Liver

10

Paul J. Kelly, Derek C. Allen, R. Iain Cameron, and Maurice B. Loughrey

10.1 Anatomy

The liver, the largest gland in the body, is concerned with the production and secretion of bile and many metabolic functions crucial to normal homeostasis. The majority of it is surrounded by a peritonealized fibrous capsule and it is situated in the right upper quadrant of the abdomen for the most part under the cover of the ribs. It is divided into a large right and smaller left lobe by the attachment of the falciform ligament. The right lobe is further subdivided into the quadrate and caudate lobes by the gallbladder and the ligamentum teres (Fig. 10.1). However, this is a purely anatomical subdivision as it has been found that the quadrate and caudate lobes are actually a functional part of the left lobe, i.e., they are supplied by the left hepatic artery and left hepatic duct. This has led to a different division of the liver into surgical lobes and segments (see below).

The hilum of the liver, or *porta hepatis*, is found on the infero-posterior surface with the lesser omentum attached to its margin. Emerging from and entering the porta hepatis (from posterior to anterior) are the portal vein, right and left branches of the hepatic artery, the right and left hepatic ducts, and autonomic nerves.

Histologically the liver is composed of lobules (Fig. 10.1). Each lobule comprises a central vein (a tributary of the hepatic veins) with the portal tracts situated at the periphery. The portal tracts contain a branch of the hepatic artery, portal vein, and bile duct. Each lobule is divided into triangular-shaped *acini* with terminal branches of the hepatic artery and portal vein at their bases and the central vein at the apex. The acinus is divided into three zones (zone 3 being the most remote from the blood supply). The liver cells (hepatocytes) are arranged in anastomosing cords, with those adjacent to the portal tract forming the limiting plate.
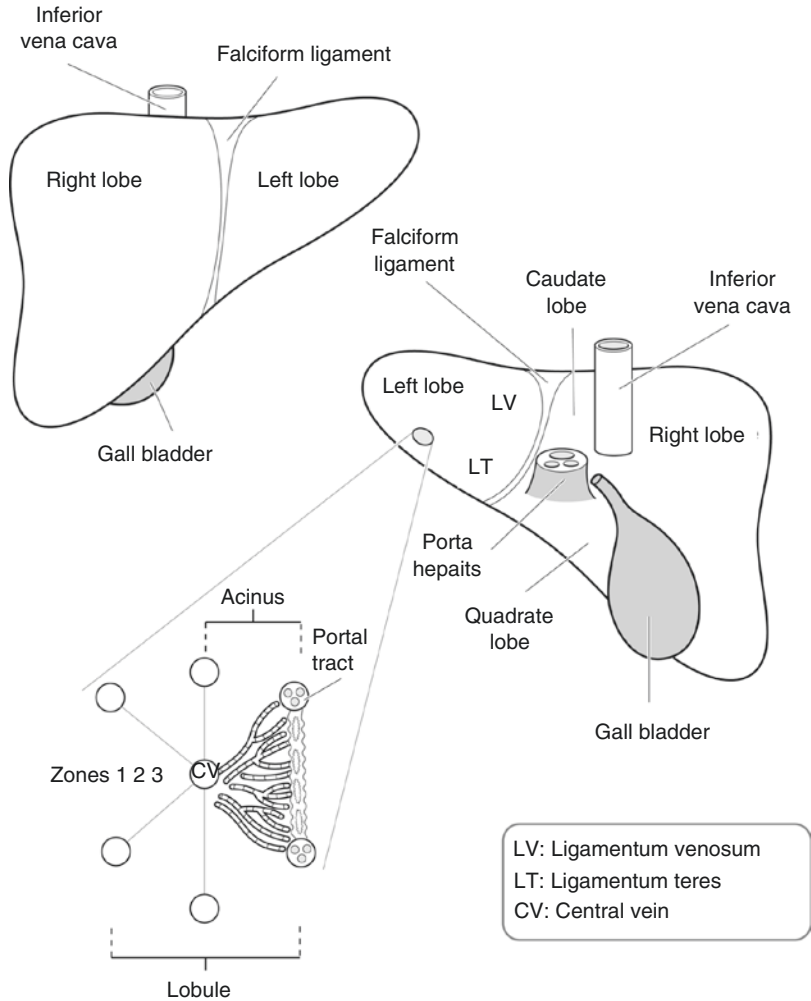
Between the cords of liver cells are vascular channels (sinusoids) lined by a discontinuous layer of endothelial cells. These sinusoids carry blood (both arterial and portal) from the portal tract to the central vein. Channels (canaliculi) formed between adjacent hepatocytes conduct bile to the ducts in the portal tracts and then to the extrahepatic bile ducts and gallbladder.

P.J. Kelly (✉) • M.B. Loughrey
Histopathology Laboratory, Institute of Pathology, Royal Victoria Hospital, Belfast Health and Social Care Trust, Belfast, UK
e-mail: paul.kelly@belfasttrust.hscni.net; maurice.loughrey@belfasttrust.hscni.net

D.C. Allen
Histopathology Laboratory, Belfast City Hospital, Belfast Health and Social Care Trust, Belfast, UK
e-mail: derek.allen@belfasttrust.hscni.net

R.I. Cameron
Histopathology Laboratory, Altnagelvin Hospital, Western Health and Social Care Trust, Londonderry, UK
e-mail: iain.cameron@westerntrust.hscni.net

Fig. 10.1 Liver anatomy and histology (Reproduced, with permission, from Allen and Cameron (2013))

Inferior vena cava

Falciform ligament

Right lobe   Left lobe

Gall bladder

Falciform ligament

Caudate lobe

Inferior vena cava

Left lobe   LV

Right lobe

LT

Porta hepaits

Quadrate lobe

Gall bladder

Acinus

Portal tract

Zones 1 2 3   CV

Lobule

LV: Ligamentum venosum
LT: Ligamentum teres
CV: Central vein

Lymphovascular drainage:

The liver receives 30% of its blood from the hepatic artery (oxygenated blood), the remaining 70% being supplied by the portal vein (venous blood rich in nutrients absorbed from the gut). The blood is conducted through the sinusoids from the portal tracts to the central veins, which in turn drain into the hepatic veins and ultimately the inferior vena cava. Most of the lymphatics drain to nodes in the porta hepatis (hepatoduodenal ligament) and then pass to the coeliac nodes. A small number pass through the diaphragm into the posterior mediastinum.

