The most frequent and important hepatic neoplasm is the primary hepatocellular carcinoma (HCC). In many parts of the world, in particular Africa and Asia, it poses a significant disease burden. In these high incidence regions, chronic infection with hepatitis B virus (HBV) is the principal underlying cause, with the exception of Japan which has a high prevalence of hepatitis C infection. HBV vaccination has become a powerful tool in reducing cirrhosis and HCC, but implementation is still suboptimal in several high risk regions. In Western countries, chronic alcohol abuse is a major aetiological factor.

Hepatic cholangiocarcinoma has a different geographical distribution, with peak incidences in Northern Thailand. Here, it is caused by chronic infection with the liver fluke, *Opisthorchis Viverrini*, which is ingested through infected raw fish.
WHO histological classification of tumours of the liver and intrahepatic bile ducts

Epithelial tumours

Benign

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular adenoma (liver cell adenoma)</td>
<td>8170/0'</td>
</tr>
<tr>
<td>Focal nodular hyperplasia</td>
<td></td>
</tr>
<tr>
<td>Intrahepatic bile duct adenoma</td>
<td>8160/0</td>
</tr>
<tr>
<td>Intrahepatic bile duct cystadenoma</td>
<td>8161/0</td>
</tr>
<tr>
<td>Biliary papillomatosis</td>
<td>8264/0</td>
</tr>
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</table>

Malignant

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular carcinoma (liver cell carcinoma)</td>
<td>8170/3</td>
</tr>
<tr>
<td>Intrahepatic cholangiocarcinoma</td>
<td>8180/3</td>
</tr>
<tr>
<td>Bile duct cystadenocarcinoma</td>
<td>8190/0</td>
</tr>
<tr>
<td>Combined hepatocellular and cholangiocarcinoma</td>
<td>8190/3</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>8970/3</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
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</table>

Non-epithelial tumours

Benign

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiomyolipoma</td>
<td>8860/0</td>
</tr>
<tr>
<td>Lymphangioma and lymphangiomatosis</td>
<td>9170/0</td>
</tr>
<tr>
<td>Haemangiomata</td>
<td>9120/0</td>
</tr>
<tr>
<td>Infantile haemangioendothelioma</td>
<td>9130/0</td>
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</table>

Malignant

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelioid haemangioendothelioma</td>
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</tr>
<tr>
<td>Angiosarcoma</td>
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</tr>
<tr>
<td>Embryonal sarcoma (undifferentiated sarcoma)</td>
<td>8991/3</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>8900/3</td>
</tr>
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</table>

Others

<table>
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<tr>
<th>Tumour Type</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Solitary fibrous tumour</td>
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</tr>
<tr>
<td>Teratoma</td>
<td>9080/1</td>
</tr>
<tr>
<td>Yolk sac tumour (endodermal sinus tumour)</td>
<td>9071/3</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>8980/3</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>9140/3</td>
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<td>Rhabdoid tumour</td>
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Haemopoeitic and lymphoid tumours

Secondary tumours

Epithelial abnormalities

<table>
<thead>
<tr>
<th>Tumour Type</th>
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</thead>
<tbody>
<tr>
<td>Liver cell dysplasia (liver cell change)</td>
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<tr>
<td>Large cell type (large cell change)</td>
<td></td>
</tr>
<tr>
<td>Small cell type (small cell change)</td>
<td></td>
</tr>
<tr>
<td>Dysplastic nodules (adenomatous hyperplasia)</td>
<td></td>
</tr>
<tr>
<td>Low-grade</td>
<td></td>
</tr>
<tr>
<td>High-grade (atypical adenomatous hyperplasia)</td>
<td></td>
</tr>
<tr>
<td>Bile duct abnormalities</td>
<td></td>
</tr>
<tr>
<td>Hyperplasia (bile duct epithelium and peribiliary glands)</td>
<td></td>
</tr>
<tr>
<td>Dysplasia (bile duct epithelium and peribiliary glands)</td>
<td></td>
</tr>
<tr>
<td>Intraepithelial carcinoma (carcinoma in situ)</td>
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Miscellaneous lesions

