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Complications of Liver Biopsy - Risk Factors, Management and Recommendations

Norman Oneil Machado
Sultan Qaboos University Hospital
Oman

1. Introduction

The role of liver biopsy (LB), the traditional gold standard for assessing liver disease, continues to evolve[1-4]. Fewer biopsies are being done for diagnosis as noninvasive tests such as new imaging techniques and accurate serological tests can now be done instead in many cases[2-4]. Most biopsies are currently performed for parenchymal disease not to make specific diagnosis but to assess the liver damage (the degree of inflammation, fibrosis) or the response to therapy[5]. In contrast to past when nearly all biopsies were done for diagnostic purpose, presently more than 50% are being done for staging versus 15% for diagnosing the parenchymal liver disease[5]. In addition, biopsies are often done to help in guiding the management of hepatitis C and nonalcoholic steatohepatitis and to assess the response to therapy[2, 3]. The increased use of liver transplantation as standard treatment of end stage liver disease of diverse etiologies has led to more biopsies being performed to differentiate the cause of graft dysfunction and to assess the suitability of potential liver donors for transplantation[1-3]. The dramatic increase in obesity, diabetes, hyperlipidaemia and hypertension (the metabolic syndrome) in western societies and its accompanying fatty liver problems are requiring liver biopsy for histological assessment[2]. Evaluation of liver histology remains very important as LB is reported to change the clinical diagnosis in 8-14%, management in 12-18% and frequency of liver test monitoring in 36% of cases[5]. Hence the main indication are a) chronic hepatitis- for grading, staging, establishing a therapeutic strategy and monitoring therapy, b)unexplained abnormal liver function tests or hepatomegaly and c) follow up of patients after liver transplantation. However no liver biopsy is free of risk as it is an invasive procedure. Rational assessment of overall risk in LB however is hampered by the wide variation in the indication and its outcome reported in the existing literature.

2. Factors that may influence the risk of complication following liver biopsy

Several factors my influence the risk of complication following liver biopsy and are listed in table 1

Uncooperative patient- The risk of bleeding is enhanced in an uncooperative patient who may inadvertently move when the biopsy needle is in the liver leading to tear or laceration[1-4]. In such uncooperative patients if liver biopsy was required it could be achieved by performing the procedure under moderate or deep sedation or under general anaesthesia[6, 7]. A

transjugular approach is an alternative option[8]. Conscious sedation for LB are performed using midazolam and fentanyl or mepverdine[6,7]. This adds to small risk and the cost of conscious sedation to the procedure. However patients are found to be remarkably cooperative and usually breathe somewhat superficially and will hold their breath if instructed[6,7]. However while sedation may allay anxiety and pain there is no strong evidence to suggest that it either increases or reduces the risk of major complications. It however makes an uncooperative patient cooperative[1].

Factors that may influence the risk of complication following liver biopsy
Patient cooperation
Coagulation status / bleeding disorders
Operator experience
Advanced age
Certain pathologies (liver cirrhosis, amyloidosis, malignancy, renal failure)
Use of image guidance
ascites
Type of technique (percutaneous / transvenous)
Number of needle passes
Needle diameter (large needle)
Type of needle (cutting or Automatic)
Blind technique

Table 1.

Ascites-_Moderate to severe ascites_is likely to make it difficult to hit the liver via the standard intercostal approach. In such patients, options would include total therapeutic paracentesis performed immediately prior to palpation /percussion guided transcutaneous biopsy or transvenous or laparoscopic biopsy[9].There are however reports of successful LB under CT scan or US guidance without increasing the risk of bleeding[9].

Mass lesion- Although LB in patients with mass lesion is generally safe, biopsy of known vascular lesion should be avoided[10]. Similarly biopsy of potentially malignant lesion should be avoided because it is believed that tumour vessels are more likely to bleed. However with the use of ultrasound colour Doppler to guide the site of biopsy, large tumour vessels and liver vessels can be identified and avoided[1,11,12]. Biopsy of malignant lesion is also associated with a risk of tumour spread usually along the biopsy tract. The risk is estimated to be around 0 to 0.13%[12] and the risk decreases with use of co-axial approach (i.e. utilization of a 17 gauze introducer and 18 gauze biopsy needle introduced along a co-axial plane[13].

