Pathology of liver tumours

Vikram R Prabhu
Alastair D Burt

Abstract
The liver is an important site for primary and secondary tumours. In western countries, the commonest malignant neoplasm of the liver is metastatic carcinoma, but hepatocellular carcinoma is a common and important cause of death elsewhere. There is a strong association with infection by hepatitis-B and -C; the latter explains the growing incidence of hepatocellular carcinoma in western countries. It is a complication of cirrhosis of any cause; male sex is an important risk factor. Such associations do not exist for the rare variant fibrolamellar carcinoma, which carries a better prognosis than the common form (where survival is measured in weeks). Cholangiocarcinoma, a malignant tumour of bile ducts, accounts for about 15% of primary intrahepatic malignancies; recent epidemiological studies have shown dramatic increases in its incidence. There is a strong association with primary sclerosing cholangitis and, in the Far East, with hepatolithiasis and infection by liver flukes. Epithelioid haemangioendothelioma and angiosarcoma are the commonest malignant mesenchymal tumours in the liver. A number of benign tumours and tumour-like lesions may mimic malignant neoplasms.

Keywords hepatocellular carcinoma; cholangiocarcinoma; fibrolamellar carcinoma; hepatocellular adenoma; bile duct adenoma

The liver is an important site of malignant neoplasms; most of these represent metastatic spread of (mainly) epithelial tumours. Of these, the commonest are primary tumours arising in the gastrointestinal tract and pancreatobiliary system but, given the rich blood supply of the liver, it is a common site for metastasis for many tumours. Some organs have a better ‘soil’ for tumours than others, and the liver appears to be ‘fertile’ for metastasis. Frequently, patients presenting with disseminated disease have liver involvement and it is quite common for liver biopsy to be carried out; various algorithms provide information regarding the likeliest primary source of disseminated malignancy in such circumstances. Some of this information relies on basic histopathological interpretation and some on immunohistochemical findings; this is increasingly supported by proteomic and genomic evidence.

Secondary tumours are the commonest cause of malignant neoplasms of the liver in the UK, but this contribution concentrates on primary tumours, particularly epithelial neoplasms. A truncated version of the classification of liver neoplasms is shown in Table 1.

Epithelial tumours

Liver cell (hepatocellular) adenoma
Liver cell (hepatocellular) adenoma is a benign tumour of the liver that may be mistaken for hepatocellular carcinoma.

Risk factors: in most cases, it arises in women of childbearing age and shows a strong association with synthetic gonadal steroids. Oral contraceptives are implicated (modern low-oestrogen preparations appear to carry less risk of adenoma formation), as are androgenic and anabolic steroids. Other rarer associations are with:

- metabolic syndromes such as glycogen-storage diseases (types I, III and IV)
- mucopolysaccharidosis type I (Hurler disease)
- familial diabetes mellitus

Presentation: the adenoma usually declares itself by its large size, causing an abdominal mass or abdominal pain. It does not secrete α-fetoprotein.

Table 1

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular</td>
<td>Hepatocellular adenoma</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td></td>
<td>Focal nodular hyperplasia</td>
<td>Fibrolamellar carcinoma</td>
</tr>
<tr>
<td></td>
<td>Dysplastic nodule</td>
<td>Combined hepatocellular-cholangiocarcinoma</td>
</tr>
<tr>
<td>Biliary</td>
<td>von Meyenburg complex</td>
<td>Biliary cystadenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>Bile duct cyst</td>
<td>Cholangiocarcinoma</td>
</tr>
<tr>
<td></td>
<td>Ciliated foregut cyst</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peribiliary gland hamartoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Biliary papillomatosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Biliary cystadenoma</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>Haemangioma</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td></td>
<td>Infantile haemangioendothelioma</td>
<td>Epithelioid haemangioendothelioma</td>
</tr>
<tr>
<td>Other</td>
<td>Angiomyolipoma</td>
<td>Primary lymphomas</td>
</tr>
<tr>
<td></td>
<td>Mesenchymal hamartoma</td>
<td>Other sarcomas and rare tumours</td>
</tr>
<tr>
<td></td>
<td>Inflammatory pseudotumour</td>
<td></td>
</tr>
</tbody>
</table>

Classification of primary tumours and tumour-like lesions of the liver (truncated version)

Vikram R Prabhu MBBS is a Specialist Registrar in Histopathology in the Northern Deanery, UK. Conflicts of interest: none declared.