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
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<tr>
<td>Nodular transformation</td>
<td></td>
</tr>
<tr>
<td>nodular regenerative hyperplasia</td>
<td></td>
</tr>
<tr>
<td>Inflammatory pseudotumour</td>
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</tr>
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</table>

TNM classification of tumours of the liver and intrahepatic bile ducts

TNM classification\(^1\,\,^2,\,\,^3\)

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
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<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
</tbody>
</table>

Stage Grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
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<td>T4</td>
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<td>M0</td>
</tr>
<tr>
<td>IVA</td>
<td>Any</td>
<td>Any</td>
<td>M0</td>
</tr>
<tr>
<td>IVB</td>
<td>Any</td>
<td>Any</td>
<td>M1</td>
</tr>
</tbody>
</table>

\(^1\) Morphology code of the International Classification of Diseases for Oncology (ICD-O) \((542\)\) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /1 for unspecified, borderline or uncertain behaviour, /2 for in situ carcinomas and grade III intraepithelial neoplasia and /3 for malignant tumours.

\(^2\) This classification applies only to primary hepatocellular and cholangio-(intrahepatic bile duct) carcinomas of the liver.

\(^3\) A help desk for specific questions about the TNM classification is available at http://tnm.uicc.org.
Hepatocellular carcinoma

Definition
A malignant tumour derived from hepatocytes. Most common aetiological factors are viral infections (HBV, HCV), dietary aflatoxin B1 ingestion and chronic alcohol abuse.

Epidemiology
Primary liver cancer (PLC) is a major public health problem worldwide. In 1990, the global number of new cases was estimated at 316,300 for males and 121,100 for females, accounting for 7.4% (males) and 3.2% (females) of all malignancies, excluding skin cancer (1469). Hepatocellular carcinoma (HCC) is the most common histological type of PLC. Population-based cancer registries show that HCC as a percentage of histologically specified PLCs varies considerably (1471) but in over half of the registries, the fraction is above 70%. Regions with percentages less than 40% are exceptional, e.g., Khon Kaen (Thailand), where intrahepatic cholangiocarcinoma is predominant, due to endemic infection with liver flukes (Opisthorchis viverrini) (1470). Owing to the limited availability of histological data, the following epidemiological survey is based on PLC but it can be assumed that it largely reflects HCC incidence and mortality.

Geographical distribution
The estimated PLC incidence in 1990 for 23 areas of the world is shown in Figure 8.01 (1469). High-risk areas with an age-standardized incidence rate (ASIR, standardized to world population) of more than 20.1 per 100,000 for males are Sub-Saharan and South Africa, East Asia, and Melanesia. Low-risk areas with an ASR < 3.2 are North and South America, South-Central Asia, Northern Europe, Australia and New Zealand. Thus, developing countries carry the greatest disease burden, with more than 80% of accounted global cases. The geographical distribution of PLC is similar for males and females, although males have a considerably higher risk of developing PLC. Geographical variations in PLC risk are present even in relatively homogeneous populations and environments (1471, 176). Geographical variations in HCC incidence and mortality can be ascribed to different levels of exposure to HCC risk factors: chronic infections with hepatitis B virus (HBV) and aflatoxin exposure in developing countries, and smoking and alcohol abuse in developed countries (1545, 1482, 1417). In Japan, local differences in the age-standardized mortality rate (ASMR, standardized to world population) reflect the sero-prevalence of anti-hepatitis C virus (anti-HCV) antibodies among blood donors (1973, 1893, 1471, 67).

