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## Complications of Liver Biopsy

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### 1. Introduction

The liver is the second largest organ in the body after the skin and has important storage, detoxification and synthetic functions. Liver diseases encompass a multitude of pathologies and the management of these diseases involves diagnostic and therapeutic investigations and interventions; some of which are invasive. Histological assessment of the liver and lesions within via liver biopsies are an important tool in the armamentarium of invasive investigations for liver diseases of both a surgical and non-surgical nature.

Liver biopsy has been used for over 100 years in the assessment of liver diseases (Valori and Elias 1989). Paul Ehrlich performed one of the first percutaneous liver biopsies in the late 19<sup>th</sup> century in Germany to assess glycogen levels in the liver of a diabetic patient (Grant and Neuberger 1999). However, the procedure did not really gain popularity until Menghini refined the technique in the mid 20<sup>th</sup> century (Menghini 1958). In the last fifty years the techniques for liver biopsy has been continuously refined and although today there are several biochemical and imaging techniques to assess liver disease biopsy remains important in assessment. Today, widespread application allows for blind, open and image guided liver biopsies, although ultrasound guided biopsies are considered superior (Younossi, Teran, Ganiats and Carey 1998). Image guided percutaneous liver biopsies remains the mainstay of this procedure while open biopsies may be undertaken as an adjunct to laparoscopic or other open surgical procedures. There are presently various techniques and equipment for percutaneous liver biopsies and this procedure is performed by both gastroenterologists/hepatologists and radiologists. The choice of technique and equipment is however operator dependent.

### 2. Indication

In the past the indications for liver biopsies and the practice thereof varied significantly between institutions. This was born out in an audit conducted by the British society of Gastroenterology and the Royal College of Physicians of London (Gilmore, et al. 1995). Subsequent to this the British Society of Gastroenterology published guidelines on the use of liver biopsy in an attempt to standardize indications and technique for this procedure

(Grant, et al. 1999). Similar guidelines have since been published by the American Association for the Study of Liver Diseases (Rockey, Caldwell, Goodman, Nelson and Smith 2009). These indications are beyond the remit of this chapter and can be sourced from the guidelines.

### 3. Methods

There are various methods for performing liver biopsies. In the main most liver biopsies are performed percutaneously. In the UK this method is performed by radiologists under image guidance. In support of image guided biopsies Vautier et al suggests that the ideal liver biopsy is one that is performed under ultrasonic guidance (Vautier, Scott and Jenkins 1994). However there are still some clinicians who practice liver biopsies without image guidance. In a survey conducted by Muir et al about current practice of liver biopsy 53.2% of clinicians still performed liver biopsies without image guidance (Muir and Trotter 2002). Guided liver biopsies are undertaken with real time imaging using ultrasound or CT scans. Real time imaging allows for accurate biopsy of lesions and avoidance of major vascular, biliary or bowel structures and thus reduce the incidence of complications. This can be via the transthoracic or the subcostal route and may be plugged or unplugged. Plugged percutaneous liver biopsies involves the injection of a gelatin substance into the biopsy cavity after withdrawal of the specimen. It reduces the complication of bleeding and can be used in patients with impaired coagulation (Fandrich, Davies and Hall 1996). In patients with coagulopathy in whom a percutaneous biopsy is considered inappropriate a transvenous (transjugular or transfemoral) approach can be used (Lebrech, Goldfarb, Degott, Rueff and Benhamou 1982, Sawyerr, et al. 1993). Laparoscopic liver biopsy is used in centres where expertise in the transvenous approach is unavailable for patients with a bleeding coagulopathy. A general anaesthetic is necessary where the laparoscopic approach is contemplated. In many instances it is undertaken when a liver lesion is found incidentally during diagnostic or staging laparoscopy. It can also be used in assessing the degree of cirrhosis of the future liver remnant in patients who are undergoing staging laparoscopy for consideration of liver resection for hepatocellular carcinoma. Laparoscopic liver biopsy allows direct visualisation of the area to be biopsied and immediate control of any haemorrhage. The complications of this procedure includes those associated with the anaesthesia, the laparoscopy and the biopsy. In our institution, we believe that all percutaneous liver biopsies should be image guided. As a result of the associated risks our patients are admitted for post biopsy observation for 6 hours as per the British society of Gastroenterology and the American Gastroenterological Association guidelines (Grant, et al. 1999, Rockey, et al. 2009). In other centres in the USA percutaneous liver biopsy is performed as an outpatient procedure with one of the stipulations being the patient is able to return to the hospital within 30 minutes if symptoms of a complication develop (Jacobs and Goldberg 1989).

### 4. Complications

The complications of liver biopsy can be divided into those in the immediate, early or late period (Table 1). The overall reported complication rate varies significantly (Galati, et al. 1994, Gilmore, et al. 1995, Grant, et al. 1999). These can range from minor complications

such as pain and transient hypotension to major complications such as visceral perforation or significant bleeding which may lead to death. The incidence of major complications was reported to be as high as 4% with a mortality rate ranging from 0.01% to 0.33%(McGill, Rakela, Zinsmeister and Ott 1990). Differences in complication rate has been reported between blind and ultrasound guided liver biopsies with ultrasound guided biopsies proving superior for both accuracy and risk of complications(Riley 1999, Al Knawy and Shiffman 2007).

Immediate	Early(within 24 hours)	Late
Death	Death	Needle tract seeding of Tumour cells
Pain	Pain	Biliary fistula
Bleeding	Bleeding	Septicaemia
Septicaemia	Septicaemia	Biloma
Perforation of nearby organs	Biliary peritonitis	Pleural effusion
Pneumothorax Haemothorax	Haemobilia	Intrahepatic arterio-venous fistula
Needle fracture		

Table1. Complications of Liver Biopsy

In addition, it is well documented that the risk of complications increases with the increase in the number of needle passes necessary for sampling(McGill, et al. 1990). Blind biopsies require more needle passes than ultrasound guided biopsies and have been statistically proven to increase the risk of complications(Cadranel, Rufat and Degos 2000, Mayoral and Lewis 2001). The issue of the relationship of needle size or type to complication rate remains controversial. McGill et al compared a 1.6mm diameter needle to a 1.9mm needle and found no difference in the incidence of haematomas(McGill, et al. 1990). The same is true for the study by Forsell et al (Forsell, Bonkowsky, Anderson and Howell 1981). However prior to this, the multicentre retrospective study conducted by Piccinino suggested a higher incidence of bleeding with cutting type needles (Piccinino, Sagnelli, Pasquale and Giusti 1986).

Finally, as with most invasive procedures the most significant factor in the incidence of complications associated with liver biopsy is operator experience. In the nationwide survey conducted in Switzerland on the practice and complications of liver biopsy Froelich et al reported that no complications occurred with internists performing more than 50 biopsies a year but a 1.68% complication rate with internists performing less than 12 biopsies a year (Froehlich, Lamy, Fried and Gonvers 1993). The national audit of percutaneous liver biopsy conducted in England and Wales confirms Froelich’s findings. It was found that the frequency of complications was 3.2% for biopsies performed by operators with less than 20

previous biopsy procedures. In contrast, it was only 1.1% when performed by those who had conducted more than 100 biopsies (Gilmore, et al. 1995).