10.2 Clinical Presentation

Patients with liver disease may be asymptomatic. The most common clinical sign is jaundice, although other stigmata of chronic liver disease such as spider naevi, finger-clubbing, gynaecomastia, etc. may also be present. If the jaundice is obstructive, then the patient will have dark urine and pale faeces. Weight loss, anorexia, anaemia, and ascites may suggest cirrhosis and/or an underlying malignancy. Fever and rigors may be seen if an abscess is present. Hepatomegaly may be encountered in numerous conditions including cirrhosis and malignancy.

A careful clinical history including medication (prescription and otherwise), alcohol intake, foreign travel, and sexual practice is diagnostically invaluable to the pathologist.

10.3   Clinical Investigations

- U&E—electrolyte imbalance may occur and hyponatraemia (low sodium) is a poor prognostic sign in liver failure.
- Liver function tests (LFTs)—these should include tests for liver secretory capacity (bilirubin, alkaline phosphatase, and gamma glutamyl transferase (αGT)); synthetic capacity (albumin) and inflammation (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)).
- Coagulation screen—measures clotting potential and as such is a test of hepatic function (synthesis of clotting factors).
- Serology—viral titres of hepatitis A–E.
- Autoimmune screen—including anti-mitochondrial, anti-smooth muscle, and anti-nuclear antibodies.
- Serum immunoglobulins.
- Specific tests—serum iron, ferritin, total iron-binding capacity (TIBC), and HFE gene analysis (genetic haemochromatosis); serum and urinary copper (Wilson's disease); serum alpha-1 antitrypsin (alpha-1 antitrypsin deficiency).
- Tumour markers—alpha fetoprotein (AFP: hepatocellular carcinoma); CEA (metastatic colorectal carcinoma), CA19.9 (biliary obstruction, cholangiocarcinoma).
- CXR—may detect primary lung tumour (which has metastasized to the liver).
- AXR—may show calcification around a hydatid cyst.
- USS—useful for identifying intra-or extrahepatic bile duct dilatation, gallstones or gallbladder distension due to obstruction for other reasons. USS can also detect space-occupying lesions in the liver, for example primary or secondary tumours. Doppler ultrasonography can be used to assess direction and patency of blood vessels, detect portal hypertension and assess tumour vascularity.

- Computed Tomgraphy (CT)—is considered one of the most accurate imaging techniques and is commonly used to identify hepatic, biliary or pancreatic masses as well as screen the chest and pelvis for metastatic disease. It may be less helpful than USS for identifying biliary obstruction. Use of IV contrast can improve the diagnostic utility of CT. Positron emission tomography (PET) CT has an increasing role in staging malignancy in the liver and pancreaticobiliary tract.
- Magnetic Resonance Imaging (MRI)—is the test of choice for characterizing liver masses. Liver MRI has improved sensitivity and specificity for diagnosing hepatocellular carcinoma (HCC) in cirrhotic livers and is non-ionising. Magnetic Resonance Cholangiopancreatography (MRCP) has largely replaced other forms of invasive radiological imaging of the bile ducts and pancreas.
- Percutaneous Transhepatic Cholangiography (PTC)—has investigative and therapeutic functions. PTC can be used to assess obstruction of the proximal biliary tree, deploy stents, provide drainage of obstructed liver segments and obtain biliary brushings for cytological evaluation of strictures.
- Radioisotope scanning—this provides information on the liver texture and is useful in diagnosing cirrhosis or multiple tumours (if >2 cm). Tumours will have decreased uptake. This has largely been supplanted by USS and CT scanning.
- Angiography—hepatic artery angiography can be used to delineate the vascular anatomy of a tumour prior to resection although has been largely superseded by CT and MRI. It may be used for planning or performing embolization of liver tumours or haemorrhagic complications.
- Transient elastography e.g. Fibroscan[R]—uses ultasonography to assess liver stiffness to evaluate fibrosis without the need for biopsy.
- Peritoneal aspiration—may detect malignant cells in ascitic fluid.
- FNAC—percutaneous under USS/CT guidance.

- Needle core biopsy—Tru-cut needle biopsy under USS/CT guidance can be carried out on focal lesions or to assess the status of background "normal" liver prior to attempting to resect liver masses. Diagnosis of hepatocellular carcinoma is often based on a combination of serum AFP and appropriate radiological features avoiding the need for biopsy. A needle core biopsy may also be performed on a suspicious lesion during laparotomy. Alternatively diffuse medical liver conditions can be sampled percutaneously and blind by a needle (16–18 G).
- Staging laparoscopy with biopsy.

10.4   Pathological Conditions

Patients with liver disease may present with signs of liver failure or complications of it, e.g., oesophageal varices or because of biochemically detected abnormal LFTs. The latter can indicate whether the pattern of damage is hepatic (parenchymal), extrahepatic (obstructive) or mixed in nature. Hepatic assault is typified by viral hepatitis, alcohol or drug damage, and extrahepatic disease by duct obstruction due to stones or tumour, e.g., head of pancreas. Mixed biochemical profiles are not infrequently seen in these various disorders. Needle core biopsy is interpreted in close correlation with full clinical information that includes a detailed history and wide range of investigations (see above). Its aims are to distinguish between a surgical and medical cause for the damage, and, in non-neoplastic conditions, to assess the degree of necro-inflammatory activity that is present and the reparative response of the liver to it. It also establishes a baseline against which subsequent treatment can be assessed or indicated, e.g., interferon therapy in chronic viral hepatitis.

Liver damage has potential to resolve, but if it is unresponsive to treatment or ongoing, a non-specific, end-stage or cirrhotic pattern may be reached with few histological clues as to its aetiology. It is due to lobular damage and collapse of its framework with fibrous repair expanding and linking portal tracts with each other and the central veins. This micronodular (<0.3 cm diameter) or macronodular pattern disturbs liver function and also its internal vascular relationships. As a consequence, liver failure (jaundice, anaemia, generalized oedema, and ascites due to hypoalbuminaemia, hepatic encephalopathy) and portal venous hypertension with the risk of catastrophic haemorrhage from oesophagogastric varices can ensue. In neoplasia or hepatic mass lesions, the biopsy may be for diagnostic purposes to distinguish between primary disease, metastatic carcinoma, malignant lymphoma and abscess, or, for staging of known primary tumour elsewhere, e.g., colorectal carcinoma. Liver biopsy is less likely to be performed if there is a potentially resectable liver tumour due to the risks of tumour seeding along the biopsy tract. The information accrued is then factored into future management decisions.