Time trends
In most countries, the incidence rates stayed largely constant or have decreased over the past two decades. However, they have increased in Japan and Italy, especially for males (982, 1522). A changing prevalence of risk factors among populations as well as changes in diagnostic techniques and in classification of the disease and appreciably affected the disease incidence.
**Age and sex distribution**

Regional age-specific incidence rates differ significantly (Fig. 8.03). Qidong and Hong Kong (China) are high-risk populations for HBV-related HCC. Characteristics of their curves are a steep increase in the ages 20-34 years; in Qidong the curve levels off already at the age of 40. Osaka (Japan) is a high-risk area, but Varese (Italy) is a low to intermediate risk area: approximately 70% of HCC in these populations is related to chronic HCV infection (1417). Their rates increase at older ages and show relatively high rates over age 55-59. The curve for whites in the USA (SEER data) is representative of both low-risk populations. Males are always more frequently affected than females but high male to female ratios of > 3 in the age-specific rates occur particularly in populations with a high incidence of HCC (1534, 402, 1906, 391, 452).

**Aetiology**

Chronic infection with HBV, HCV or both is the most common cause of HCC worldwide (889). Among Western populations, alcohol-induced liver injury is a leading cause of liver cirrhosis and constitutes the most important HCC risk (426). In Southern China and sub-Saharan Africa, dietary ingestion of high levels of aflatoxin may present a special environmental hazard, particularly in individuals chronically infected with HBV. Other exogenous factors have also been incriminated, including iron overload (1155), long-term use of oral contraceptives (1158, 2034), and high-dose anabolic steroids. The development of liver cirrhosis, particularly in association with inherited genetic diseases such as alpha-1-antitrypsin deficiency or haemochromatosis, place the individual at a greatly increased risk of HCC development.

HCC risk is increased if aetiological risk factors exist in combination, e.g., HCV infection and alcohol use (341) or HBV infection and exposure to aflatoxin (1864).

**Liver cirrhosis**

The major clinical HCC risk factor is liver cirrhosis, largely independent of its aetiology (Fig. 8.04). Approximately 70–90% of HCCs develop in patients with macronodular cirrhosis which is characterised by the presence of large nodules of varying size (up to several centimeters in diameter), containing portal fields and efferent veins, separated by broad, irregularly shaped connective tissue septae and scars. Macronodular and mixed macro-micro-nodular cirrhosis are typically caused by or associated with viral hepatitis, metabolic disorders, and toxic liver injury. Micronodular cirrhosis is characterised by uniform nodules of approximately 3 mm that lack the typical liver architecture and do not contain a central vein. They are typically observed as a consequence of alcoholic liver disease, haemochromatosis, and biliary cirrhosis.

**Hepatitis B virus (HBV)**

HBV is a small DNA virus belonging to the group of hepatotropic DNA viruses known as hepadnaviruses. HBV consists of an outer envelope, composed mainly of hepatitis B surface antigen (HBsAg), and an internal core (nucleocapsid), which contains hepatitis B core antigen (HBcAg), a DNA polymerase/reverse transcriptase, and the viral genome. The genome consists of a partly double-stranded circular DNA molecule of about 3200 base pairs with known sequence and genetic organisation. In recent years, HBV variants with mutations in viral genes and in some regulatory genetic elements have been detected in patients with HBV infection; these mutations can have biological consequences. Epidemiological studies have convincingly shown that HCC development is closely associated with chronic HBV infection. The incidence of HCC in chronically HBV-infected individuals is approximately 100 times higher than in the uninfected population, and the lifetime HCC risk of males infected at birth approaches 50%. In the absence of a common molecular mechanism for HBV-induced hepatocarcinogenesis, definitive proof for a direct oncogenic role of HBV is still lacking. Nevertheless, at least three lines of evidence support a direct oncogenic role for HBV in the development of HCC: (1) integration of HBV DNA into the chromosomal DNA of HCCs, (2) the role of the HBV X gene in the pathogenesis of HBV-associated HCCs, in particular its binding to and inactivation of p53, and (3) HCC development in animal models of chronic hepadnavirus infection. In addition, the declining HCC incidence following HBV vaccination clearly supports the aetiological contribution (275). Chronic hepatitis D virus (HDV) infection does not increase the risk of HCC development over that of HBV infection alone, but the latency period between HDV infection and HCC development is 30–40 years.
years, compared with 30-60 years for HBV infection alone.