From the large retrospective study conducted by Piccinino it was reported that 61% of complications occurred within the first 2 hours after biopsy and 96% in the first 24 hours (Piccinino, et al. 1986). Arturo et al suggests that up to 3% of patients may require hospitalization for complications of liver biopsy, more so if the procedure is performed with a tru-cut needle (Bravo, Sheth and Chopra 2001). For the purpose of this chapter we are going to focus on the complications associated with percutaneous liver biopsy as this is the commonest method in use. The specific complications associated with other methods will be briefly discussed at the end.

#### 4.1 Mortality

Liver biopsy associated mortality is reportedly related to haemorrhage or biliary peritonitis (Vautier, et al. 1994, Shah, Mayberry, Wicks, Rees and Playford 1999). The reported incidence of mortality varies (Grant, et al. 1999) and to date the true incidence is not known. Three month post biopsy mortality rate is reported to be as high as 19% (Gilmore, et al. 1995). This is probably a result of the primary indication for the liver biopsy; i.e. liver failure and malignancy and not necessarily a result of the biopsy itself. Although logic would suggest that image guided biopsy would result in a statistically lower mortality rate compared to blind biopsies, this has actually never been born out in published reports. Griffiths et al (Griffiths, Viiala and Olynyk 2002) and others reported the mortality associated with liver biopsies to range from 0.01% to 0.1% (Piccinino, et al. 1986, McGill, et al. 1990). However, this is for both blind and guided biopsy.

Other authors have also refuted the claim that image guided biopsies reduces mortality rates. Centinkaya et al published a retrospective study of 205 patients who had either blind or guided biopsies of the liver and no difference was found in the incidence of mortality (0% in each group) (Züleyha Akkan Çetinkaya 2010). Indeed, most of the published data on mortality is from retrospective studies. In 1991 the national audit undertaken in England and Wales looked at the outcome of 1504 liver biopsies. Two patients died as a result of blind biopsy whereas there were no directly related deaths in the image guided cohort. This was not statistically significant however (Gilmore, et al. 1995). In 2010 West and Card published an epidemiological study on the mortality rates in elective percutaneous liver biopsy (West and Card 2010). Again this was a study based on retrospective data analysis. In it the all cause seven day mortality was 0.2% but mortality directly related to liver biopsy was 1 in 10,000.

In effect, the true incidence of biopsy related mortality and the effect of image guidance on the incidence of mortality is not known. Vautier et al (Vautier, et al. 1994) suggested that a large study involving an estimated 10,000 patients would be needed to demonstrate any statistical difference.

#### 4.2 Pain

Pain is the most common complication after percutaneous liver biopsy. The incidence of pain during liver biopsy is reported to be as high as 84% (Eisenberg, et al. 2003). This pain can be acute and can last for more than 24 hours after the procedure (Castera, Negre, Samii and Buffet 1999). Eisenberg et al reported that 40% of patients in their prospective study experienced pain 24 hours after the procedure. Indeed, if the pain is due to hepatic friction rub the pain may last for a few weeks (Chuah 1996). The intensity of this pain is



mainly mild to moderate (Farrell, et al. 1999, Cadranel, et al. 2000) but can be severe. In a study conducted by Christine Janes in 1993, of the four hundred and five patients who had liver biopsies as outpatients, five of the thirteen patients (1.2%) requiring post-procedure hospitalization was as a result of pain (Janes and Lindor 1993). A similar figure of 1.2% was quoted for the experience of severe pain by Christopher Pokorny in his study of radiologically guided liver biopsy, however none of these patients were admitted to hospital (Pokorny and Waterland 2002). The pain can be localized to the site of the biopsy or commonly be referred to the right shoulder tip. There is also a distinct sex difference in the experience of pain. The intensity of pain is reportedly higher in women although the cause of this is unknown (Cadranel, et al. 2000). In addition, Eisenberg et al demonstrated that there was a linear correlation between the level of pre-biopsy anxiety and the intensity of the experienced pain. It is possible that there is a positive correlation between levels of anxiety and gender but this has yet to be assessed and reported.

The etiology of post liver biopsy pain is thought to be multi-modal. Pain can indicate post biopsy peritoneal irritation if bleeding or peritoneal soiling from biliary leakage or visceral perforation occurs. However, pain at the biopsy site may emanate from stimulation of nociceptive fibres in the skin and liver capsule. In contrast, shoulder tip pain may be viscerosomatic in origin (Hederstrom, Forsberg, Floren and Prytz 1989). The use of ultrasound guided biopsy has been reported to decrease the incidence of post biopsy pain. In the study conducted by Lindor et al nine patients required post biopsy hospitalization when ultrasound was not used compared to two patients in the biopsy under ultrasound guidance group. More importantly, of the nine patients, seven were hospitalized for pain (Lindor, et al. 1996). This view is supported by the review of the literature on blind versus ultrasound guided biopsy by Knawy et al. They found that ultrasound guidance resulted in a 10.9% decrease in biopsy pain ( $P < 0.0001$ ) and a decrease in pain related morbidity (1.8% vs 7.7%) (Al Knawy, et al. 2007).

Interestingly, both local anaesthetic with or without conscious sedation has been used in an attempt to control pain and in spite of this pain continues to be the commonest complication of liver biopsy. Conscious sedation has however shown some promise in reducing pain during and after liver biopsy. It is also possible that the administration of anxiolytics pre-biopsy may alleviate some of the pain experienced. Despite pain being a significant issue there is no published data on the optimization of pain control in patients undergoing liver biopsy.

#### **4.3 Bleeding**

Bleeding after percutaneous liver biopsy is a well documented complication second only to pain (Chuah 1996). This can be minor or be significant enough to warrant intervention. The reported incidence of bleeding varies significantly (Piccinino, et al. 1986, Chuah, Moody, Wicks and Mayberry 1994, Thampanitchawong and Piratvisuth 1999) and is the main cause of mortality after biopsy (Froehlich, et al. 1993). McGill reports it to be between 2%-4% in their 21 year experience with a mortality rate of 0.01%-0.03% (McGill, et al. 1990). The admission of those with bleeding is about 0.2%. The fatalities are usually due to inadvertent perforation of the hepatic or portal vein or aberrant hepatic artery. It may also result from a laceration in the liver if the biopsy needle is intrahepatic while the patient inhales deeply (Chuah 1996).

The risk is reportedly increased with the presence of ascites (Grant, et al. 1999) probably as a result of the dilutional effect of the ascitic fluid on clotting factors however the incidence is not affected by the use of ultrasound (Stone and Mayberry 1996). Like the use of ultrasound, the risk of haemorrhage is not related to needle diameter or type (Froehlich, et al. 1993). However, the relationship between coagulopathy and bleeding remains controversial. In the United States the conventional approach is to withhold percutaneous biopsy if the INR is greater than 1.5 (Rockey, et al. 2009). The survey conducted by Chuah et al suggested that coagulopathy should be corrected prior to biopsy (Chuah, et al. 1994). This is supported by other studies. Caldwell et al reviewed 2740 percutaneous liver biopsies in patients with hepatitis C. They recorded 16 out of 29 adverse events caused by severe bleeding. Statistically, the factors that were associated with increased bleeding included a platelet count of less than 60,000, INR greater than 1.3, the presence of varices and low albumin (Caldwell and Northup 2010). They suggested that the increase in bleeding with low albumin and varices is likely to be due to the changes in hepatic vasculature and not a clotting abnormality.