10.4.1 Non-neoplastic Conditions

Viral hepatitis: Commonly hepatitis A, B, C, D, or E (hepatotropic viruses). Hepatitis A (faeco-oral transmission) is usually of short duration, self-limiting without sequelae, and not biopsied. Hepatitis B and C (transmission by blood, serum, secretions—hepatitis D is often a cofactor) are strongly associated with blood transfusion, sharps injuries, and shared needles in drug abusers. Occasionally there is acute fulminant hepatitis, but a significant minority go on to chronic carriage of viral antigen that can lead to chronic active hepatitis (>6 months clinical duration) with eventually cirrhosis and hepatocellular carcinoma. Diagnosis is by positive serology matched to distinctive histological features (e.g., portal tract lymphoid follicles and bile duct damage in hepatitis C) which are also graded (the degree of necro-inflammation) and staged (the absence or presence of fibrosis/cirrhosis) as a gauge of need for treatment, treatment response, and/or evolution of disease. Tissue localization of viral antigens can be demonstrated immunohistochemically or by in situ hybridization. Hepatitis E (faeco-oral transmission, epidemic, or sporadic) is now becoming the most common cause

of hepatitis worldwide and can cause a mild, cholestatic hepatitis (resembling hepatitis A), classical non-cholestatic hepatitis or fulminant disease with decompensation, particularly in those with preexisting liver disease.

Alcohol (*C_2H_5OH*): Chronic excess alcohol intake is a common aetiological factor in liver disease and is noted for variable individual susceptibility to it. Its hepatotoxic effect causes a spectrum of change from simple steatosis (fatty change), alcoholic steatohepatitis (lobular necro-inflammation with ballooning and Mallory's hyaline—tufts of intracytoplasmic intermediate filaments) to perivenular fibrosis, cirrhosis, and hepatocellular carcinoma. Abstinence short of the stage of cirrhosis leads to potential reversibility of even severe damage. Similar morphological features are seen in NASH (non-alcoholic steatohepatitis) commonly associated with hypertension, diabetes mellitus, and obesity (metabolic syndrome), and also gut bypass procedures and some drugs.

Drugs: The vast majority of drugs are metabolized in the liver and cause damage either due to excess dosage (actual or apparent due to preexisting decreased liver function) or individual idiosyncratic reaction to them. Various effects are seen with different agents: steatosis, cholestasis (commonest), granulomas, necrosis, hepatitis, veno-occlusion, and peliosis (dilated blood channels). Location of damage varies within the acinar zones related to the blood supply and the particular agent involved. Diagnosis is strongly dependent on an appropriate clinical history and chronology of drug usage correlating with the liver dysfunction. Common agents are—tricyclic antidepressants (chlorpromazine), methotrexate, NSAIDs, anaesthetic agents (halothane), antibiotics (tetracyclines, erythromycin, amoxicillin—clauvanate), and paracetamol.

Autoimmune and cholangiodestructive diseases: Characteristically in late middle-aged females, autoimmune hepatitis is associated with a range of autoantibodies, including antinuclear and anti-smooth muscle antibodies, and is steroid responsive. In this respect, it is of paramount importance to separate it from an infective hepatitis in which steroids are contraindicated.

Primary biliary cirrhosis (may also be referred to as primary biliary sclerosis in more modern texts), may overlap with autoimmune hepatitis, affects a similar patient demographic and is a non-suppurative, destructive, granulomatous disorder of bile ducts that leads to their disappearance (ductopenia), fibrosis and ultimately cirrhosis. Serum IgM anti-mitochondrial antibody is typically elevated and progress can be gradual over a long time period, treatment being with ursodeoxycholic acid to reduce bile acid accumulation and symptomatic to relieve related itch. Primary sclerosing cholangitis can affect intra- or extrahepatic bile ducts with a chronic inflammatory infiltrate and surrounding fibrosis, leading to obstructive tapering of the ducts and their eventual disappearance. Diagnosis is often by ERCP—there is a strong association with ulcerative colitis and predisposition to cholangiocarcinoma. IgG4-related disease may also involve the intra-and extrahepatic bile ducts and can cause a sclerosing cholangiopathy on imaging. Liver biopsies will classically show infiltration of IgG4 positive plasma cells with an elevated IgG4:IgG ratio on immunohistochemistry, obliterative venulitis and storiform fibrous nodules in affected portal tracts.

Systemic diseases: The liver can be involved in many other generalized conditions, e.g., diabetes, coeliac disease, Crohn's disease, systemic vasculitis, amyloid (primary or secondary, e.g., due to rheumatoid arthritis) and hereditary disorders such as glycogen storage diseases, alpha-1 antitrypsin deficiency, cystic fibrosis, Wilson's disease (defect of copper metabolism) and haemochromatosis (defect of iron metabolism).

Focal mass lesions: These need to be distinguished radiologically and histocytologically from neoplastic conditions (see below) and include simple sporadic cysts (often biliary in origin), multiple simple cysts (polycystic disease of liver and kidneys), infective cysts, abscess, haemangioma, and focal nodular hyperplasia. Abscess may arise from septicaemia, acute cholecystitis, or portal pyaemia after perforated appendicitis or diverticulitis. Focal nodular hyperplasia is usually solitary and more commonly diagnosed in young-to-middle-aged

women. Exogenous oestrogens for example, the oral contraceptive pill, are thought to exert trophic effects on these lesions leading to an apparent female preponderance. FNHs are characterized by a central, branching stellate fibrous scar that separates nodules of liver cells which often show a peripheral proliferation of bile ductules. It is thought to be due to a localized vascular abnormality. The main differential diagnosis includes hepatocellular adenoma, fibrolamellar hepatocellular carcinoma and well-differentiated hepatocellular carcinoma. Peribiliary hamartomas (formerly referred to as bile duct adenomas) and biliary hamartoma (von Meyenberg complex) are usually encountered as small, pale, subcapsular nodules at laparotomy, e.g., at staging of gastric carcinoma and submitted as a wedge biopsy for frozen section to exclude metastatic cancer deposits.