Impaired haemostasis- Standard percutaneous liver biopsy is often withheld in patients with a PT-INR above 1.5[1-4]. However while alteration in haematological parameters are of utmost importance when considering the risk associated with liver biopsy, strict cutoffs for PT-INR may not be prudent in light of the risk associated with plasma infusion[1-4]. While it is often presumed that abnormal increase in the PT-INR correlates with an increased risk of bleeding and that correcting the abnormal PT-INR with plasma replacement therapy or agents such as recombinant activated factor V11 will reduce or eliminate the risk of bleeding, the available data in the literature are not sufficient to support this presumption particularly in mild coagulopathy defined as INR of less than 2.0[14-15]. Hence it is not clear whether prolongation of the INR in chronic liver disease while of prognostic significance actually represents a net diathesis or not[2]. Thus better tests are needed to more acutely define the net

bleeding risks in these patients. A new measure of coagulation in liver disease has recently been introduced, the INR_{Liver}[16,17] . It recalculates the international sensitivity index from a reference point of patients with liver disease rather than Coumadin –treated patients as has been the convention[16.17]. Whether this test will provide a reliable measure of bleeding risk remains to be determined. Therefore a large randomized controlled trial of plasma replacement therapy in patients undergoing invasive therapy appears to be warranted[1].
There are however several conditions which are more definitely associated with enhanced risk of bleeding and therefore warrant additional caution. These include patients with factor V11 (FV11) or 1X (F1X) deficiency, von Willebrand's disease, other hereditary bleeding disorders and those with sickle cell anaemia[17]. Patients with known underlying coagulopathy requiring liver biopsy represents a challenge but liver biopsy can be performed in these patients with definitive factor replacement. Nonetheless the risk benefit ratio must be carefully considered on a case by case basis

2.1 Ultrasound guided LB

This has been done to reduce the risk of both minor and major complications by avoiding large intra-hepatic vessels and other structures in the vicinity (gall bladder, colon, lung) and by decreasing the passes to sample a good specimen[18-21]. Ultrasound (US) may influence in selecting the site of puncture as was noted in 15% of cases in one study[19]. The main causes for the change in site were due to ascites or small liver. US guided liver biopsy is reported to be performed in 56% of cases in France and in 76% of cases in USA[20,21]. This could either be performed as US guided or US assisted LB. US guided LB is particularly reserved for small liver, interposition of colon or lung, focal liver lesion (Haemangioma or cysts) or in patients with increased risk of bleeding[19-21].

3. Post biopsy care and complications

Rate of complications vary in different case series and relate in part to operator experience although the most experienced clinician still will encounter complications[1-4]. The risk of major complications is listed in table 2. Intraoperative needle biopsy observation indicates that almost all patients have transient bleeding from the capsular puncture site[1,2]. Following outpatient LB the period of observation varies among different institution but usually does not exceed 6 hours[1-4]. Patients who have had uneventful single pass biopsy may be discharged after 3 hours observation and if patients require analgesia may need observation for at least 4 hours[2-4]. The majority of major complications requiring hospitalization have been shown in prospective observational series to occur within 3 hours of biopsy, although later complication can occasionally ensue[1-4].

3.1 Complications

Pain- Pain is the most common complication of percutaneous liver biopsy and is seen in up to 84% of patients including those with mild discomfort[22]. Often pain can be managed with small amounts of narcotics typically codeine[1-4]. The pain immediately after the procedure at times can be very distressing and some patients remember the procedure as a very unpleasant experience. Moderate to severe pain however is seen in 1-5% of the patients and should raise the possibility of a complication such as active bleeding or trauma to adjacent structures like gall bladder[23]. The mechanism of pain following percutaneous biopsy is most likely a result of bleeding or perhaps bile extravasation from the liver puncture wound with

subsequent capsular swelling although the exact mechanism for the pain remains uncertain in most cases[2-4]. The site of biopsy (intercostal or subcostal) did not influence the incidence of pain[24]. However the use of US guidance, premedication with midazolam and fenatnyl and self delivering of mixture of N_2o and oxygen via mask decreased significantly the incidence of post biopsy pain and anxiety[24,25]. For LB performed with US guidance the incidence of pain decreased from 47% to 35%. The 2 factors that were demonstrated to be associated with increased use of post procedure analgesics are, cutting biopsy needles and less experienced operator[25,26]. Other controversial factors associated with more pain are larger needle, increasing number of biopsy passes, hepatitis C infection, younger age and history of intravenous drug abuse[27]. The use of automatic cutting needles are associated with a low incidence of postbiopsy pain with a reported incidence 31.4 to 34.3% in comparison to hand held needles(40.6 to 52.6%)[25,26].Besides the above factors the patient characteristics play an important role in pain medication requirement after LB . Thus previous intravenous drug abusers and those with significant anxiety prior to LB are associated with 9 and 4 fold increase in post biopsy analgesia respectively[27].