**Hepatitis C virus (HCV)**

HCV has a single-stranded RNA genome of positive polarity, around 10 kb in length, that codes for a single polyprotein consisting of 3010-3033 amino acids. Post-translational processing in the 5'-3' direction yields the structural protein C (RNA-binding nucleocapsid protein) and the E1 and E2 envelope proteins, and the non-structural proteins NS1-NS5, including RNA-dependent RNA polymerase [321]. As soon as the HCV genome was cloned, it became evident that viruses isolated from various geographic regions have marked genetic heterogeneity. Sequence comparison shows at least 6 different HCV genotypes. Although mutations have been identified in all regions of the HCV genome, the genes for the envelope proteins E1 and E2 appear to be particularly variable. A mutation rate of 1 or 2 nucleotides per 1000 bases per infection-year appears to be characteristic of chronic HCV infection. This mutation rate is about 10 times higher than that of HBV. Some HCV genotypes may be more frequently associated with HCC development than others [321]. Anti-HCV antibodies are found in 15–80% of HCC patients, depending on the patient population studied. HCV appears to be a major cause of HCC in Japan, Italy, and Spain, but it seems to play a less important role in South Africa and Taiwan [321]. HCV-associated HCCs typically develop after 20-30 years of infection and are generally preceded by liver cirrhosis. Thus far, there is no evidence to suggest that HCV integrates into the cellular genome or has another direct role in the molecular pathogenesis of HCC. Rather, HCC develops via HCV-induced chronic liver injury, progressing to fibrosis and cirrhosis.

**Alcohol**

Among Western populations, alcohol-induced liver injury is the leading cause of chronic liver disease and liver cirrhosis and constitutes the most important HCC risk factor [426]. Regular daily consumption of > 50g ethanol in females or > 80g in males is generally considered sufficient to induce liver cirrhosis, although individual susceptibility can vary considerably. Patients who abuse alcohol and have coexisting liver disease from other causes (such as chronic HCV infection) have the highest risk for HCC development [341, 1432, 1508, 2106].

**Aflatoxin B1 (AFB1)**

AFB1 is a potent liver carcinogen in several animal species as well as in humans [2128]. It is produced by the moulds *Aspergillus parasiticus* and *Aspergillus flavus* which under hot and humid conditions in tropical countries typically contaminate grain, particularly ground nuts (peanuts). Dietary ingestion of high levels of aflatoxins presents a significant environmental hazard, particularly in the context of coexisting chronic HBV infection [1864, 1265] which leads to a more than 50-fold increase in the risk of developing HCC (Fig. 8.05). AFB1 is metabolized by cytochrome P450 enzymes to its reactive form, AFB1-7,9-oxide, which covalently binds to cellular macromolecules. Reaction with DNA at the N7 position of guanine preferentially causes a G:C > T:A muta-
tion in codon 249 of the TP53 tumour suppressor gene, leading to an amino acid substitution of arginine to serine (188). In Southern China and Subsaharan Africa, the two world regions with the highest levels of food contamination with AFB1, this mutation is present in > 40% of HCC (1265) and can be detected in serum DNA of patients with preneoplastic lesions and HCC (924). In regions where AFB1 levels in food are very low or undetectable, codon 249 transversion mutations are either very rare or absent.

