tumour markers and dynamic imaging (Rockey et al, 2009). The debate comes with lesions of less than 2 cm. In practice small, equivocal lesions are monitored with interval imaging and there is little evidence to suggest benefit of biopsy unless the operator is skilled and the lesion is well visualized on ultrasound. Sampling error, tumour recurrence and tumour seeding are potential

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disadvantages of biopsying small lesions (Rockey et al, 2009). However, this must be weighed against the potential benefits of gaining a histological diagnosis, which may affect the decision to transplant. Currently the American Association for the Study of Liver Disease recommends no biopsy in lesions larger than 1 cm if two dynamic imaging modalities have agreed a diagnosis of hepatocellular carcinoma (Bruix and Sherman, 2005).

Indeed there are numerous cases of lesions that are not characteristic on imaging which need histology, especially in non-cirrhotic patients. In particular, fibrolamellar hepatocellular carcinoma often needs histological sampling for diagnosis, as the patients are young with normal liver parenchyma. Additionally an increase is being seen in the incidence of patients with non-alcoholic steatohepatitis, who have the potential to develop hepatocellular carcinoma without cirrhosis. In these non-cirrhotic patients, liver biopsy is vital for correct diagnosis and subsequent treatment. This will become more apparent as the incidence of alcoholic liver disease is decreasing and non-alcoholic liver disease increases.

Other forms of cancer within the hepatobiliary system, such as cholangiocarcinoma, also require histological diagnosis, which is often done via endoscopic retrograde cholangiopancreatography. In cases where there is only biliary duct dilatation and endoscopic retrograde cholangiopancreatography is performed, as no focal nodular lesion is present, there could be a role for percutaneous liver biopsy.

Metastases to the liver are the commonest form of liver cancer and histology with molecular and oncogene analysis is extremely helpful for primary tumour diagnosis. In colorectal cancer with metastases to the liver, determining whether a liver tumour is metachronous rather than synchronous can be imperative to determine prognosis; synchronous tumours indicate a more aggressive tumour subtype and this dictates liver-directed therapies (Slesser et al, 2013). Biopsy in this instance is enormously important.

Liver biopsy techniques

Three main types of approach to the liver are currently used – the percutaneous, transvenous and laparoscopic routes.

Percutaneous liver biopsy

Percutaneous liver biopsy has its foundations in the original method described by Menghini (1958). Landmarks are identified with the patient in the supine position. Percussion down the hemithorax between the anterior and mid-axillary lines identifies the dullest point on maximal expiration. The intercostal space below this is the point of access. However, image-guided biopsy has taken over from blind biopsy. This can be undertaken with ultrasound, computed tomography or magnetic resonance, but ultrasound is the most readily available.

Plugged biopsy is a variation of the percutaneous technique. The biopsy track is 'plugged' with collagen or thrombin in order to minimize the risk of bleeding when the needle is removed (Rockey et al, 2009). The technique appears to be safe and efficacious particularly in patients where routine percutaneous biopsy is contraindicated. Both the British Society of Gastroenterology and the American Association for the Study of Liver Disease acknowledge the role of plugged biopsy in the coagulopathic patient.

Transvenous liver biopsy

The transvenous approach, commonly performed via the internal jugular vein (transvenous) or femoral vein, is often used in patients in whom percutaneous biopsy is contraindicated, such as those who are coagulopathic and/or have ascites. This was first described by Dotter (1964) and uses fluoroscopy, a catheter kit, an aspiration needle and intravenous contrast. It is thought that the transvenous approach limits injury to the liver capsule and therefore bleeding. The advent of cutting needles (Tru-Cut) and semi-automated systems (Quick-Core) has increased the yield obtained from this approach, compared to simple aspiration needles (Dohan et al, 2014).

This technique also has the added benefit of being able to measure the hepatic pressure gradient, which gives invaluable information regarding response to drug therapy and identifying patients at risk of bleeding from varices. It is of significant importance in post-transplant patients who need continual reassessment of graft function as well as complications including venous thrombosis.

Laparoscopic liver biopsy

The laparoscopic approach was used frequently before the advent of effective percutaneous routes and biomarkers. It allows a visual macroscopic assessment of the liver surface and samples are taken under direct vision using either wedge or needle biopsy. A wedge biopsy provides a larger histology sample, but needle biopsies are more accurate in diagnosis of diffuse parenchymal liver disease. Wedge biopsies often overestimate the stage of disease as a result of inflammation of the subcapsular region from the surgical procedure and therefore are only used for focal lesions or if biochemical sample testing is indicated (Geller and Pitman, 2002). Added benefits of laparoscopic liver biopsy are in patients with ascites or coagulopathy; complications can be dealt with immediately, particularly where transvenous techniques are not readily available. Newer techniques, including minimally-invasive mini-laparoscopy, have shown promise and may be increasingly used in the future (Dechêne et al, 2014).