Although one other study has corroborated the cut off value of platelet count as 60,000 (Sharma, McDonald and Banaji 1982) there are other studies that suggest otherwise. Sherlock et al reports a cut off platelet count of 80,000 and Sue et al a cut off count of 50,000 (Grant, et al. 1999). In the retrospective study conducted by Pornpen et al they found that coagulopathy was related to bleeding complications and death (Thampanitchawong, et al. 1999). The bleeding complication rate increased from 3.6% to 10.5% and the death rate increased from 1% to 7% when the thrombin time increased by greater than 3 seconds over control and the prothrombin time increased by more than 10 seconds over control. The same was true for patients with a platelet count of greater than 70,000. However, platelet count was the only independent variable on logistic regression analysis. In effect, the absolute cut off point is unknown. In addition to this it is thought that platelet function also plays a more important role in the risk of bleeding after biopsy than platelet number (Tripodi, et al. 2006). Other risk factors include multiple passes with the biopsy needle, the presence of cirrhosis (Janes, et al. 1993) and the use of cutting needles (Piccinino, et al. 1986).

In contrast, Ewe et al and others demonstrated no effect of bleeding abnormalities on the risk of bleeding with either laparoscopic or percutaneous liver biopsy (Ewe 1981, McVay and Toy 1990, Dillon, Simpson and Hayes 1994). Even in Caldwell's study three of the patients with haemorrhagic complications after biopsy had a platelet count of over 150,000. Finally, the question of ultrasound reducing the risk of haemorrhage remains unanswered. Several studies have demonstrated that ultrasound reduces the incidence of complications, none of these studies reported any specific difference in haemorrhage (Lindor, et al. 1996, Stone, et al. 1996, Manolakopoulos, et al. 2007). In our unit, we accept a platelet count of greater than 80,000 and an INR of less than 1.5 in order to proceed to biopsy.

The haemorrhage associated with percutaneous liver biopsy can present as intraperitoneal bleeding, intrahepatic bleeding, haemobilia and subcapsular haematoma (Figure 1) (Caldwell, et al. 2010). Intraperitoneal bleeding although rare, when clinically significant generally becomes apparent within the first 2-3 hours after biopsy (Van Thiel, Gavaler, Wright and Tzakis 1993) and is usually heralded by a drop in haemoglobin of greater than 2g/dL or haemodynamic instability (Knauer 1978). If intraperitoneal haemorrhage is suspected the patient should be resuscitated, have imaging studies (CT or ultrasound) to confirm this and if resuscitation fails then angiography and embolisation or less commonly surgery to halt

bleeding. Intrahepatic or subcapsular haematomas tend to be asymptomatic (Raines, Van Heertum and Johnson 1974) and occurs in about 23% of patients (Minuk, Sutherland, Wiseman, MacDonald and Ding 1987). However, large haematomas can present with pain or signs of intravascular depletion i.e hypotension and tachycardia (Van Thiel, et al. 1993). In the main these haematomas can be treated conservatively with resuscitation and correction of coagulopathy or thrombocytopenia if it exists.

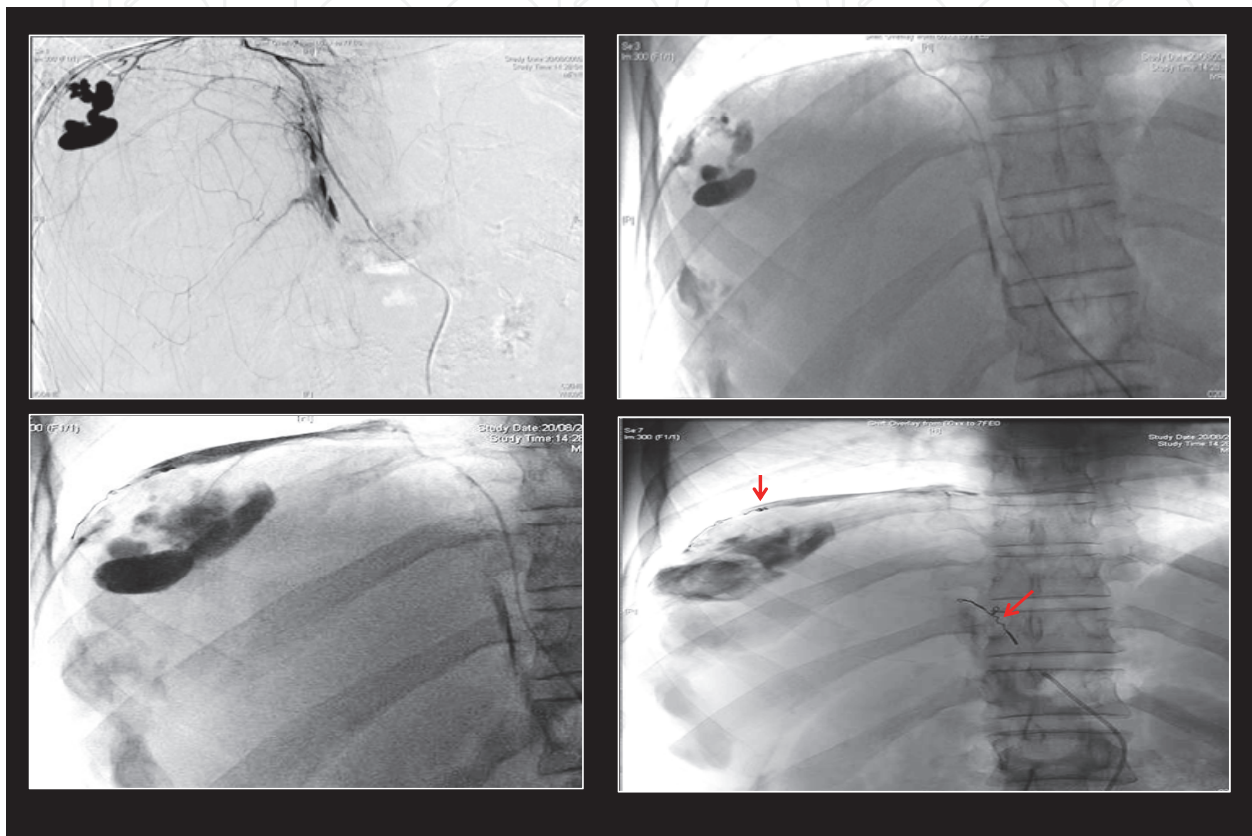


Fig. 1. This patient with hepatitis C became haemodynamically unstable following a percutaneous liver biopsy. A superselective angiogram of the liver shows a subcapsular bleed, which was embolized with microcoils (red arrows).