Clinical features

Symptoms and signs
Most HCC patients have a past or current history of chronic liver disease from different causes (1681). The major clinical risk factor for HCC development is liver cirrhosis; 70–90% of HCCs develop in a macronodular cirrhosis (452). The presenting symptoms in patients with HCC include abdominal pain, general malaise, anorexia or weight loss, and nausea or vomiting. The symptoms are caused by the underlying chronic liver disease or cirrhosis and its clinical complications, or by the HCC itself. The most common clinical signs in HCC patients are hepatomegaly, ascites, fever, jaundice, and splenomegaly. The laboratory findings are in part determined by the underlying liver disease, which results in elevations of various liver enzymes, such as aspartate amino transferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), gamma-glutamyltranspeptidase (GGT), and bilirubin. These laboratory parameters are not HCC-specific, however. A significantly raised level of alpha-fetoprotein (AFP) of > 500 ng/ml, or continuously rising values even if less than 100 ng/ml, strongly suggest HCC. However, not all cases of HCC are associated with AFP elevation, and raised AFP may also be found in liver disease without HCC. Furthermore, in the early stages of HCC development, AFP levels do not closely correlate with clinical HCC stage. AFP levels, therefore, have to be interpreted individually in the context of other clinical symptoms and signs as well as imaging studies. Another HCC-specific marker is des-gamma-carboxyprothrombin (DCP), which is roughly equivalent to AFP. Occasionally, HCC patients develop a paraneoplastic syndrome, with erythrocytosis, hypoglycaemia or hypercalcaemia.

Imaging

Imaging studies are important in patient management for the identification and localization of HCC. Useful techniques include ultrasonography of the liver and the abdomen, colour Doppler ultrasonography, computed tomography (CT), lipiodol CT, magnetic resonance imaging, angiography, and possibly positron emission tomography. The standard imaging techniques are ultrasonography and CT. In most cases, these allow HCC detection and staging. In patients...
with suspected HCC metastases, a chest X-ray, bone scan, or other imaging modalities may be indicated.

**Liver biopsy**
The definitive diagnosis of HCC depends on the histological examination of the lesion, especially in AFP-negative patients. Ultrasound- or CT-guided percutaneous biopsy with a 22-gauge needle usually provides sufficient tissue for diagnosis with minimum risk of bleeding or seeding of tumour cells along the needle tract. However, in patients with significantly elevated AFP levels who are potentially eligible for HCC resection or liver transplantation, liver biopsy is not recommended to eliminate the residual risk of tumour cells spreading before surgery.

**Macroscopy**
Macroscopic features of HCCs vary depending on the size of the tumour and the presence or absence of liver cirrhosis. In general, most HCCs associated with liver cirrhosis tend to present as an expansile tumour with a fibrous capsule and intratumoural septa, while those without cirrhosis tend to be massive and non-encapsulated. Varying degrees of infiltrative growth, tumour thrombi in the portal veins, and intrahepatic metastases, which are common in advanced tumours, modify the gross appearance. Occasionally, numerous minute tumour nodules are distributed throughout the liver and may be difficult to be distinguished from regenerative nodules in liver cirrhosis. Hepatocellular carcinomas are occasionally pedunculated. Patients are usually females and the tumours are thought to arise in accessory lobes of the liver. Following surgical resection, the prognosis is excellent.

**Table 8.01**

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocyte (Dako)</td>
<td>Positive (most useful in diagnosis)</td>
</tr>
<tr>
<td>Polyclonal carcinoembryonic antigen</td>
<td>Positive (canalicular pattern)</td>
</tr>
<tr>
<td>Alpha fetoprotein</td>
<td>Positive or negative</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Positive or negative</td>
</tr>
<tr>
<td>Cytokeratins 8 and 18</td>
<td>Usually positive</td>
</tr>
<tr>
<td>Cytokeratins 7 and 19</td>
<td>Usually negative</td>
</tr>
<tr>
<td>Cytokeratin 20</td>
<td>Usually negative</td>
</tr>
<tr>
<td>Epithelial membrane antigen</td>
<td>Negative</td>
</tr>
<tr>
<td>BER EP4</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Tumours of the liver and intrahepatic bile ducts

Tumour spread

Invasion into the blood vessels, in particular into the portal vein, is a characteristic of HCC. Tumour thrombi in the portal veins are present in more than 70% of autopsies of advanced HCCs. Intrahepatic metastases is caused mostly by tumour spread through the portal vein branches. Tumour invasion into the major bile ducts is infrequent clinically, but found in about 6% of autopsy cases. Extrahepatic metastasis is mostly haematogenous, the lungs being the most common target.