10.4.2 Neoplastic Conditions

Adenoma: Rare, causing acute abdominal presentation due to lesional haemorrhage in a middle-aged female with a history of oral contraception. Devoid of portal tracts or central veins within the nodule but there is a lack of cellular atypia with preservation of the pericellular reticulin pattern and liver cell plates—these features help distinguish it from well-differentiated hepatocellular carcinoma. Adenomas can be subclassified into four types based on their molecular biology: HNF1A-mutated, Beta-catenin mutated, inflammatory (previous classified as telangectatic variant of FNH) and hepatic adenoma, not otherwise specified (NOS). This molecular classification has been found to have clinical relevance.

Macroregenerative or dysplastic nodules: Irregular nodules in background cirrhosis, 1–3 cm diameter with cytoarchitectural atypia and potentially premalignant.

Hepatocellular carcinoma: Often in background cirrhosis, and serum AFP is elevated in 25–40% of cases. Single, diffuse or multifocal, bile stained, and prone to venous invasion with metastases to lung, adrenal gland, and bone. The commonest patterns are trabecular, plate-like, or sinusoidal comprising variably differentiated hepatoid cells.

A minority are encapsulated, pedunculated, or, in a younger patient, fibrolamellar in type, these variants having a better prognosis than usual hepatocellular carcinoma.

Hepatic mucinous cystic neoplasms: formerly referred to as "biliary cystadenomas with ovarian type stroma", these lesions represent the hepatic analogue of the pancreatic lesion of the same name. The ovarian type stroma may be only identified after careful examination. May be misdiagnosed preoperatively as simple cysts and initially de-roofed. Further completion excision is indicated given their neoplastic nature although malignant transformation appears to be rare.

Cholangiocarcinoma: Scirrhous, solitary, or multifocal adenocarcinoma with a ductuloacinar pattern and predisposed to by primary sclerosing cholangitis, ulcerative colitis, liver fluke, and biliary tree anomalies. Can be classified according to origin—intrahepatic, extrahepatic—perihilar or extrahepatic—distal, which can have implications for staging. Peripheral intrahepatic cholangiocarcinomas tend to form a mass. Perihilar bile duct carcinomas, which include "Klatskin tumours" originate from the right, left or main hepatic ducts proximal to the insertion of the cystic duct. These may show an aggressive periductal growth pattern without forming a discrete mass. Intraductal tumours, which are usually perihilar, tend to be papillary and may be non-invasive (i.e. intraductal papillary neoplasms) or invasive. Intraductal papillary neoplasms share similarities with pancreatic papillary mucinous neoplasms and may be detected on imaging as cystic lesions or cystic dilatation of the bile ducts. Distal extahepatic bile duct carcinomas arise in the common bile duct, distal to the junction of the common hepatic duct and the cystic duct. These are discussed in more detail in Chap. 4. The molecular biology and cells of origin for perihilar, peripheral intrahepatic, and indeed intraductal cholangiocarcinomas are thought to be different which may explain the morphological variability between these tumours.

Mixed cholangiocarcinoma-hepatocellular carcinoma: encountered more commonly than

suggested in older literature. Diagnosis typically requires morphological evidence of both components and is not made solely on results of immunohistochemistry. Staging and prognosis is determined by the cholangiocarcinoma component.

Metastatic carcinoma: Commonly from gastrointestinal tract, lung, and breast, there are some characteristic clues as to origin.

Colorectum—multiple, large nodules with central necrosis/umbilication, ± mucin ± calcification

Gallbladder—bulk of disease centred on the gallbladder bed

Lung—medium-sized nodules

Stomach, breast—medium-sized nodules or diffuse cirrhotic-like pattern

Note that carcinoma rarely metastasizes to a cirrhotic liver.

Other cancers: Well differentiated neuroendocrine tumours ("carcinoids") metastatic from gastrointestinal tract (particularly ileum), pancreas or lung, malignant lymphoma (portal infiltrates or tumour nodules), leukaemia (sinusoidal infiltrate), malignant melanoma, angiosarcoma, epithelioid haemangioendothelioma.

Prognosis: In hepatocellular carcinoma, this relates to size (>5 cm), differentiation, encapsulation, multifocality, high serum AFP levels, vascular invasion, and the presence of background cirrhosis (adverse). The majority of untreated patients will die within several months of presentation. However depending on the stage of disease and treatment modality, the 5-year survival may reach 70–80%. Surgical resection and transplantation are considered curative surgical strategies in select patients. Thermal ablation with or without transarterial chemoembolization (TACE) is also potentially curative in patients for whom surgical management is not appropriate. Thermal ablation and TACE can also be used in the palliative setting. Systemic internal radiation therapy (SIRT) may also be used in select patients. Few patients with cholangiocarcinoma survive longer than 2–3 years due to late presentation and limited resectability. Surgery offers the best option for long-term survival in patients with resectable

cholangiocarcinoma. This will be determined by the location of the tumour and potential to achieve a complete resection. Currently transplantation for intrahepatic and hilar cholangiocarcinomas is not recommended in UK guidelines. Chemotherapy has a role in inoperable disease. Solitary metastases, e.g., colorectal carcinoma or carcinoid tumour can be resected to good effect. Thermal ablation, TACE, SIRT and chemotherapy are also be used to manage metastatic colorectal carcinoma and may render previously unresectable disease resectable. Metastatic carcinoid tumour can show good chemoresponsiveness.

10.5 Surgical Pathology Specimens: Clinical Aspects

10.5.1 Biopsy Specimens

FNAC and needle core biopsy can be carried out percutaneously either blind or preferably under radiological guidance, during laparoscopy, laparotomy, or as a radiologically guided transvascular (vena cava) procedure. Coagulation status is checked prior to core biopsy to avoid risk of haemorrhage.