Although post biopsy haemorrhage usually presents itself within the first 2-3 hours there have been reports of delayed bleeding (Reichert, Weisenthal and Klein 1983). Yeo et al described a case of a patient who was hepatitis C positive with haemophilia who presented 10 days after an image guided percutaneous liver biopsy (Yeo, Tan, Dan and Wai 2008). He presented to the emergency department complaining of hypochondrial pain and investigations demonstrated a haemothorax and subcapsular haematoma. He decompensated and had an emergency resuscitative thoracotomy. In another case a 46 year old gentleman who presented 4 days after percutaneous biopsy with right hypochondrial pain. He was diagnosed with a bleeding pseudoaneurysm of the right hepatic artery which was embolised. Subsequently, he continued to bleed and had a laparotomy which demonstrated a right hepatic lobe laceration (Ren, Piao and Jin 2006). Although this is very rare there have been other reports of post biopsy pseudoaneurysm formation (Figure 2 a & b) (Kowdley, Aggarwal and Sachs 1994, Own, Balzer and Vogl 2005). Surprisingly, Terjung



et al reported the incidence of delayed bleeding in their series to be 70% (Terjung, et al. 2003). In their series they defined delayed bleeding as occurring after 24 hours. This is a particularly high incidence and it may well reflect the definition criteria or the enthusiasm with which patients are investigated for haemorrhage. There may well be a large cohort of post biopsy delayed haemorrhage who are asymptomatic and therefore the true incidence is not known.

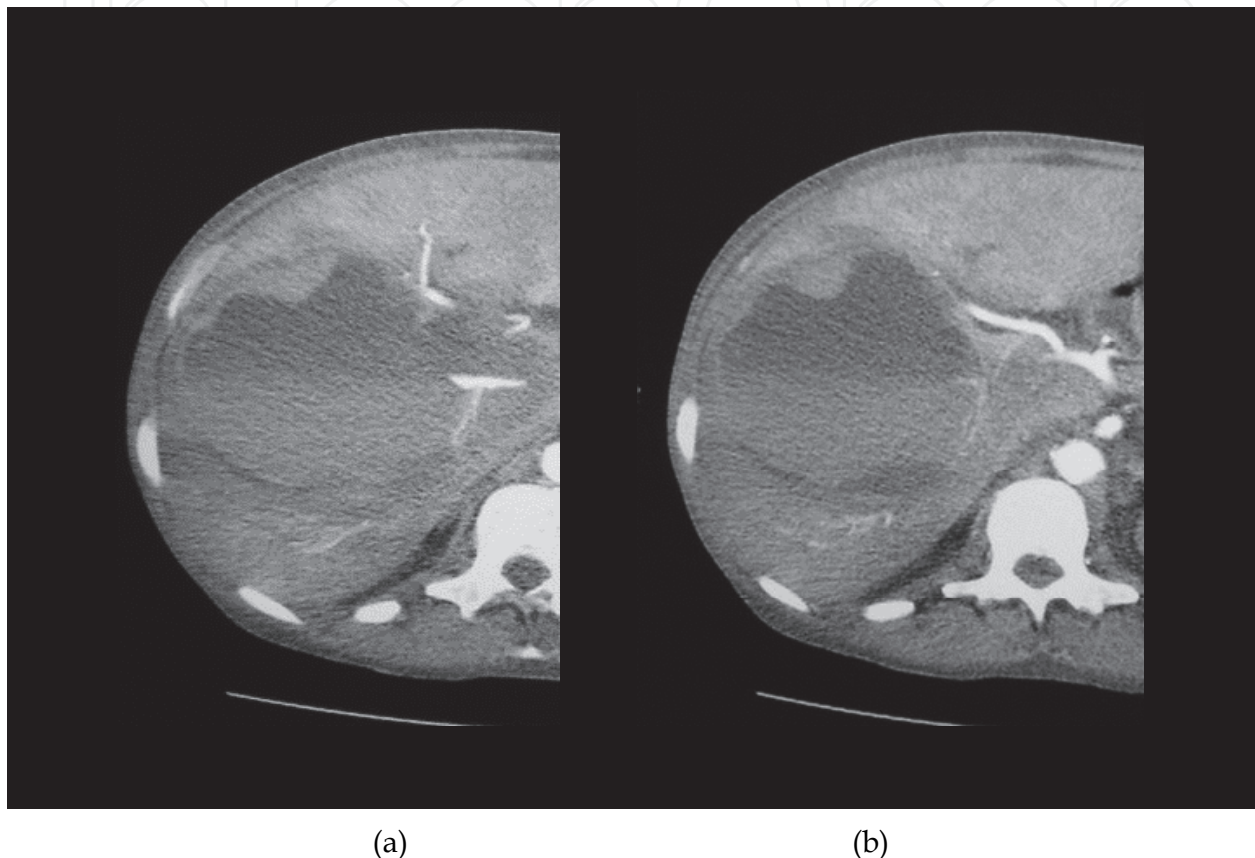


Fig. 2. (a & b) CT scans on a patient with a past history of a percutaneous liver biopsy showing a ruptured pseudoaneurysm with active bleeding.

Haemobilia is a rare complication of liver biopsy and was first reported by in 1967 by Cox (Cox 1967). In 1991 Merrell and Schneider described the evolution of haemobilia and suggested a lag time between biopsy and presentation to be about 5 days. Interestingly, haemobilia after biopsy has been associated with acute pancreatitis (Pena, Horn and Cross 2009). It is thought that the pancreatitis is induced in the same manner as gallstones; impairment of pancreatic drainage. The treatment required is ERCP and sphincterotomy. Angiography has also been used to stem the bleeding but only in a few cases.

#### 4.4 Septicaemia

Septicaemia is a result of bacteraemia during needle biopsy. It can also result from the development of intrahepatic abscesses (Figure 3). The incidence of bacteraemia is reported to be as high as 13 % (McCloskey, Gold and Weser 1973, Le Frock, Ellis, Turchik, Zawacki and Weinstein 1975). However more commonly the figure is quoted to be less than 1% (Larson, et

al. 1997). It is more common in patients with biliary abnormalities including biliary obstruction, cholangitis and those who have had biliary bypass (Bubak, Porayko, Krom and Wiesner 1991, Larson, et al. 1997, Bravo, et al. 2001). However, one of these studies was in patients who had liver transplant and therefore may be immunosuppressed and at higher risk of infections. McCloskey et al reported an incidence of liver biopsy related septicaemia of 2.9%. They suggested that in patients with liver disease there is a defect in the defence mechanisms related to a deficiency of complement and inhibition of chemotaxis among others (McCloskey, et al. 1973). In those with septicaemia the commonest organism cultured from the blood is *E. Coli* (Moreira Vicente, Hernandez Ranz, Ruiz Del Arbol and Bouza 1981) although polymicrobial organism infection has been reported (Dhawan, Thadepalli, Ulmer and Akhtar 1983) including klebsiella and streptococcus.