Scenario	*Reported frequency (%)*
Pain at biopsy site or right shoulder (pleuritic, peritonel, diaphragmatic)	0.056-22
Haemorrhage	
-intraperitoneal	0.03-0.7
-intrahepatic or subcapsular	0.59 -0.23
-haemobilia	0.058-0.2
Bile peritonitis	0.03-0.22
Pneumothorax and /or pleural effusion	0.08-0.28
Haemothorax	0.18-0.49
Arteriovenous fistula	5.4
Anaesthetic reaction	0.029
Biopsy of adjacent organs	0.001-0.044
lung	-0.001- 0.014
gall bladder	-0.034- 0.117
kidney	-0.029- 0.096
colon	-0.0038- 0.0044
Reaction to anaesthetic agent	0.029
Breakage of needle	0.02- 0.059
Death	0.0083-0.03

Table 2. Potential complications and the range in reported frequencies

A decision about when to investigate with imaging and or to hospitalize the patient for observation due to pain should be made on a case by case basis[1-4]. When pain is severe enough to require hospitalization radiological evaluation is usually warranted. While some would prefer the use of ultrasound as an initial investigation due to the ease with which it can be performed , others would perform an abdominal CT with contrast to be more definitive[1-4](figure 1).

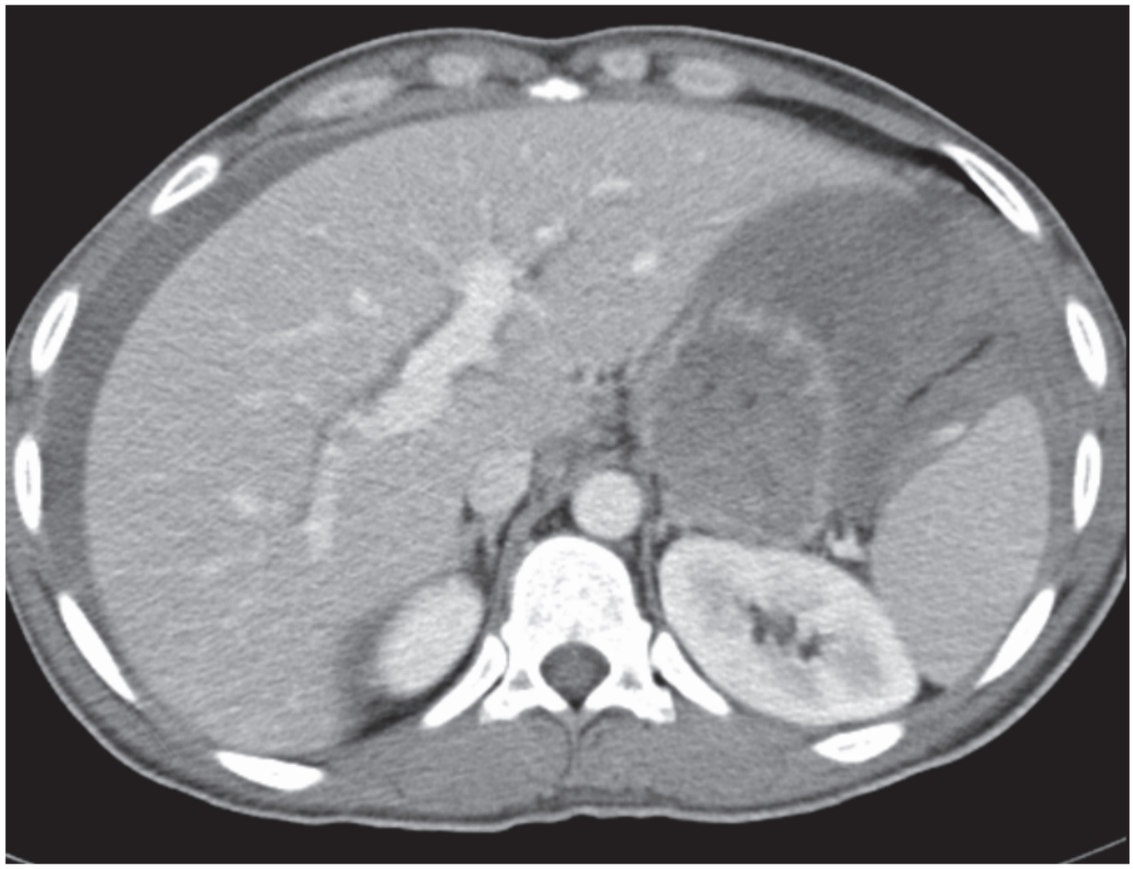

Fig. 1. CT scan revealing intraperitoneal bleeding following subcostal percutaneous liver biopsy. The bleeding was successfully managed conservatively

Bleeding- Bleeding could either be major or minor. The risk of major bleeding is reported to be around 0.16%[1-4,28-30]. Major bleeding is severe bleeding defined clinically by change in vital signs with radiographic evidence of intraperitoneal bleeding that requires hospitalization with the likelihood of transfusion or even radiologic intervention or surgery. Such bleeding has been estimated to occur in between 1 in 2500, to 1 in 10,000 biopsies after intercostal percutaneous approach for diffuse nonfocal liver disease[23,31-33]. Minor bleeding is less severe bleeding which is characterized by pain or reduced blood pressure or tachycardia but not requiring transfusion or intervention and occurs in approximately in 1 in 500 biopsies. About 