Imaging assistance and guidance

Percutaneous liver biopsy can be performed blind, image-assisted or image-guided using ultrasound or computed tomography. Guidance entails real-time visualization of the liver and biopsy needle. Assistance uses imaging before the biopsy to 'mark the spot'.

An audit of UK-wide practice showed that the majority of biopsies were undertaken with the aid of imaging, largely ultrasound (Howlett et al, 2012). Image guidance is used more frequently than image assistance in diffuse liver disease, despite no apparent difference in diagnostic yield, sample size or fragmentation. In focal lesions there is understandable higher diagnostic yield with image guidance.

There has been some debate regarding the need for imaging in recent years. Flemming et al (2009) describe a selection of 100 patients who underwent liver biopsy for chronic hepatitis C. Fifty were allocated to blind biopsying and the remaining fifty to ultrasound guidance; the ultrasound group had higher quality samples but this had no effect on staging or outcome. However, in operator- and patient-matched series, there is some benefit in reducing the risk of complication, for example pain, without affecting diagnostic yield (Farrell et al, 1999). In their study of 328 ultrasound-marked biopsies *vs* 152 blind biopsies, DiTeodoro et al (2013) found reduced biopsy failure rate and number of passes required with better yield. A small series actually demonstrated that use of ultrasound marking changed the planned biopsy site in 13% of patients who had been palpated for blind biopsy beforehand (Riley, 1999).

The risk of adverse of events is higher in blind biopsies. Despite this, Howlett et al (2012) identified that 11% of respondents to a UK survey declared that they performed blind biopsies within their departments. This may be driven by cost, convenience and availability of operators or imaging modalities. However, in light of cost, taking into account complication rates without ultrasound use, image guidance is cost-effective. The British Society of Gastroenterology suggest the use of ultrasound guidance, particularly in the context of focal liver lesions (Grant et al, 2004). The availability of radiological-guided biopsy is problematic for gastroenterologists as it is difficult for non-radiologists to gain accreditation in this imaging modality.

Sampling in liver biopsy

Within the UK, liver biopsies are conducted using either suction or cutting needles. Suction or aspiration needles were first described by Menghini (1958); suction is applied to a syringe attached to the needle on entry into the liver. Cutting needles can either be manual or automated. The needle is passed into the liver parenchyma then an outer sheath slides over this to obtain a core tissue sample. Sampling variability is a concern when biopsying, particularly as a result of the asymmetrical distribution of lesions in most liver disease (Rockey et al, 2009). Sample size will be affected by the diameter, length and number of specimens acquired, and also whether there is focal or diffuse liver pathology.

Needle type

There has been much debate about what type of needle to use. Cutting needles produce a longer and larger tissue sample when compared to the suction-type. They also minimize the fragmentation that can occur using the aspiration technique and are therefore less likely to cause specimen degradation. Newer automated cutting needles are now in use and allow variable specimen length, which is desirable compared to conventional needles.

However, some evidence suggests that there is an increase in complications with cutting needles, possibly as a result of the increased length of time in which cutting needles remain in the liver parenchyma. In their prospective study of over 2000 liver biopsies, Mueller et al (2012) found a 1.8% bleeding risk using cutting needles compared to 0.3% with aspiration needles (P=0.03). Newer techniques incorporating smaller gauge needles with aspiration and cutting features have shown comparable diagnostic yield with favourable complication rates. It is currently recommend that larger gauge cutting needles should be used in the assessment of cirrhosis and diffuse liver disease (Grant et al, 2004).

Diffuse liver disease

In diffuse parenchymal liver disease, acceptable specimens should contain a minimum of 6–10 complete portal tracts. Bedossa et al (2003) found that the accuracy of fibrosis measurement in patients with hepatitis C increased with sample length and suggest a minimum length of 25 mm. The American Association for the Study of Liver Disease guidelines suggest a minimum length of 20–30 mm and 16-gauge needle in the diagnosis of diffuse liver disease to fully assess liver architecture (Rockey et al, 2009).

Maximizing specimen yield can be also achieved by increasing the number of passes, particularly as diffuse disease can be patchy. With more than three passes, complication rates increase (Grant et al, 2004). The majority of percutaneous biopsies in the UK occur with one or two passes (Howlett et al, 2012).

Focal liver disease

The diagnostic rate is higher for focal liver lesions than diffuse disease; this is likely related to the comparative ease of acquiring a specimen. In a large study of over 2000 focal neoplastic liver lesions, diagnostic accuracy was over 93% for both aspiration and cutting needles (Buscarini et al, 1990). The current American Association for the Study of Liver Disease guidance states that the use of narrow gauge needles is sufficient for focal neoplastic lesions (Rockey et al, 2009).