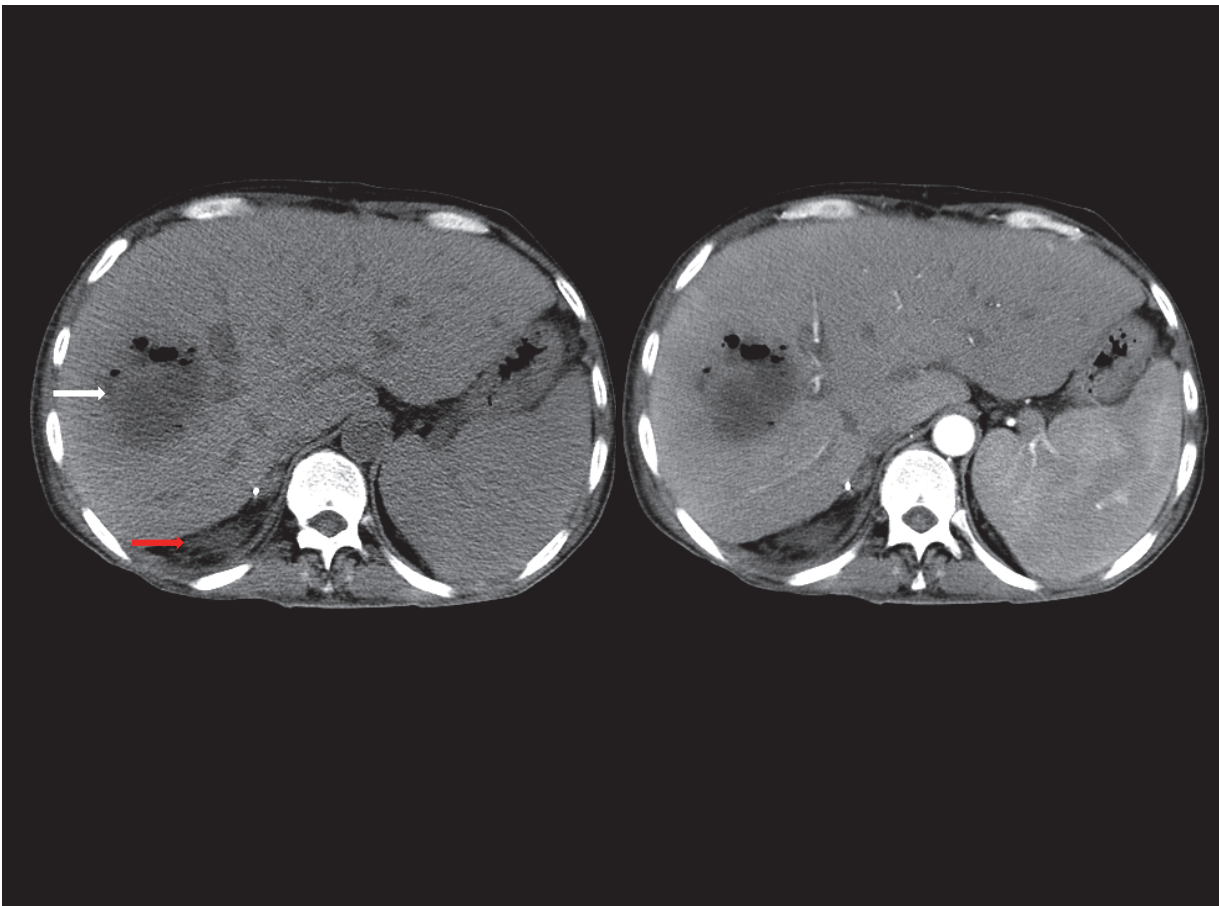


Fig. 3. This patient presented with right upper quadrant pain and pyrexia 4 days following a percutaneous liver biopsy. Note the liver mass associated with air within and surrounding the mass. The patient was treated for a liver abscess. Note echogenic contents within the pleural sac indicative of blood or pus (arrow).

Although bacteraemia with or without septicaemia is a rare but recognized complication of liver biopsy the question of whether prophylactic antibiotics is warranted remains unanswered. This is mainly because there are no randomized trials examining this and most of the reported data are either case reports or retrospective studies. It is probably worthwhile in patients who are immunocompromised (e.g transplant patients). It would be

considered prudent to delay this invasive procedure if possible in patients who have confirmed sepsis. In addition, patients with obstructive jaundice or who are considered at risk should also probably have prophylactic antibiotics.

#### 4.5 Pulmonary complications

The transthoracic approach traverses the pleural space. The incidence of complications was reported to be 25% in the Swiss survey (Froehlich, et al. 1993). Hydrothorax occurs as a result of leakage of ascitic fluid via the biopsy tract into the pleural cavity (Zamcheck and Sidman 1953). Pneumothoraces tend to occur in about 0.35% of cases (Piccinino, et al. 1986) (Figure 4). In addition, haemothoraces are also possible but rare with a reported incidence of 0.018% (Piccinino, et al. 1986). It is thought to be a result of injury to the diaphragmatic vessels (Majid 1990) and the event usually declares itself early on.

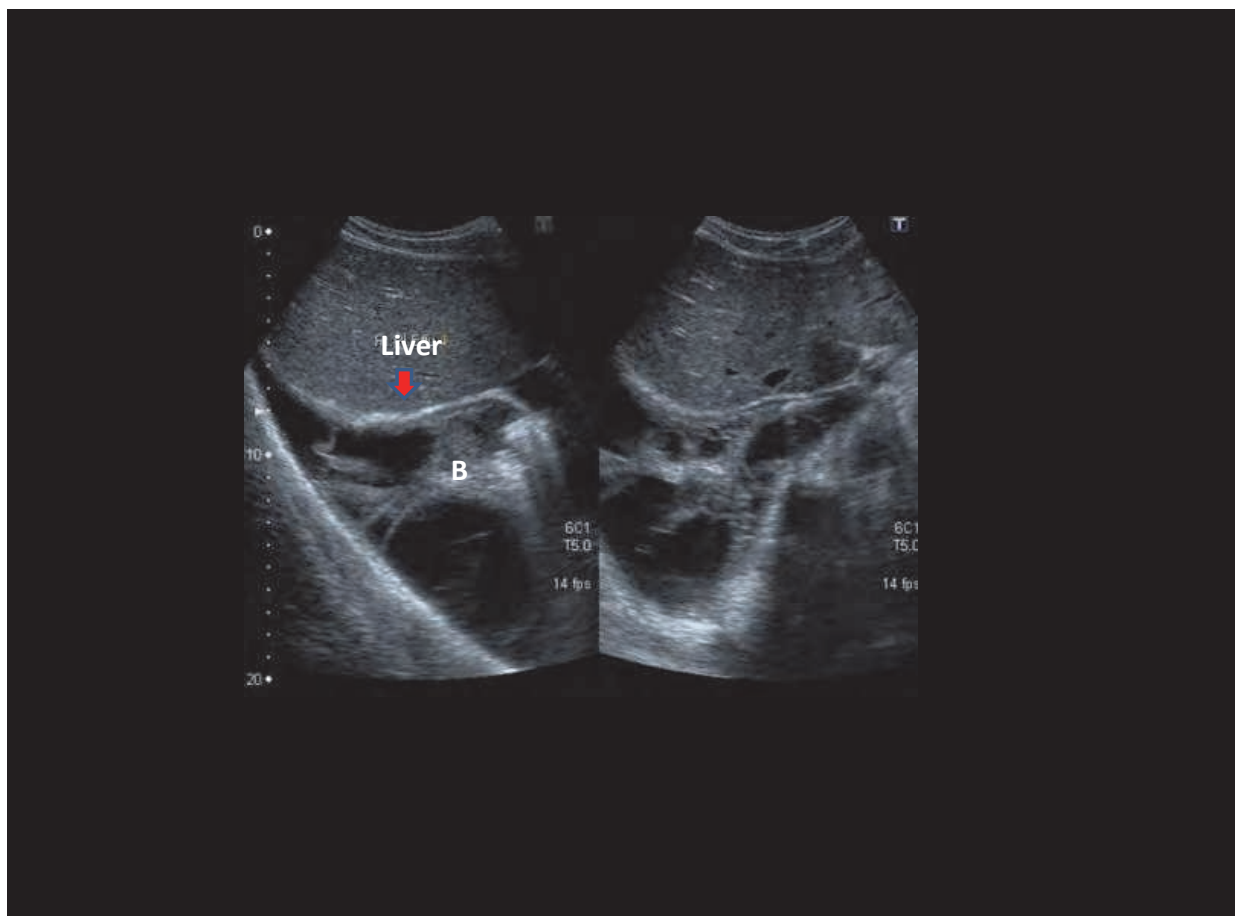


Fig. 4. Attempted liver biopsy on a 36-year old female with non-specific hepatic dysfunction. The needle entered the pleural cavity. Ultrasound examination shows blood in the pleural sac (B) at various stages of organization. The diaphragm is marked by a red arrow.