18 to 20% of intrahepatic and perihepatic bleeding is also detected on ultrasonography[28]. Severe bleeding is usually clinically evident within 2 to 4 hours but late haemorrhage can occur even up to one week after biopsy[34]. Premature clot dissolution due to liver disease associated with hyperfibrinolysis has been proposed to play a role in some patients especially those with delayed bleeding, although this has not been extensively studied[35]. Some degree of bleeding occur after all percutaneous liver biopsies based on observation made on laparoscopy.

Bleeding can manifest as haemoperitoneum(0.3 to 0.7%), intrahepatic haematoma(0.59 to 0.23%) or haemobilia(0.058- 0.2%) [28-30](figure 1). Bleeding into peritoneal cavity produces pain, hypotension or less frequently may be asymptomatic. Intrahepatic haemtoma occurs in 1 to 23% of cases and are localized to intrahepatic or subcapsular region[28,29]. Usually they

are small and asymptomatic but larger haematomas may cause pain from stretching of the liver capsule, hypotension or a delayed decrease in haematocrit[28,29]. The incidence of haematoma after LB seems to be high after LB with larger needles[30]. Conservative treatment of haematoma together with a close follow up by US is generally sufficient[1-2,36]. The least common of the haemorrhagic complications is haemobilia which presents with the classical triad of upper gastrointestinal bleeding, pain and jaundice[4,18,36]. It may appear acutely following simultaneous perforation of adjacent intrahepatic bile ducts and blood vessels or more commonly much later following the erosion of haematoma or psuedoaneurysm into a bile duct[37]. This occurs typically 5 days following the biopsy[31]. Haemobilia is a very rare event with a frequency of 0.0006 to 0.023% in large series[31,37,38]. If bile is checked routinely after LB, haemobilia may be detected in 10% of cases[31,37,38]. Large volume of haemobilia may cause acute pancreatitis, although this is a very rare event with only 5 cases being reported in the literature[39].