Alastair D Burt FRCPa is a Professor of Pathology and Dean of Clinical Medicine at Newcastle upon Tyne University, Newcastle, UK. Conflicts of interest: none declared.
**Basic science**

**Macroscopically**, it may measure >10 cm, is well circumscribed and solitary, though cases associated with anabolic and androgenic steroids may be multiple (adenomatosis). It is located anywhere within a relatively normal liver but, if in a subcapsular location, may rupture to cause intraperitoneal haemorrhage, particularly during pregnancy. It displays a variegated cut surface.

**Histologically**, it comprises normal or mildly enlarged hepatocytes arranged in plates up to three cells thick. Bile ducts and portal structures are absent, but there is prominent vasculature and delicate sinusoids insinuate between the plates. Mitoses are exceedingly rare and vascular invasion absent. Degenerative changes may be present. Distinction from a well-differentiated hepatocellular carcinoma on core biopsy may be extremely difficult.

**Hepatocellular carcinoma**

Hepatocellular carcinoma is the commonest form of malignant primary tumour of the liver.

**Risk factors**: most cases occur in Asia and Africa, where it affects young adults and is associated with infection by hepatitis-B or -C virus and exposure to aflatoxins. In western countries, it usually occurs against a background of cirrhosis due to infection by hepatitis-C or alcohol abuse, and tends to affect adults aged >60 years. Less common associations include:

- tyrosinaemia
- haemochromatosis
- deficiency of α1-antitrypsin
- exposure to naturally occurring carcinogens (e.g. pyrroldizidine alkaloids).

Use of oral contraceptive is associated with a seven-to-twentyfold increased relative risk after eight years of use; the absolute risk of developing the tumour remains small. Thorotrust, although linked with cholangiocellular carcinoma and angiosarcoma, is also implicated in the development of hepatocellular carcinoma. There is a four-to-eightfold male preponderance. Atypical macroregenerative nodules and small cell change (dysplasia) have been identified as precancerous lesions; the role of large cell change is less certain.

**Presentation**: in western countries, the tumour usually presents as a sudden deterioration with hepatic decompensation in a patient with longstanding cirrhosis. There may be pain in the right upper quadrant and weight loss. Occasionally, there may be rupture of the tumour with intraperitoneal haemorrhage. The concentration of α-fetoprotein in serum is a useful surrogate tumour marker, but is not entirely specific and sensitivity is relatively low. Prognosis is poor and most patients die of hepatic failure within a few months.

**Macroscopically**, the tumour is classically described as massive (solitary), multinodular or diffusely infiltrative; the latter may be difficult to identify in a cirrhotic liver. The tumour is soft and white, but may be stained by bile (Figure 1). It is frequently haemorrhagic or necrotic. Small (<2 cm) tumours tend to be unencapsulated, but acquire a capsule as they grow due to passive compression of surrounding parenchyma. Intravascular spread of the tumour is prominent and many satellite nodules may be present. Macroscopic invasion of the portal vein or hepatic vein may be visible.

**Microscopically**, the tumour is usually trabecular, comprising liver plates ranging from two to many cells in thickness separated by sinusoids (Figure 2); there is little intervening stroma. Another pattern is pseudoglandular, thought to be due to breakdown of thick trabeculae. The degenerative spaces left behind contain debris that is replaced by eosinophilic material, causing a resemblance to colloid lying within thyroid follicles; an appropriate stain for fibrin is positive. Another pattern, compact, may be due to compression artefact and is usually noted after radiotherapy or chemotherapy. The cells in hepatocellular carcinoma are usually polygonal and exhibit varying degrees of nuclear enlargement and atypia. Pleomorphic giant cells, clear cells and sarcomatoid areas may also be present. Oncocyte-like cells may be seen, but are more common in the fibrolamellar variant of hepatocellular carcinoma (see below). The tumour cells may be identified with routine histological stains, but can be highlighted

**Figure 1** Resection specimen showing multifocal hepatocellular carcinoma (arrows) in a cirrhotic liver. Source: Professor Mark Bennett, Newcastle upon Tyne, UK.