#### 4.6 Visceral perforation

Visceral perforation includes puncture of the colon, kidney, lung or gallbladder. Piccinino et al reported the incidence of visceral perforation to be between 0.01%-0.1% (Piccinino, et al.

1986). This is supported by others (van der Poorten, et al. 2006). These complications can resolve with conservative management or can result in peritonitis requiring surgery.

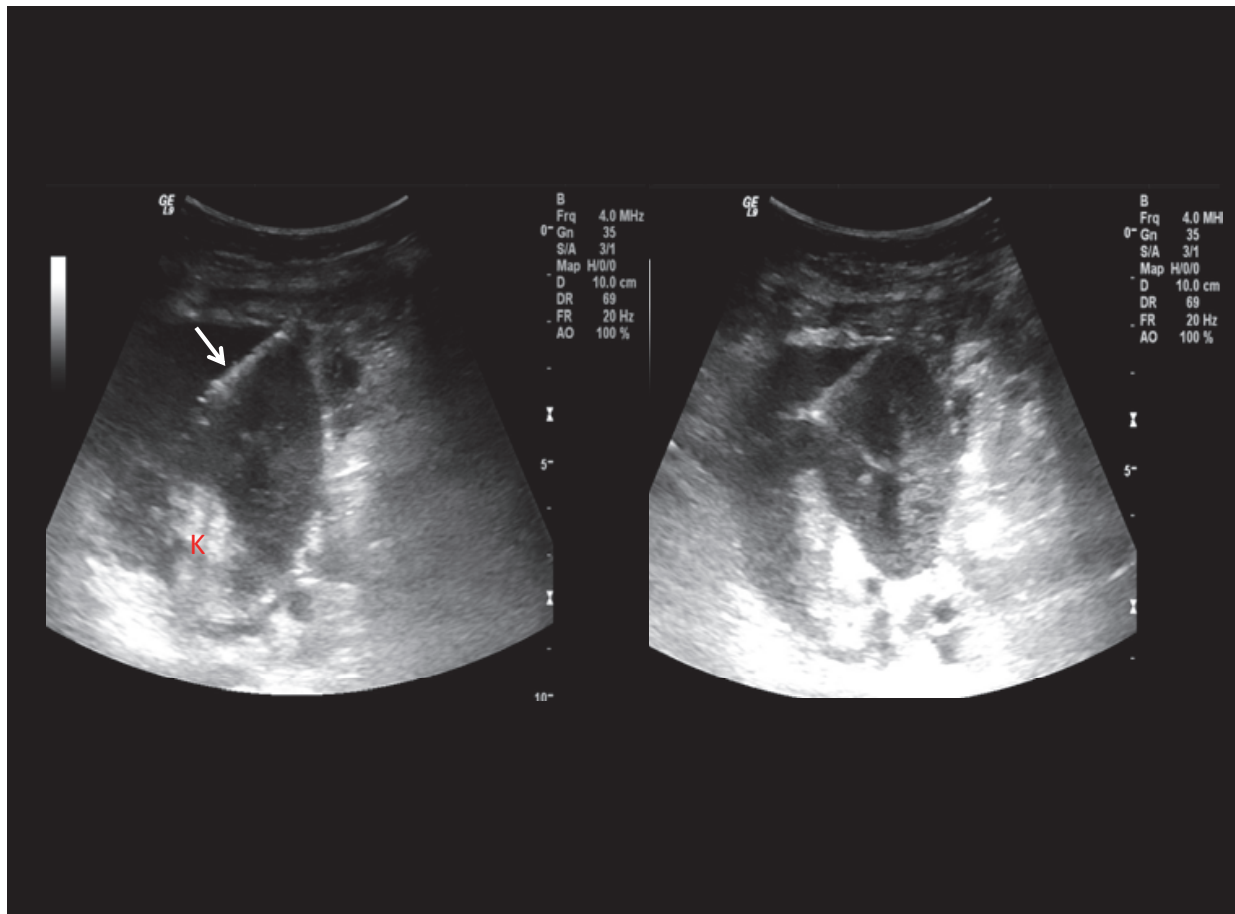


Fig. 5. Attempted liver on a 16 year old with a Riedle's lobe. The needle has entered the kidney (white arrow) the kidney is labelled K. The patient subsequently developed intractable haematuria and had to have several blood transfusions.

#### 4.7 Needle fracture

Fracture of the needle is a very rare complication. Robert Peters reported a case of a Menghini needle fracture during liver biopsy in 1968 leaving the distal end in the patient's chest wall (Peters 1968). Subsequent to that Purow et al in 1977 and Lazar et al in 1978 reported this as a complication of liver biopsy (Grant, et al. 1999). It is thought to be a result of thrusting the needle onto the rib in the transthoracic approach. However, there have only been a few reported cases of needle fracture. Indeed, a search of the literature has not resulted in any reported cases in the last decade. This is probably due to the increasing expertise in those carrying out liver biopsies and possibly the use of image guidance.

#### 4.8 Arteriovenous fistula

Traumatic arteriovenous fistulas in relation to the biliary vasculature has been described as early as 1952 (Strickler, Lufkin and Rice 1952). The incidence is reported to be as high as 50% if an angiogram is performed within one week of the biopsy (Hellekant 1976). A number of



other authors have quoted a much lower incidence(Okuda, et al. 1978). This is probably a function of the fact that these lesions are not investigated unless the patients are symptomatic and they tend to resolve spontaneously(Hurwitz and Thompson 2002). These patients tend to present as delayed haemorrhage in the form of frank intraperitoneal haemorrhage with shock, intrahepatic haematoma with pain and anaemia or haemobilia (Ormann, Starck and Pausch 1991). However, late presentations occur in the form of portal hypertension for arterio-portal fistulas and congestive cardiac failure in the case of hepatic arteriovenous fistulas(Wallace, Medellin and Nelson 1972). The occurrence of fistulas is not isolated to percutaneous liver biopsy. Guarkuqi et al described a case of fatal haemobilia after transjugular liver biopsy in a patient with alcoholic cirrhosis 1 day after biopsy(Gurakuqi, et al. 2008). The haemobilia itself can cause pancreatitis(Machicao, Lukens, Lange and Scolapio 2002) and may result from an arteriovenous fistula(Cacho, et al. 1996) or a portobiliary or arterio-biliary fistula. Interestingly, arteriovenous fistulas after liver biopsy have been described elsewhere. In 1975 Satava et al described a case of an arteriovenous fistula of the omentum after liver biopsy. Whatever the presentation of the fistula, the main components of treatment is resuscitation, investigation and treatment. Treatment in the form of embolisation is usually successful and if not then surgery with the aim of ligation of the arterial component is the next best step.