10.5.2 Resection Specimens

10.5.2.1 Neoplastic Lesions

The key to successful hepatic resection of malignant disease is careful patient selection. In general:

- A primary liver tumour may be considered for resection if it involves a single lobe and there is no invasion of the portal vein or inferior vena cava. There should be no evidence of cirrhosis in the surrounding liver.
- A solitary metastatic deposit (the vast majority of which will be from a primary colorectal carcinoma) localized to a single lobe may be considered for resection. There should be no evidence of metastatic spread elsewhere. More recently, this criterion has been extended

to include multiple hepatic metastases provided resection is technically feasible leaving sufficient functioning hepatic remnant. Use of neoadjuvant chemotherapy, intravascular embolization, or radiofrequency ablation facilitates operative resection by downsizing the tumour deposits.

Obviously the background physiological state of the patient has to be taken into account before surgery is considered, i.e., resection is only justi-

fied in relatively young and medically fit individuals.

As was stated above, the liver is divided into right and left "surgical lobes," which are different to the anatomical lobes. The surgical lobes are separated along a plane that extends from the gallbladder bed to the inferior vena cava—the main portal plane. The surgical lobes are then subdivided into eight segments—each segment is supplied by its own portal venous and hepatic arterial pedicle (Fig. 10.2).
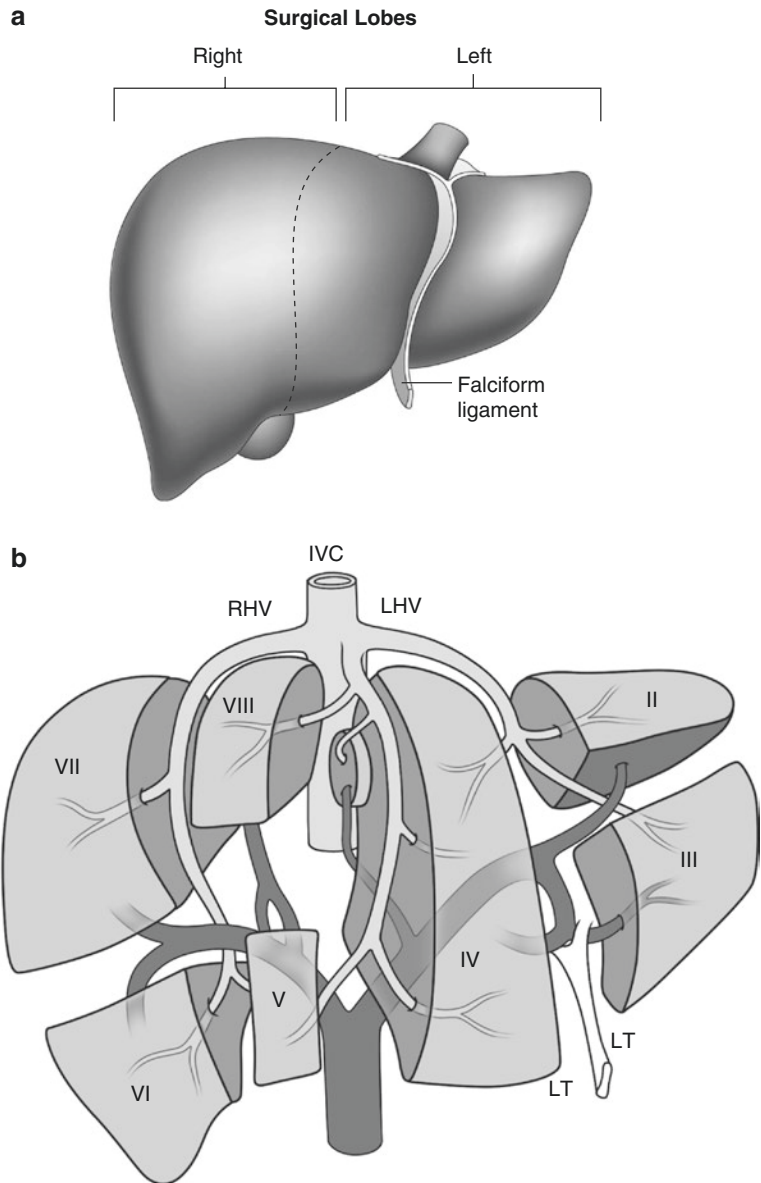

Fig. 10.2 (**a**) Surgical lobes of the liver. The surgical lobes of the liver compared with the usual anatomical division into *left* and *right* lobes by the falciform ligament. (**b**) Segments of the liver (after Couinard). *IVC* inferior vena cava, *RHV* right hepatic vein, *LHV* left hepatic vein, *LT* ligamentum teres

Major Liver Resection

An S-shaped right subcostal incision is used in all cases and once the abdomen is opened an initial laparotomy examination is done to ensure no other metastatic deposits are present. The definitive type of resection will depend on the site and extent of the tumour. Preoperatively portal vein embolization to the lobe to be resected may be used to hypertrophy the remaining liver tissue. Perihilar cholangiocarcinomas will usually be resected by partial hepatectomy but the specimen will include an extra portion of extrahepatic biliary tree (usually down to the common bile duct) and a margin of the contralateral main hepatic duct. Distal extrahepatic cholangiocarcinomas are usually resected without the need for a hepatectomy.

- *Right hepatectomy*—Segments V–VIII.
- *Left hepatectomy*—Segments II–IV.
- *Extended right hepatectomy*—Segments IV–VIII.
- *Extended left hepatecomy*—Segments I–V & VIII
- *Left lateral sectionectomy*—Segments II–III.

As well as neoplastic conditions, major liver resection may also be used for other conditions such as trauma.

Segmental Liver Resection

Although major hepatic resection may be employed for large tumours, when a small tumour (either primary or secondary) occupies one or two segments, a segmental resection can be carried out. This removes a segment(s) of liver, which is supplied by its own vascular pedicle, and is, therefore, an anatomically based procedure. Whatever the segment to be resected, its vascular anatomy is delineated by intraoperative USS before dissection.

Segmental resection has several advantages over major resection; namely as much functioning parenchyma is left as possible and the vascular supply to this is less likely to be compromised, there is reduced blood loss, and the procedure is less likely to leave residual tumour.

If a metastatic deposit is single, small, and superficial, a simple *wedge resection* (or atypical resection) using diathermy can be employed. This procedure may be performed during resection of the primary tumour, e.g., colorectal carcinoma, and sent for frozen section.