**Figure 2** Histology specimen showing well-differentiated hepatocellular carcinoma.
immunohistochemically by hepatocellular cytokeratin-8 and -18 and by hepatocyte paraffin-1 monoclonal antibody. α-fetoprotein is a specific, but insensitive, marker of hepatocellular carcinoma. Mucin stains are negative, differentiating the tumour from many metastases and cholangiocellular lesions. Monoclonal carcinoembryonic antigen is negative, but polyclonal carcinoembryonic antigen highlights small bile canaliculi.

**Histological grading** was previously based on the Edmundson and Steiner criteria and ranged from grade I (the best-differentiated grade applied to tumours with thin trabeculae, relatively small cells and minimal nuclear atypia) to grade IV (applied to tumours with poor differentiation, enlarged hyperchromatic nuclei and loss of the normal trabecular architecture).

The most recent WHO system classifies tumours as:
- well differentiated (Edmundson and Steiner grade I/II)
- moderately differentiated (Edmundson and Steiner grade II/III)
- poorly differentiated (Edmundson and Steiner grade III/IV).

Small tumours tend to be well differentiated.

**Staging** is according to the TNM system of the International Union against Cancer (UICC; **Table 2**).

### Fibrolamellar carcinoma
Fibrolamellar carcinoma is a distinct variant of hepatocellular carcinoma. Unlike conventional hepatocellular carcinoma, this:
- has an equal sex distribution
- has a striking predilection for young adults (90% of cases occur in those aged <35 years)
- accounts for up to 5% of cases of liver cell carcinoma.

The cause is unknown. There is no association with cirrhosis and only a minority of cases are associated with infection by hepatitis-B virus. In contrast to conventional hepatocellular carcinoma, this tumour is usually slowly progressive and has a much better prognosis; five-year survival is 50%.

**Macroscopically,** the tumour is solitary, large and well circumscribed. It contains fibrous septa and may be lobulated. It contains large polygonal cells with granular eosinophilic cytoplasm (‘oncocytic cells’, **Figure 3**). Parallel lamellae of dense collagen are deposited between the islands of neoplastic cells, causing the characteristic scirrhous appearance and giving rise to the name of the lesion. The tumour cells express cytokeratins of hepatocellular (cytokeratin-8 and -18) and biliary type (cytokeratin-19).

### Hepatoblastoma
Hepatoblastoma is the commonest primary tumour of the liver in children. Two-thirds present by the age of two years and 90% by the age of five years. There is a slight male preponderance.

**Risk factors:** a small proportion of cases are associated with congenital malformations (e.g. cleft palate (see Mosahebi, **CROSS REFERENCES**), cardiac and renal abnormalities, Down’s syndrome). Familial adenomatous polyposis also presents a substantially increased relative risk of developing the tumour.

**The clinical presentation** is of failure to thrive and a rapidly growing abdominal mass. This is usually associated with a very high concentration of α-fetoprotein in serum.

**Radiographically,** the hepatic lesion may show areas of calcification.

**Macroscopically,** the tumour is usually solitary with a prominent vasculature; it may be very large and displays a variegated surface according to the proportion of the various components.

**Histologically,** it is classified into one of two groups split into several subtypes.

- **Pure epithelial tumours** comprise:
  - fetal (comprising large cells arranged in irregular trabeculae)
  - embryonal (comprising less differentiated epithelial cells forming poorly defined acini, tubules and papillary structures)
  - macrotubular (comprising trabeculae that are ≥10 cells thick, and mimicking hepatocellular carcinoma)
  - small cell (carrying a very poor prognosis and resembling other primitive childhood tumours).