The risk of bleeding is influenced by several factors including bleeding disorders, advanced age, ascites, high number of passages, large needle size, blind technique and certain liver pathologies including liver cirrhosis , amyloidosis, malignancy and renal failure[1-4,28,31]. The factors that are also related to the risk of bleeding include arterial bleeding and operator experience. Whether cutting needle(eg Trucut and automated variants) have a different risk than aspiration needles(eg, Menghini or Jamshidi) is unknown although some retrospective data suggest that cutting needle may be associated with slightly greater risk[31]. At particular risk for bleeding are patients with chronic renal failure, those with underlying coagulopathy due to congenital abnormalities in coagulation parameter (such as haemophilics) and those with cirrhosis who may have acquired abnormalities in coagulation parameter. Use of DDAVP immediately before liver biopsy (0.3ug/kg) body weight in patients with renal failure undergoing invasive procedure is useful[40,41]. In patients on chronic renal replacement therapy, dialysis is often performed prior to liver biopsy[1,2]. Although platelet count less than 60,000/cmm, INR greater than 1.3 and bleeding time > 10 minutes are well known practical contraindication to percutaneous LB, bleeding from liver does not correlate with the indices of peripheral coagulation when these are mildly impaired thus making bleeding an unpredictable event[42,43]. The accurate prediction of bleeding based on coagulation indices is problematic as the available data suggest poor relationship between bleeding and common laboratory tests (such as platelets, PT-NR etc)[42,43]. As a result there is wide variation in “acceptable” prebiopsy coagulation parameter[44]. Whether the use of prophylactic blood products alters the risk of bleeding is currently unknown[1-3]. Furthermore because of the conventional parameter of coagulation correlate poorly with risk of bleeding, recommendation regarding correction of coagulation indices is limited and tempered by the risk of blood product exposure[42,43].

Transvenous liver biopsy (typically with jugular approach) is often recommended in patients with known or suspected bleeding diathesis because it is commonly perceived to be safer[8]. However a recent systematic review reported minor and major complication in 6.5% and 0.6% respectively among the 7649 patients who underwent transvenous biopsy and may be related to capsular piercing with subsequent haemorrhage[32]. However as this study was retrospective, there may have been a selective bias (i.e. it is highly likely that patients suspected to be at risk of bleeding would have been preferred for transvenous rather than percutaneous biopsy).

3.2 Miscellaneous

A number of other complications have been reported after liver biopsy. These include pneumothorax, hemothorax, perforation of any of the several viscous organs, bile peritonitis, infection (bacteraemia. abscess, sepsis), haemobilia, intrahepatic arteriovenous fistula, neuralgia and rare complication such ventricular arrhythmias with transvenous biopsy[1-4].

3.2.1 Infective complications

Transient bacteraemia which has been reported in 5.8 to 13.5% of patients after LB, is in most cases harmless[31]. Intrahepatic abscess, septicaemia and septic shock are much rare events occurring only in patients with biliary obstruction and cholangitis or when the colon is incidentally punctured[18]. Infectious complication appear to be increased in post transplant patients who underwent choledochojejunostomy during liver transplantation[45]. There is however no recommendations of prophylactic antibiotics in patients scheduled for LB except in those with valvular heart disease

3.2.2 Complications in the thorax

Haemothorax, pneumothorax, leakage of ascites in the pleural cavity, subcutaneous emphysema occur after injury of pleura or lung or right diaphragm[18,31,46]. Haemothorax can occur even in US assisted LB when the patient changes his position or takes a deep inspiration after the site of puncture was set, the cause of bleeding being an injury to a diaphragmatic vessel[46] . Pneumothorax is critical to recognize immediately after biopsy in presence of reduced breath sounds and typical radiographic findings because it can lead to immediate catastrophic outcome if not promptly recognized and treated[18,31].

3.2.3 Puncture of other viscera

This occurs rarely (0.01 to0.1%) and involves usually gall bladder, colon, and right kidney. The incidence is significantly reduced when LB is performed under US guidance[49,48] . Bile peritonitis , formation of bilioma or bilious pleural effusion occur mainly in patients with biliary obstruction although they are reports of them occurring even in patients without biliary obstruction or when the gall bladder is incidentally punctured[48,49].

Other very rare complications include reaction to the anaesthetic agents, breakage of the needle and arterioportal fistula, neuralgia and ventricular arrythmias [42,45].

Death- Is very uncommon after percutaneous biopsy but precise figure vary widely in the literature ranging from 0.009% to 0.11% .and is usually related to haemorrhage[10,20,24,31,41,45,49]. Mortality after transvenous biopsies was 0.0009% (9 in 10,000) in a recent report of 7649 transvenous biopsies but again may reflect the selection of higher risk patients for this intervention[40]. The main cause of death after LB is intraperitoneal bleeding mainly occurring in patients with malignancy or cirrhosis[45]. The incidence of fatal complications can be significantly reduced by careful post biopsy observation with prompt recognition of bleeding and aggressive subsequent therapy which may involve transfusion followed by therapeutic embolisation or laparotomy[18]

3.3 Management

The most critical aspect of management of complications such as bleeding, pneumothorax and visceral perforation is to recognize that one these complications has occurred.