10.5.2.2 Non-neoplastic Lesions

Liver Cysts

Liver cysts may be congenital or acquired (e.g., neoplastic, inflammatory/infective, traumatic, etc.). When surgery is to be carried out for a liver cyst, an extensive preoperative clinical and radiological workup is required to ascertain, as closely as possible, its aetiology. An initial thorough laparotomy examination is undertaken. For non-infective cysts, the cyst is opened and the contents aspirated and sent for cytological and microbiological examination. The cyst wall can then be excised using cautery. In non-neoplastic lesions (e.g., simple cyst) complete excision may not be necessary and a large opening is made in the cyst to allow free drainage into the peritoneal cavity. Neoplastic liver cysts, in particular hepatic mucinous cystic neoplasm (discussed above) may only be diagnosed after histological evaluation of the specimen and so be initially treated by de-roofing the cyst *in vivo*. Due to their potential for malignant transformation complete resection is usually indicated if the patient is surgically fit and may lead to a formal liver resection.

Hydatid cysts (echinococcus tapeworm) may vary in size and situation within the liver. They may be excised without removing adjacent liver parenchyma (*pericystectomy*) or if the cysts are large or multiple, a segmental or major resection may be needed. When a pericystectomy is carried out and the cyst is opened, pads soaked in saline are packed around the cyst to prevent spillage of its contents into the peritoneal cavity.

For pyogenic abscess/cyst there are three main forms of treatment: long-term antibiotics, percutaneous drainage under radiological guidance, and open surgical drainage. Percutaneous drainage is now by far the most popular method. However, if surgical drainage is employed, the

abscess is identified and separated from the peritoneal cavity by pads. The abscess contents are then aspirated and the cavity washed out. The cyst wall is then de-roofed to facilitate resolution. Pyogenic abscesses may also be treated by laparoscopic drainage.

Transplantation

The first successful human liver transplant was carried out in 1967 and today over 80% of recipients survive 1 year. Not only can adult livers be transplanted to adult recipients, but the shortage of donor organs has led to adult donor organs being transplanted to children. This is facilitated by resecting and transplanting only part of the donor liver, e.g., left liver (segments I–IV). General indications for transplantation are acute liver failure, end-stage chronic liver disease, and neoplasms. Conditions encountered in the explant specimen can, therefore, be diverse including viral, autoimmune and alcoholic hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, end-stage cirrhosis, and primary hepatocellular. Current UK guidelines do not recommend transplant for cholangiocarcinoma. The liver transplant can be subject to various pathologies including rejection, effects of immunosuppression, and recurrence of the original disease.

10.6   Surgical Pathology: Laboratory Protocols

10.6.1 Biopsy Specimens

For needle core and wedge biopsy specimens see Chap. 1.

Note that viral hepatitis is a category III pathogen—it should be submitted to the laboratory with an attached "hazard of infection" sticker and handled appropriately after 24–48 h of thorough formalin fixation.

Routine histochemical stains that should be provided to help assess the degree of hepatic parenchymal loss, reticulin collapse/elaboration, and fibrous distortion/replacement, respectively, are, PAS (± diastase), silver reticulin, and Masson Trichrome or haematoxylin Van Gieson. Elastin

stains such as Shikata's orcein or elastic-van Gieson can help distinguish recent collapse (elastin negative) from old fibrosis (elastin positive). Haemochromatosis is diagnosed using biochemical and genetic investigations and the degree of iron deposition on biopsy is graded by Perl's Prussian Blue or the dry weight iron concentration. Other stains are: rhodanine/Shikata's orcein for copper or copper-associated protein deposition in Wilson's disease, primary biliary cirrhosis, or other chronic cholestatic disorders; PAS + diastase (positive globules in alpha-1 antitrypsin deficiency); and Congo Red (amyloid).

Needle cores may have an adherent fragment of skin if obtained percutaneously. They can also fragment in diseased liver with cirrhosis or tumour. Fatty liver is pale; haemochromatosis rust-colored. One aspect of a wedge biopsy is covered by peritonealized capsule and its cut margin is often frayed by diathermy. This margin should be painted and the wedge then cut into multiple perpendicular serial slices.

### 10.6.2 Resection Specimens

Specimen:

- Liver resection is more commonly performed for a focal mass lesion such as a cyst, adenoma, focal nodular hyperplasia, or metastatic colorectal carcinoma and is, therefore, limited in extent, e.g., segmentectomy, lobectomy, or partial hepatectomy. Other indications are major trauma and a small minority of resectable primary liver cancers. Specimen handling and reporting should document the nature of the abnormality, its extent, completeness of excision, vascular invasion, and status of the background parenchyma. Total hepatectomy is encountered in transplantation surgery—aims are to identify the cause of hepatic failure, and for tumour to determine the stage and assess porta hepatis margins.

Initial procedure:

For liver cyst de-roofing

- Weight (g) and dimensions of the specimen (mm)