- **Mixed epithelial and mesenchymal tumours** contain varying proportions of fetal and embryonal cells, in addition to sheets of primitive spindle-shaped mesenchymal cells and osteoid. They

---

**UICC TNM staging for liver tumours**

- **T1** tumours are solitary and do not show vascular invasion
- **T2** tumours are solitary with vascular invasion or are multiple, with each tumour measuring ≤5 cm
- **T3** tumours are multiple and measure >5 cm, or alternatively involve a major branch of the hepatic or portal vein
- **T4** tumours perforate the visceral peritoneum or invade adjacent structures other than the gallbladder
- Local metastasis to regional lymph nodes ( hilar, hepatic, periporal, and those along the abdominal inferior vena cava barring the inferior phrenic nodes) is classified as N1

---

**Table 2**

**Figure 3** Histology specimen showing fibrolamellar carcinoma; note the broad bands of collagen (arrows).
are further classified according to whether they show teratoid features (e.g. keratinizing squamous epithelium, skeletal muscle, cartilage, neural tissue) or not.

**Bile duct adenomas**
Bile duct adenomas (peribiliary gland hamartomas) are well circumscribed lesions composed of ductular structures and fibrous stroma. These were originally thought to comprise a true neoplasm of bile duct epithelium, but it has been argued that they resemble peribiliary glands in terms of their antigen expression; others believe that they represent a reactive phenomenon caused by focal parenchymal extinction with proliferation of ductular structures and an associated mesenchymal response. They are frequently subcapsular and may be mistaken for metastatic cancer at laparoscopy or operation. They may also be mistaken for a malignant neoplasm on frozen section, but the bland appearance of the epithelial component should point to the correct diagnosis at higher power.

**Biliary cystadenoma with mesenchymal stroma**
Biliary cystadenoma with mesenchymal stroma is analogous to similar neoplasms in the pancreas. It accounts for 5% of hepatic cysts and overwhelmingly occurs in women. It usually presents in the fifth decade as a mass causing pain, or jaundice (rare). Most cases are intrahepatic, but it may also affect the extrahepatic biliary tree. Cyst fluid and the concentration of cancer antigen 19-9 and carcinoembryonic antigen in serum may be raised.

**Radiographically**, the tumour may contain calcifications. The encapsulated cyst is solitary but usually multiloculated. It measures between 2 cm and 30 cm and contains a predominantly smooth inner lining with occasional papillary excrescences. Solid areas raise the suspicion of malignant transformation. The cyst fluid is usually clear and gelatinous. Rarely, there may be intracystic gallstone formation.

**Microscopically**, the lining epithelium comprises a single layer of cuboidal to columnar cells containing apical mucin. Intestinal or squamous metaplasia is sometimes observed. There may be features of low-grade cytological atypia or borderline malignancy. Frequently, there is a dense muscle-specific actin-positive stroma around the cyst, described as ‘ovarian-like’, that may contain fat or smooth muscle. This is often separated from the epithelium by a collagenous zone.

**Bile duct carcinoma**
Bile duct carcinoma may be intrahepatic (when it arises above the level of the hilum). It may also arise in the hilum (hilar adenocarcinoma, Klatskin tumour) or be extrahepatic.

**Intrahepatic bile duct carcinoma (cholangiocarcinoma)** accounts for 10–20% of malignant tumours of the liver. It has an equal sex distribution, apart from when it is associated with primary sclerosing cholangitis, where it shows a male preponderance. Other associations include:
- congenital polycystic disease
- Caroli’s disease
- cholelithiasis
- multiple bile duct hamartomas.

It is endemic in Southeast Asia, where infestation with the liver flukes *Clonorchis sinensis* and *Opisthorchis viverrini* are associated with tumour development. It is also associated with recurrent bacterial cholangitis with hepatolithiasis. Thorotrast has been implicated as a causative agent; most cases are idiopathic.

**Presentation** – the tumour presents in the fifth or sixth decade with fever, weight loss, loss of appetite and vague abdominal pain; it may present earlier in those with primary sclerosing cholangitis. Jaundice is not usually a presenting feature. The concentration of α-fetoprotein in serum is normal, but concentrations of carcinoembryonic antigen and cancer antigen 19-9 may be increased. By the time it is detected, it has usually progressed to an advanced stage and prognosis is poor, with a median survival of 6–7 months and a one-year survival of 25%.