Transvenous liver biopsy and sampling

Transvenous biopsy sampling typically offers smaller sized specimens with greater rate of fragmentation. A comprehensive systematic review revealed a fragmentation rate of 34.3%, median length of 12 mm with median complete portal tracts of 6.5 (Kalambokis et al, 2007). Diagnosis, staging and grading improve when multiple core specimens are taken in this technique.

Complications in liver biopsy

As with any other invasive procedure, liver biopsy has inherent risk. Pain is the most common complication of liver biopsy, occurring in over 80% of patients to some degree (Rockey et al, 2009). Pain itself may be related to several factors; it occurs less frequently in those who have image guidance, more experienced operators and smaller gauge needles (Howlett et al, 2013).

Major complications include haemorrhage, haemobilia, colonic or gallbladder perforation, kidney or pancreatic injury and pneumothorax (Al Knawy and Shiffman, 2007). Major haemorrhage encompasses bleeding that causes haemodynamic instability, requirement for blood transfusion, intervention and hospitalization. The risk of this is between 0.1 and 0.5% (Machado, 2011). There is evidence that patients with malignancy and cirrhosis have increased risk of post-procedure bleeding (Grant et al, 2004; Rockey et al, 2009). Other factors include impaired coagulation, technical aspects including larger needle gauge and type (cutting), focal disease and the uncooperative patient (Machado, 2011).

Mortality rates vary within the literature as a result of small case numbers. Retrospective data indicate that biopsy-related mortality rates range between 0.11% and 0.48% (Buscarini et al, 1990). UK audit data of over 3400 cases identified a fatality rate of 0.11% (Maharaj and Bhoora, 1992). All deaths in this series were attributable to major haemorrhage and had an underlying malignant focal lesion or cirrhosis; this was also observed in one of the largest series to date of over 68 000 cases (Piccinino et al, 1986).

Transvenous biopsies are considered in patients who are at high risk of bleeding. It has a similar complication profile to the percutaneous route ranging from 1.3–20%, major complications being very rare (Grant et al, 2004). Procedure-specific complications include neck haematoma, transient Horner's, pneumothorax and arteriovenous fistulae (Grant et al, 2004). The current American Association for the Study of Liver Disease guidelines acknowledge the lack of direct comparison between transvenous and transcutaneous routes but suggest use of the transvenous route in those with increased risk of bleeding (Rockey et al, 2009).

Prevention

Choice of needle gauge, type and use of guidance are ways to minimize bleeding. There is poor correlation between clotting parameters and bleeding. It has been found that 90% of patients who bleed after a liver biopsy have an international normalized ratio <1.3 (Strassburg and Manns, 2006). In their UK-wide audit, Howlett et al (2013) demonstrated a significant relationship between abnormal international normalized ratio and major complication, including major haemorrhage. It is generally suggested that patients should have an international normalized ratio <1.3 and platelets >60 000/mm^3 before biopsy (Rockey et al, 2009).

The time for observation after liver biopsy is another contentious topic. Piccinino et al (1986) identified that 96% of complications occur within 24 hours, with 61% occurring within the first 2 hours. The current British Society of Gastroenterology guidance advises monitoring vital signs regularly for 6 hours post biopsy (Grant et al, 2004).

Management of complications

Recognition of a major complication is the most important part of initial management. If major bleeding is identified, there is a possibility that this can be dealt with at the time of biopsy. Transcatheter embolization can be used if the liver capsule is perforated during transvenous biopsy. This method is also useful after percutaneous biopsy; however, not all departments have access to interventional radiology (Howlett et al, 2013). The lack of current data and benefit of obviating the need for surgical management should make this a topic for further research.

Operators and training

Historically, physicians carried out liver biopsy in ward-based environments. Gilmore et al (1995) found that 28% of biopsies were performed by gastroenterologists, 33% by general medics and 34% by radiologists 20 years ago. However, now the majority of liver biopsies are being undertaken by radiologists (95% performed by consultants or trainees) (Howlett et al, 2012). This highlights the shift to image-assisted or image-guided procedures in the UK. There remains some debate about whether liver biopsy should remain within the realm of physicians. The European gastroenterology curriculum acknowledges the need for abdominal ultrasound proficiency in its trainees, but not specific biopsy competency (Al Knawy and Shiffman, 2007).

Operator experience is another factor to consider and currently there is no universally accepted figure of how many procedures constitutes competency. Chevallier et al (2004) compared those with less experience (fewer than 15 solo biopsies) to those with more (over 100 solo biopsies) and identified no significant difference in final histological diagnosis or pain scores. The British Society of Gastroenterology suggests that if an operator has performed fewer than 20 biopsies he/she should be supervised (Grant et al, 2004).