Fig. 10.3 Partial hepatectomy specimen (Reproduced, with permission, from Allen and Cameron (2013))
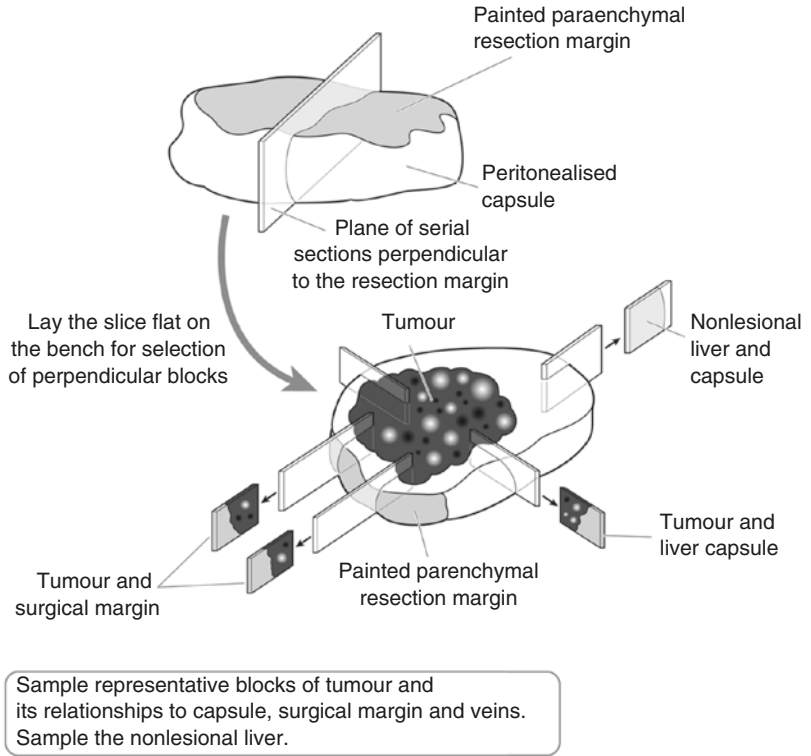
- Note and record the size of any focal abnormalities such as solid areas, nodules or septa
- Sample at least one block per cm in addition to sampling focal abnormalities. Submission of the entire specimen should be considered to identify or exclude an epithelial lining or presence of ovarian-type stroma.
  For partial resection
- Weight (g) and measurements (mm) in each dimension.
- Identify the capsular and cut parenchymal surfaces—the latter constitutes the surgical margin. Further orientation can only be given if marked appropriately by the submitting surgeon.
- Identify bile duct margins if cholangiocarcinoma suspected. Sample limits prior to slicing the liver. Record what ducts are involved grossly and identify any non-peritonealised margin.
- Identify vascular margins, particularly if there is tumour nearby.

- Paint the surgical margin and any areas of capsular bulging, retraction, or reaction that might be related to an underlying mass lesion.
- Serially section the liver perpendicular to the parenchymal resection margin at 0.5 cm intervals (Fig. 10.3).
- Photograph.
- Fixation by laying flat and immersion in 10% formalin for 36–48 h.
  Description:
- Note the number, size, and distances (mm) to the capsule and surgical margin for each lesion.
- Specific points are:
  Abscess
  – Contents (pus: pyogenic/"anchovy sauce": amoebiasis), walled-off, capsular reaction
  Cyst
  – Contents (fibrin, fluid (serous/mucoid)), wall (chitinous-hydatid) and presence of any thickened area, nodules or septa
  Trauma
  – Capsular tear, subcapsular haemorrhage, parenchymal laceration

Tumour mass
- Edges: circumscribed/irregular/nodular/ elevated
- Central scar: focal nodular hyperplasia
- Haemorrhage: haematoma, adenoma
- Bile stained: hepatocellular carcinoma
- Central necrosis/umbilication/mucinous/ peripheral calcification: metastatic carcinoma
- For suspected perihilar cholangiocarcinomas record if it is mass forming or periductal, characterized by thickening around the bile ducts, or intraductal. Note if invasion of hepatic parenchyma
- Look for and record vascular invasion, especially within the main branches of the hepatic arteries or portal veins.
- Non-lesional liver
  Fatty change/cholestasis/necrosis/cirrhosis/ haemochromatosis.
  Blocks for histology (Fig. 10.3):
- For abscess, or trauma, four or five representative blocks of the wall, any capsular tear or haemorrhage, and adjacent hepatic parenchyma are usually sufficient.

- For cyst consider submitting the entire cyst wall as discussed above
- For a tumour mass, also sample a minimum of four or five representative blocks to demonstrate the lesion in relation to the capsule, surgical margin, uninvolved liver, and any other relevant structures, e.g., veins, bile duct. Where the tumour is close to the hilum this should be sampled to include the large vessels and main branches of the portal and hepatic vein. Additional blocks are taken as required, e.g., if in close proximity to the surgical margin. Sections from the periphery of a tumour are often more informative than from the center as there is less necrosis with preservation of tumour tissue, and its interface with the parenchyma can be demonstrated.
- Sample non-lesional liver as far away from the main lesion as possible and preferably not subcapsular.

For total hepatectomy specimens (Fig. 10.4):
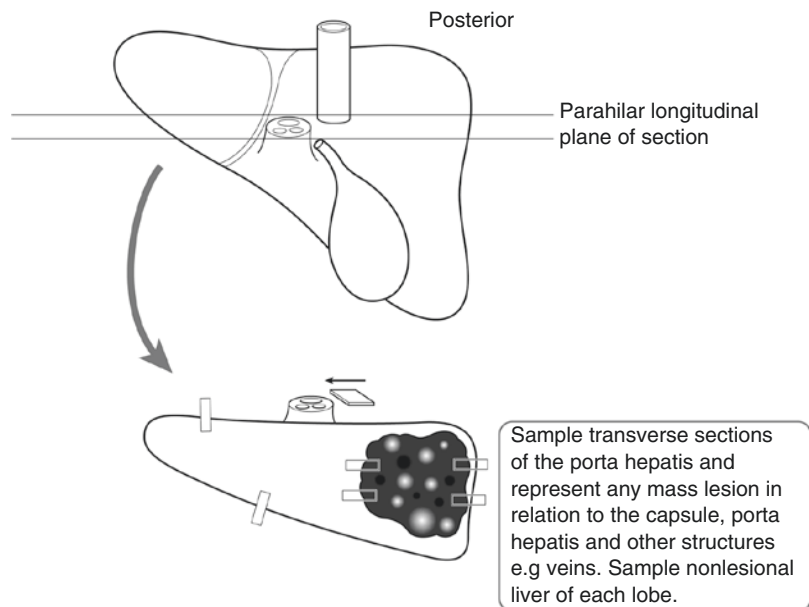
- Weight (g) and measure (cm) in three dimensions.

Posterior

Parahilar longitudinal plane of section

Sample transverse sections of the porta hepatis and represent any mass lesion in relation to the capsule, porta hepatis and other structures e.g veins. Sample nonlesional liver of each lobe.