**Macroscopically**, it is identified as a white to tan, firm, and gritty unencapsulated nodule in a non-cirrhotic liver (Figure 4). It may exhibit finger-like processes or have a disseminated appearance if there is spread along lymphatic channels.

**Microscopically**, most cases appear as infiltrative well to moderately differentiated adenocarcinoma. Tubular structures comprising cuboidal epithelium can be seen to express neutral and acidic mucins with appropriate stains. There is an investing desmoplastic stroma. Perineural infiltration is prominent and portal tracts may be involved (Figure 5). The tumour does not secrete bile, but the surrounding rim of liver parenchyma may be bile-stained. The tumour cells express cytoplasmic (not luminal) carcinoembryonic antigen, and biliary-type cytokeratin-7 and -19. Several variants are recognized, including mucinous, clear cell, papillary, signet ring cell, squamous and adenosquamous.

**Grading** is based on the proportion of gland formation; grade 1 (well-differentiated) tumours display >95% gland formation, and grade 4 (undifferentiated) tumours display <5% gland formation. Clear cell and papillary adenocarcinoma are not graded. Signet ring carcinoma is assigned a grade of 3, and small cell carcinoma a grade of 4. Distinction from metastatic adenocarcinoma may be extremely difficult.

**Figure 4** Resection specimen showing hilar cholangiocarcinoma (Klatskin tumour; arrow). Source: Professor Mark Bennett, Newcastle upon Tyne, UK.
Basic science

Surgey 25:1 © 2006 Published by Elsevier Ltd.

Staging uses essentially the same TNM system as for hepatocellular carcinoma.

Vascular tumours

Given the nature of the hepatic mesenchyme, it is unsurprising that the commonest ‘non-epithelial’ tumours are of endothelial origin.

Cavernous haemangioma

Cavernous haemangioma is the commonest benign tumour of the liver. The liver is the commonest solid-organ site of haemangiomas. In general, this is an asymptomatic lesion, but it may lead to pain and a mass in the upper abdomen. It may occasionally spontaneously rupture; this may be related to trauma. It may be multiple (rare) but, if single, is usually in the right lobe.

Microscopically, they comprise blood-filled spaces lined by a single layer of flat endothelial cells; thrombi may be present. There may be marked fibrosis and the whole lesion may become replaced by scar tissue (‘sclerosed haemangioma’).

Infantile haemangioendothelioma

Infantile haemangioendothelioma is regarded a benign neoplasm, although it may exhibit more aggressive behaviour in some instances. It occurs almost exclusively in the first year of life. It can be solitary or multicentric and, like haemangiomas, comprises vascular channels that are lined by a single layer of endothelial cells on a mesenchymal lattice. It is one of the commonest intrahepatic tumours in the first few years of life.

Presentation is with an abdominal mass; congestive cardiac failure occurs in some children, with consumptive coagulopathy and anaemia; it may be multifocal.

Histologically, there is a spectrum of changes, with some appearing very similar to adult haemangiomas although there is marked extra-medullary haematopoiesis in many. In some, with a spindle cell element, the appearances are more aggressive. This has been regarded as ‘malignant transformation’, while others believe there is a spectrum with two principal components: type I infantile haemangioendothelioma being ‘benign’, and type II representing a variant of angiosarcoma.

Angiomyolipoma

Angiomyolipoma is a benign tumour comprising admixtures of adipose tissue, smooth muscle and classical endothelium. Unlike the equivalent lesion in kidney, tuberous sclerosis is an associated finding in about only 6% of cases. It is mainly found in the right lobe and, in general, these are small and well circumscribed, although occasionally they can be large (giant angiomyolipoma).

Histologically, they comprise mature adipose tissue, tortuous thickwalled vessels and smooth muscle cells, some of which are epithelioid. Some of the cells are positive by immunohistochemistry for S100 protein and with the antibody HMB45.

Epithelioid haemangioendothelioma

Primary malignant mesenchymal tumours of the liver are uncommon, but most are of endothelial origin. Epithelioid haemangioendothelioma is a low-grade malignant neoplasm associated with a fibrous stroma of variable density. It can involve other organs and has been described at almost all sites. The tumour appears to have a proclivity for growing along blood vessels, hence it can be associated with a Budd–Chiari-like syndrome and portal hypertension (see page 28).