Non-invasive liver assessment

The last 20 years have seen a significant expansion in non-invasive investigations in liver assessment, largely as a result of developments in evaluating chronic viral hepatitis.

Elastography

Elastography measures liver stiffness as a surrogate marker of liver fibrosis. First-generation dynamic ultrasound elastrography (Fibroscan) uses an external shear wave pulse that is measured using one-dimensional ultrasound. A score is given in kilopascals (kPa) with the notion that stiff

KEY POINTS

- Liver biopsy techniques are developing alongside better imaging techniques to assist in accurate image-guided sampling.
- In coagulopathic patients, transvenous and laparoscopic liver biopsy are used to reduce the risk of complications.
- New non-invasive forms of liver assessment, such as elastography, have reduced the need for biopsy specifically in diffuse liver disease.
- In focal liver lesions, liver biopsy remains of great importance to determine histology when suspecting malignancy.

tissue allows the shear wave to propagate faster. Transient elastography is now widely available and has good diagnostic accuracy in assessing liver fibrosis. A large prospective study found 15.8% of over 13 000 transient elastography studies had unreliable results; this was related to increased body mass index, metabolic syndrome and operator experience (Castera and Pinzani, 2010). Manufacturers have responded to this with the introduction of newer probes (XL probe in Fibroscan). Second generation elastography methods including acoustic radiation force imaging use focused ultrasound waves to generate internal shear waves. This modality has shown promise with similar diagnostic accuracy to transient elastography and lower failure rates in patients with high body mass index and ascites.

Indeed elastography is of use in diffuse liver disease but limited in focal disease, especially when a liver with metastatic disease has been shown to be 5–10% stiffer than in a non-diseased state. In this instance liver biopsy still plays a key role.

The European Association for the Study of the Liver (2015) recommendations state that the diagnostic accuracy of transient elastography is greater for patients with cirrhosis than fibrosis. It is the most validated form of non-invasive liver assessment, and current recommendations state that it is the most accurate way of assessing cirrhosis in viral hepatitis. It may not be suitable as the sole assessment of fibrosis but may guide biopsy in those patients with moderate fibrosis scores on elastography in order to ascertain the histological level of fibrosis.

Magnetic resonance elastography is another way of assessing liver stiffness with the added ability of assessing the whole liver substance and may be superior to ultrasound-based transient elastography (Huwart et al, 2008). The European Association for the Study of the Liver (2015) recommendations currently acknowledge the use of magnetic resonance elastography in research settings, but state it is too costly and time consuming for general clinical use.

Transient elastography may also be useful in evaluating prognostic features. Liver stiffness has been shown to correlate to portal hypertension in post-transplant patients. Takuma et al (2013) identified patients with features of portal hypertension through measurement of spleen and liver stiffness compared to endoscopic results. Spleen stiffness was sensitive in detecting oesophageal varices in 98% of patients. Liver stiffness may also be useful in focal liver disease such as hepatocellular carcinoma, but only in conjunction with biochemical markers (Wong et al, 2014).

Novel liver biopsy techniques

Technological advances have seen the development of newer techniques in order to maximize gain and minimize risk. One new technique is endoscopic ultrasound-guided liver biopsy for use in targeted fine needle aspiration. An echoendoscope is able to identify both lobes of the liver and transgastric needle biopsy can be undertaken. This minimizes complications through avoidance of major vessels and structures including bowel through use of high-resolution endoscopic ultrasound images and is a potential for use in focal lesions. A multicentre study of 110 patients identified adequate diagnostic yield with minimal complications (Diehl et al, 2015). Overall yield consisted of a median of 14 complete portal tracts and median length of specimens was 38 mm with a complication rate of 0.9%.

In clinical practice endoscopic ultrasound is not widely used for diagnosis; magnetic resonance imaging or simple ultrasound are often more helpful in this instance. Contrast-enhanced ultrasound is of particular use in non-cirrhotic patients with equivocal lesions and is often the imaging modality of choice alongside magnetic resonance.

Conclusions

Despite recent advances in liver assessment, liver biopsy remains an integral part of diagnosing, staging and treating liver disease. Its role is continually changing and adapting to the significant developments that occur in hepatology. We are now seeing an increase in non-invasive investigations and streamlining of patients that are selected for liver biopsy. The past few decades have seen a significant development of techniques and increased safety profile. The field is continuing to strive to optimize practice and the recent introduction of guidelines has improved standards of biopsying. The next decade will see potential changes to technique and training but liver biopsy will continue to be an essential tool for clinicians. **BJHM**

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