Fig. 10.4 Total hepatectomy specimen (Reproduced, with permission, from Allen and Cameron (2013))

– If there is a previous diagnosis of hepatitis, incise deeply at several points to ensure an adequate period (48–72 h) of fixation prior to further handling.
– Identify the porta hepatis and transverse section its surgical margin to include the distal limit of the bile duct, hepatic artery, and portal vein. Further transverse sections at mid-duct and hilar levels can be submitted.
– Count and sample all lymph nodes.
– Dissect off the gallbladder and routinely process if macroscopically normal.
– Section the liver in its long axis either side of the hilum.
– Sample representative blocks from the anatomical lobes and additionally as indicated by any mass lesion to demonstrate its relationship to the capsule, vessels, and porta hepatis. Careful attention should be paid to involvement of the main portal and hepatic veins as well as the right and left main portal branches as this may have staging implications.
– Serially slice the rest of the liver to detect any further lesions and sample accordingly.

Histopathology report:

• Tumour type—hepatocellular carcinoma/cholangiocarcinoma/mixed cholangiocarcinoma hepatocellular carcinoma/metastatic carcinoma. If perihilar cholangiocarcinomas record pattern of invasion as periductal, intraductal and if there is a cystic component.
• Tumour differentiation—well/moderate/poor
• *Extent of local tumour spread: TNM 8: hepatocellular carcinoma*

pT1	Solitary tumour pT1a. ≤2 cm ± vascular invasion, or, pT1b. >2 cm without vascular invasion
pT2	Solitary tumour >2 cm with vascular invasion or multiple tumours, none more than 5 cm in greatest dimension
pT3	Multiple tumours any more than 5 cm in greatest dimension
pT4	Tumour(s) involving a major branch of the hepatic or portal vein with direct invasion of adjacent organs (including diaphragm) other than the gallbladder or with perforation of visceral peritoneum

Extent of local tumour spread: TNM 8: intrahepatic cholangiocarcinoma and combined hepatocellular and cholangiocarcinoma

pTis	Carcinoma *in situ* (may be used for non-invasive papillary neoplasms)
pT1	Solitary tumour without vascular invasion: pT1a. ≤5 cm, pT1b. >5 cm
pT2	Solitary tumour with intrahepatic vascular invasion, or, multiple tumours, ± vascular invasion
pT3	Tumour perforates peritoneum
pT4	Tumour involving local extrahepatic structures by direct hepatic invasion

• *Extent of local tumour spread: TNM 8: perihilar cholangiocarcinoma*

pTis	Carcinoma *in situ* (may be used for non-invasive papillary neoplasms)
pT1	Tumour confined to bile duct
pT2a	Tumour invades beyond the bile duct wall into fibroadipose tissue
pT2b	Tumour invades hepatic parenchyma
pT3	Tumour invades unilateral branches of portal vein/hepatic artery
pT4	Bilateral main vessel/duct involvement

• Lymphovascular invasion—present/not present. Note the propensity for hepatocellular carcinoma to invade portal tract veins, major branches of portal and hepatic veins, and inferior vena cava. Cholangiocarcinoma typically shows perineural space invasion with spread to lymph nodes, lungs, and peritoneum. Note invasion of the main portal vein and hepatic artery branches alters the staging of perihilar cholangiocarcinomas.
• Regional lymph nodes: hilar (hepatoduodenal ligament), hepatic (along the proper hepatic artery), periportal (along the portal vein), and those along the abdominal inferior vena cava above the renal veins (except the inferior phrenic nodes). A regional lymphadenectomy will ordinarily include 3 (hepatocellular carcinoma), 6 (intrahepatic cholangiocarcinoma), or 15 (perihilar cholangiocarcinoma) or more lymph nodes

| pN0 | No regional lymph node metastasis |
| pN1 | Metastasis in regional lymph node(s) |

- Perihilar cholangiocarcinoma: pN1 = 1–3 nodes, pN2 = 4 or more nodes.
- Excision margins
  Distances (mm) to the capsule and limits of excision of the hepatic parenchyma, bile ducts, and major veins
- Other pathology
  Hepatocellular carcinoma—hepatitis, cirrhosis (hepatitis/alcohol/haemochromatosis, etc.), dysplastic nodules, liver cell dysplasia. Cholangiocarcinoma—primary sclerosing cholangitis, ulcerative colitis, liver fluke, biliary tree anomaly.

Bibliography

Allen DC. Histopathology reporting. Guidelines for surgical cancer. 3rd ed. London: Springer; 2013.

Allen DC, Cameron RI. Histopathology specimens: clinical, pathological and laboratory aspects. 2nd ed. Berlin: Springer; 2013.

Beckingham IJ, editor. ABC of liver, pancreas and gall bladder diseases. London: BMJ Books; 2001.

Bioulac-Sage P, Cubel G, Balabaud C. Pathologic diagnosis hepatocellular adenoma in clinical practice. Diagn Histopathol. 2011;17:521–9.

Brierley JD, Gospodarowicz MK, Wittekind C, editors. TNM classification of malignant tumours. 8th ed. Oxford: Wiley-Blackwell; 2017.

Brunt EM. Histopathologic features of hepatocellular carcinoma. Clin Liver Dis. 2012;1:194–9.

Burt A. In: Portmann B, Ferrell L, editors. MacSween's pathology of the liver. 6th ed. Churchill Livingstone Elsevier: London; 2012.

Carter D, Russell RCG, Pitt HA, Bismuth H, editors. Rob and Smith's operative surgery: hepatobiliary and pancreatic surgery. 5th ed. London: Chapman and Hall; 1996.

Ishak KG, Goodman ZD, Stocker JT. Tumors of the liver and intrahepatic bile ducts, Atlas of tumor pathology, vol. 3rd series. Fascicle 31. AFIP: Washington; 2001.

Kumagi T, Hiasa Y, Hirschfield GM. Hepatocellular carcinoma for the non-specialist. BMJ. 2009;339:1366–70.

The Royal College of Pathologists. Cancer datasets (oesophageal carcinoma, gastric carcinoma, carcinomas of the pancreas, ampulla of vater and common bile duct, colorectal cancer, gastrointestinal stromal tumours (GISTs), liver resection specimens and liver biopsies for primary and metastatic carcinoma, endocrine tumours of the gastrointestinal tract (including pancreas) and tissue pathways (gastrointestinal and pancreatobiliary pathology, liver biopsies for the investigation of medical disease and for focal liver lesions). Available via https://www.rcpath.org/profession/publications/cancer-datasets.html. Accessed Aug 2016.

Wyatt JI. Cholangiocarcinoma—new concepts and classifications. Diagn Histopathol. 2011;17:539–47.