Macroscopically, there may be multiple lesions in the liver and these tend to have a pale, firm and gritty appearance; evidence of underlying chronic liver disease is rare.

Microscopic: one of the characteristic features is the preservation of the normal histological landmarks. Thus, the relationship between hepatic veins and portal tracts is preserved but there is infiltration of vessels and the intervening parenchyma by tumour cells. There is accompanying atrophy of the liver cell plates. The tumour cells may be large and ‘epithelioid’ with a round shape (Figure 6) but, in some areas, may be more reminiscent of angiosarcoma (see below).

Figure 5 Histology specimen showing well-differentiated cholangiocarcinoma with perineural infiltration (arrow).

Figure 6 Histology specimen showing epithelioid haemangioendothelioma. Large tumour cells lie within an eosinophilic matrix.
Nuclear atypia and mitoses are not always present, but some of the cells contain intracytoplasmic vascular lumina and may contain erythrocytes. The cells may express vascular markers (e.g. CD31, CD34) and epithelial markers (e.g. cytokeratin).

**Angiosarcoma**

Angiosarcoma is a more malignant tumour that has less stromal component than epithelioid haemangioendothelioma. Several epidemiological studies have shown an association with exposure to environmental agents (e.g. vinyl chloride) and the association with androgenic/anabolic steroids is well documented. It is uncommon, but is the commonest sarcoma of the liver. It is principally seen in the elderly and carries a very poor prognosis.

**Macroscopically**, it is characterized by areas of white tumour tissue alternating with haemorrhagic foci; there may be associated fibrosis in some cases.

**Microscopically**, the tumours comprise atypical vascular endothelial cells growing along preformed vascular channels, in particular sinusoids and hepatic venules. A variant described as Kaposi-form angiosarcoma is described in children. (This resembles Kaposi’s sarcoma seen in association with HIV infection, but appears to be a distinct neoplasm.)

**Cysts and other tumour-like lesions**

There are a number of non-neoplastic lesions that can resemble neoplasms in the liver, which are of biliary and hepatocytic origin.

**Solitary bile duct cyst**

The solitary bile duct cyst is a unilocular cyst lined by a single layer of columnar epithelium surrounded by a layer of fibrous tissue. This occurs at all ages but is mainly seen in the fifth and sixth decades. The main differential diagnosis is from other benign cystic conditions (e.g. autosomal dominant polycystic disease of the liver, von Meyenberg complexes).

**Ciliated hepatic foregut cysts**

Ciliated hepatic foregut cysts are rare and mainly small, subcapsular and unilocular. These are lined by ciliated pseudostratified columnar epithelium supported by a loose lamina propria. This is in keeping with the concept that they arise from embryonic foregut, differentiating towards bronchial structures in the liver.

**Focal nodular hyperplasia**

Another common non-neoplastic lesion is focal nodular hyperplasia. This comprises hyperplastic liver parenchyma with a central scar and often with aberrant vessels. It tends to be a well-circumscribed lesion that histologically resembles a focal biliary cirrhosis. In general, it is a single ‘sporadic’ process but is occasionally multiple; it may be associated with vascular lesions in other organs (e.g. berry aneurysms) and tumours (including meningioma and astrocytoma) when there are several lesions.

**Inflammatory pseudotumours**

Inflammatory pseudotumours are, in general, single lesions comprising myofibroblasts, chronic inflammatory cells (mainly plasma cells, macrophages, lymphocytes) and fibrous tissue. This is a relatively uncommon lesion, but is another entity that can be seen in other organs (e.g. lungs). There are associations with bacterial infection and these are thought to have arisen on the basis of an exuberant response to sepsis (see Kumar; Hargunani, CROSS REFERENCES), but there is a subset that appear to be more aggressive and more likely to recur in which there is an association with infection by Epstein–Barr virus. In some of these, there is evidence of neoplastic transformation; in such lesions, the background ‘myofibroblastic cells’ are positive for CD21 and are thought to represent a neoplastic dendritic cell component.

**CROSS REFERENCES**


**FURTHER READING**