#### 4.9 Tumour seeding

Advances in imaging, operative procedures and chemotherapeutic agents has increased the pool of patients suitable for Liver resection of primary and secondary liver cancers and the long term survival. Needle track seeding is well documented in the literature (Davies, Tulgan, Parkinson, Goel and Budnitz 1968, Evans, Harries and Hobbs 1987)(Figure 6). This has been reported in both biopsies for primary or secondary liver tumours(Park, et al. 1989, Smith 1991, Vergara, Marucci, Marcarino, Brunello and Capussotti 1993, Jones, Rees, John, Bygrave and Plant 2005). It is thought that needling a tumour could implant up to 100,000 tumour cells along the tract(Ryd, Hagmar and Eriksson 1983). The occurrence of needle track seeding after tumour biopsy is known to result in poorer long term survival(Cresswell, Welsh and Rees 2009) and convert a potentially resectable lesion to being unresectable. In spite of this there are still reported incidences of patients undergoing biopsy of liver lesions before being referred to a specialist unit (Al-Leswas, O'Reilly and Poston 2008). The incidence of tumour seeding has been reported to be as high as 19% and in one study significantly reduced 4-year survival from 46.7% to 32.5% (Jones, et al. 2005). The same holds true for hepatocellular carcinoma. The meta-analysis and systematic review by Silva et al reported a seeding rate 2.7% in biopsy of hepatocellular carcinoma(Silva, et al. 2008). In addition, the long term survival is also significantly affected with 5 year survival reported to decrease from 52% to 24%(Young, et al. 2007).

It is clear that modern day practice of surgery dictates that all patients with liver lesions should be referred to a specialist centre for investigation and management. The advances in MRI, PET and CT along with ultrasound and measurement of tumour markers without histology have reported accuracies of over 97% and should provide enough information in the majority of cases for management decisions to be made(Torzilli, et al. 2004). The only real indication for biopsy of suspicious liver lesions would be in patients who are considered to be irresectable by a specialist centre and a histological diagnosis is necessary to determine consideration for chemotherapy.



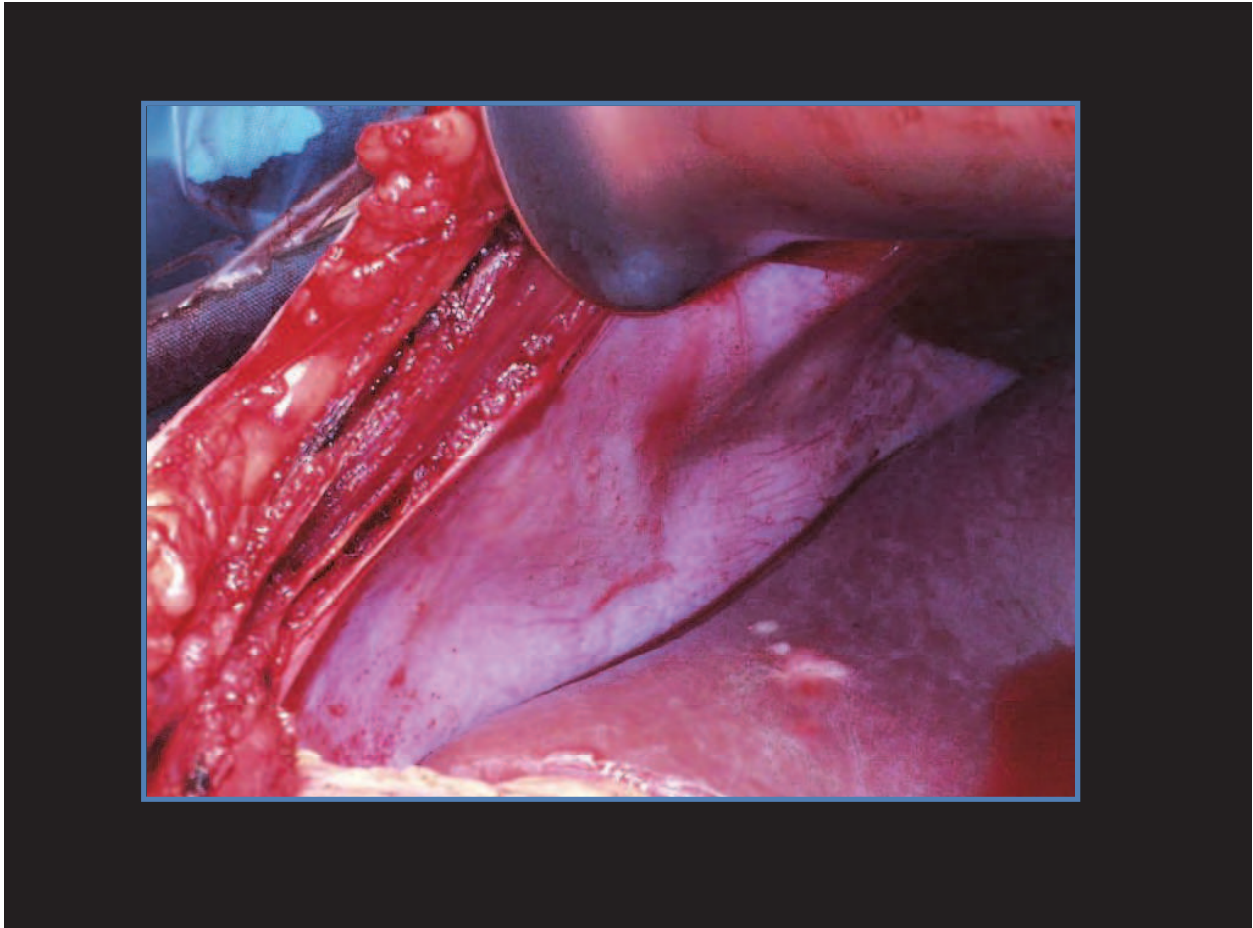


Fig. 6. This patient with a colorectal cancer had a small subcapsular lesion shown on a CT. At laparoscopy the subcapsular lesion was biopsied, which was positive for a metastasis. The patient had a laparotomy 3 weeks latter. The picture shows multiple tiny serosal deposits

#### 4.10 Biliary fistulas

Biliary fistulas are a rare complication of liver biopsy. They can be divided into internal or external fistulas. Internal fistulas occur between the biliary tree and an adjacent structure. These include arterio-biliary or bilio-venous fistulas. These patients can present with haemobilia or pancreatitis. In one large series percutaneous liver biopsy has been reported to cause haemobilia in 4 out of 68,276 patients (Piccinino et al 1986). The reported incidence of this is between 0 to 1% (Rossi et al 2002) and can usually be managed by embolisation of the vessel. More rarely, biliovenous fistulas can present as bile pulmonary embolism with fatal consequences (Brown and Walsh 1952). Fistulas can also develop between the biliary tree and an adjacent organ or cavity such as a bronchobiliary or pleurobiliary fistula (Ferguson and Thomas 1967). They can present as biliptysis and can be managed conservatively by ERCP to decompress the biliary tree and allow preferential flow of bile into the duodenum or, failing that, surgical intervention (Chong et al. 2008). Biliary fistulas can also present bilio-cutaneous fistulas (Hatzidakis et al 2006). The true incidence is not known. The management of these fistulas also varies and will depend on the underlying

pathology. The options for management include conservative, allow the fistula to heal spontaneously, radiological by embolisation of the fistula tract (Hatzidakis et al) or surgical.