Suspicion of a potential complication should be high when the patient complains of pain that is out of proportion to the clinical events that surrounded the biopsy and is associated with drop in blood pressure and tachycardia and is then confirmed by radiological investigation. All complications are supported by initial resuscitation. Bleeding is most often managed expectantly with placement of wide bore intravenous cannula, volume resuscitation and blood transfusion as necessary. Angiographic embolisation and surgery may be required in some of these patients with persistent bleeding. Pneumothorax may be self limiting but may require more aggressive intervention depending on the severity of symptoms. Visceral perforation is usually managed expectantly in most situations. Observation is all that may be required although occasionally surgical intervention may be needed in the case of gall bladder puncture with persistent bile leak or in case of secondary peritonitis

4. Recommendations

1. The person who performs the LB should be acutely aware of the multiple potential complications (including death) that may occur after liver biopsy and it is of outmost importance to discuss these appropriately with the patient's beforehand (class 1. Level C evidence)
2. Percutaneous liver biopsy with or without image guidance is appropriate only in cooperative patients and this technique should not be utilized in uncooperative patients(claas 1 level C)
3. Uncooperative patients who require liver biopsy should undergo the procedure under general anaesthesia or via transvenous route(class 1 level C)
4. In patients with clinically evident ascites requiring a liver biopsy a transvenous approach is generally recommended although percutaneous biopsy (after removal of ascites) or laparoscopic biopsy are acceptable alternatives(class 1 level C)
5. Haematological abnormalities particularly low platelet count (levels less than 50,000-60,000/ml) should be dealt with platelet transfusion prior to the procedure. This applies for both percutaneous and transvenous approach
6. The use of prophylactic or rescue strategies such as plasma, fibrinolytic inhibitors or recombinant factors should be considered in specific situations although their effectiveness remains to be established.(class 11a, level C)
7. In patients with renal failure or on hemodialysis , desmopressin(DDAVP) may be considered, although its use is necessary in patients on stable dialysis regimen(class 11a, level B)
8. Patients on chronic haemodialysis should be well dialysed prior to liver biopsy and heparin should be avoided if at all possible(class 1, level C)

5. Conclusion

The indications for liver biopsy are evolving. While liver biopsy may play a major role in management of some of the hepatic disorders, it is not without risk. Mild pain following the procedure is not uncommon however persistent and severe pain should warrant further investigation to rule out significant intraperitoneal bleed. Liver biopsy performed under ultrasound guidance and premedication is reported to significantly reduce complications including pain. The risk of major bleeding post liver biopsy is low but is of serious

consequence as it is the main cause of a rare event of death. Among the various factors that may influence complication risk, patients coagulation status and operator experience are of outmost importance. The coagulation status should be optimized to the extent possible with platelet and coagulation factor infusion and the use of DDAVP and haemodialysis in patients with renal failure. The most critical aspect of management of these complications is to be acutely aware of it and to promptly treat it.

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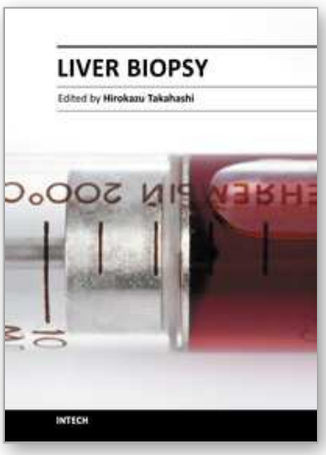

Liver Biopsy

Edited by Dr Hirokazu Takahashi

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Liver biopsy is recommended as the gold standard method to determine diagnosis, fibrosis staging, prognosis and therapeutic indications in patients with chronic liver disease. However, liver biopsy is an invasive procedure with a risk of complications which can be serious. This book provides the management of the complications in liver biopsy. Additionally, this book provides also the references for the new technology of liver biopsy including the non-invasive elastography, imaging methods and blood panels which could be the alternatives to liver biopsy. The non-invasive methods, especially the elastography, which is the new procedure in hot topics, which were frequently reported in these years. In this book, the professionals of elastography show the mechanism, availability and how to use this technology in a clinical field of elastography. The comprehension of elastography could be a great help for better dealing and for understanding of liver biopsy.

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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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