## 5. Transvenous liver biopsy

Transvenous liver biopsy can be undertaken via the femoral or the more commonly described transjugular route. It was first described by Dotter in 1964 (Dotter 1964) but the first major series was reported by Rosch et al in 1973 (Rosch, Lakin, Antonovic and Dotter 1973). The transvenous route was introduced as an alternative to the percutaneous route when there are concerns about coagulopathy or significant ascites and in those with morbid obesity (Rockey, et al. 2009). The transjugular route has the added advantage of being able to measure the hepatic venous wedge pressure where necessary. The basic principle of the procedure is the same for both techniques. The procedure is usually performed by a radiologist under fluoroscopic guidance. The inferior vena cava (IVC) is cannulated and via this one of the hepatic veins (usually the right) is entered and a biopsy is taken from within the liver. The technical failure rate is reported to be 3.2% (Kalambokis, et al. 2007).

The reported complication for the transjugular is as high as 20% (Grant, et al. 1999) with major complications occurring between 1.3 to 2.7% (Gamble, Colapinto, Stronell, Colman and Blendis 1985, McAfee, Keeffe, Lee and Rosch 1992). However, the most recent review of the literature reports a complication rate of 6.7% in adult series, comparable to complication rates reported in other series (Thampanitchawong, et al. 1999). The complications were described as both liver puncture related and non-liver puncture related and the incidence for both were similar. The non-liver puncture related complications are associated with the process of cannulating the jugular or hepatic vein or technical failure. In their retrospective study Soyer et al suggests that the complications associated with cannulation of the jugular vein can be minimized by the use of ultrasonic guidance (Soyer, Fargeaudou, Boudiaf and Rymer 2008). These include skin haematoma, pneumothorax, Horner's syndrome, dysphonia, cholangitis and cardiac arrhythmias. One particular risk associated with this route is perforation of the liver capsule and intraperitoneal haemorrhage (McAfee, et al. 1992). Even if the procedure was attempted via the femoral route capsular perforation was still a noted complication (Khosa, et al. 2003). Khosa suggested that this complication could be avoided if biopsies were taken within a central area of the liver and biplane fluoroscopy was used. The same would probably hold true for the transjugular route. In addition, Papatheodoridis et al suggested that capsular penetration was more frequent with the Menghini needle as a result of difficulty in controlling the depth of penetration (Papatheodoridis, Patch, Watkinson, Tibballs and Burroughs 1999). In their series capsular penetration only resulted in minor complications. The mortality rate is about 0.09% and like percutaneous liver biopsy was due to haemorrhage. In contrast, some deaths with transjugular biopsy were also related to ventricular arrhythmias as a result of manipulation of the catheter through the right atria and ventricle.

One of the few comparative studies between transjugular and percutaneous biopsy was reported in 1994 by Hong-Chaing Meng et al. In this study the complication rate for the transjugular route was 7% and 9% for the percutaneous route suggesting that transjugular biopsy was at least as safe as percutaneous liver biopsy and re-affirmed the idea that it is a safe alternative in patients in whom percutaneous biopsy is contra-indicated. Interestingly, Atar et al reported a comparative study of plugged percutaneous liver biopsy and

transjugular biopsy and found no difference in major complications in either group (Atar, et al. 2010). They suggested that the plugged percutaneous biopsy technique should be used instead of the transjugular route when available.

The use of the transvenous route for liver biopsy is well established. However, this technique is only practiced in a few centres mainly by radiologists or hepatologists with significant experience in the technique. The indications for this procedure is restricted and as yet the percutaneous route is still the procedure of choice as it is simpler, requires less specialized equipment and is therefore cheaper.

## 6. Laparoscopic liver biopsy

Laparoscopic liver biopsy is a well established method. It is usually undertaken when liver lesions are found incidentally during laparoscopy for diagnostic or staging purposes. In addition, staging of patients with cirrhosis and hepatocellular carcinoma who are being considered for resection can have a biopsy of the future liver remnant. Laparoscopic liver biopsy had the added advantage of direct view of the liver which reduces sampling errors and bleeding after biopsy allowing better control (Denzer, et al. 2007). This is supported by Nord et al who reported a significant decrease in sampling errors of laparoscopic biopsy compared to the percutaneous route in cirrhotic patients (Tobkes and Nord 1995).

The risks of laparoscopic liver biopsy can be divided into the risks of any laparoscopic procedure and the risks of liver biopsy. Beckmann et al did a comparative study with laparoscopic, transjugular and percutaneous liver biopsy. They found that the complication rate was similar for all groups (2.7%, 2.9% and 3% respectively) (Beckmann, et al. 2009). However, in their study the transjugular route had a low success rate and they suggested that the laparoscopic route as an alternative especially in patients with severe coagulopathy (Denzer, Helmreich-Becker, Galle and Lohse 2003). The only randomized study comparing laparoscopic with percutaneous biopsy was reported by Denzer et al (Denzer, et al. 2007). This study was undertaken in cirrhotics but found a slightly higher but not significant difference in total complication rate between the groups (8.8% vs 5.8%).

The main risks that we divulge to our patients specific to any laparoscopic procedure are bowel or aortic/inferior vena cava perforation, bleeding, post-operative shoulder tip pain and port-site pain and hernias. Specifically for laparoscopic liver biopsy our unit informs patients of the risk of bleeding or biliary leak. As a general rule we do not undertake laparoscopic biopsies of possible malignant lesions unless we know that the tumour is inoperable and a histological diagnosis is needed prior to starting chemotherapy.

## 7. Conclusion

The role of liver biopsy in the investigation of liver disease has changed over time. This is due to the advances in other non-invasive imaging techniques providing adequate information for diagnosis. It is still however a very important investigative tool in certain circumstances. These indications have been laid out in the American Association for the study of Liver Disease and the British Society of Gastroenterology. It is mainly carried out under image guidance although some centres still practice blind biopsies. Importantly, it is not without its risks and complications that both physicians and surgeons should be aware of. The role of bleeding parameters and other adopted protocols may not necessarily be

rooted in good quality evidence and there is scope for well designed randomized trials in certain aspects of this procedure. Finally, any patient discovered to have a lesion in the liver either from radiological investigation or during surgery should be referred to a specialist hepato-biliary unit for further evaluation.

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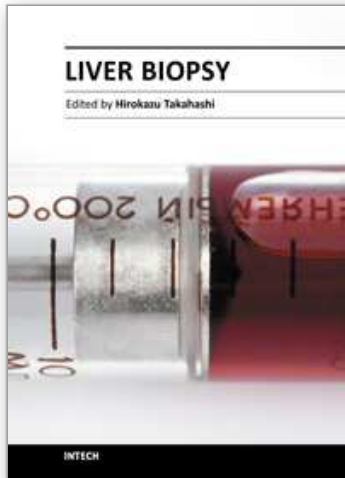
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## **Liver Biopsy**

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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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