Regional lymphatic metastasis is frequent though distant lymph nodes are rarely involved.

Histopathology

HCCs consist of tumour cells that resemble hepatocytes. The stroma is composed of sinusoid-like blood spaces lined by a single layer of endothelial cells. Unlike the sinusoidal endothelial cells in normal liver tissue, those of HCC are immunohistochemically positive for CD34 and factor-VIII-related antigen. Ultrastructural observation shows a basement-membrane-like structure between the endothelial cells and tumour cell trabeculae, and basement-membrane-like materials are immunohistochemically positive with antibodies for laminin and type IV collagen. Thus, the sinusoid-like blood spaces resemble capillary vessels. This phenotypic change of sinusoids is called 'capillarization' (472, 919, 917). In the sinusoidal blood spaces, varying numbers of macrophages, which show immunohistochemical positivity with anti-lysosome and CD68, are also present and resemble Kupffer cells in well differentiated tumours (1894). HCCs vary architecturally and cytologically. The different architectural patterns and cytological variants frequently occur in combination. Immunohistochemical features of HCC are summarized in Table 8.01.

Architectural patterns

Trabecular (plate-like). This pattern is the most common in well and moderately differentiated HCCs. Tumour cells grow in cords of variable thickness that are separated by sinusoid-like blood spaces. Well-differentiated tumours have a thin trabecular pattern and trabeculae become thicker with de-differentiation. Sinusoid-like blood spaces often show varying degrees of dilatation, and peliosis hepatis-like change are occasionally observed in advanced HCCs.

Pseudoglandular and acinar. HCC frequently has a glandular pattern, usually admixed with the trabecular pattern. The glandular structure is formed mostly by a single layer of tumour cells, and some glandular or acinar structures are formed by dilatation of the bile canaliculus-like structure between cancer cells. Pseudoglands frequently contain proteinaceous fluids, which often stain with PAS but do not stain with mucicarmine or Alcian blue. Bile may be present. Cystic dilatation of the pseudoglands sometimes occurs, such dilated glands are occasionally formed by degeneration of thick trabeculae. Generally, the glandular structure is smaller in well differentiated tumours than in moderately differentiated tumours.

Scirrhous. This uncommon type is characterised by marked fibrosis along the sinusoid-like blood spaces with varying degrees of atrophy of tumour trabeculae. It is observed even in small tumours. The scirrhous type should not be confused with cholangiocarcinoma or fibrolamellar carcinoma. Similar fibrotic changes occur following chemotheraphy, radiation, and transchemo arterial embolization. Such post-therapeutic fibrosis should be distinguished from the scirrhous variant.

The term 'sclerosing hepatic carcinoma'...
Sarcomatous change. HCC occasionally may of clear cell type. It is sometimes difficult to distinguish from metastatic renal cell carcinoma. This type is sometimes difficult to distinguish from metastatic renal cell carcinoma.

The tumour consists predominantly of cells with clear cytoplasm due to the presence of abundant glycogen. The tumour is called sarcomatoid HCC or sarcomatous HCC. In many cases, however, the sarcomatous change is present in a part of the tumour, and transitional features between trabecular HCC and sarcomatous components are frequent. Sarcomatous change is more frequent in cases with repeated chemo-therapy or transscleral arterial embolization (953), but it is also seen in small tumours. Most sarcomatous cells are positive for vimentin and alpha-fetoprotein. Some are also positive for cytokeratin.

Fatty change. Diffuse fatty change is most frequent in small, early-stage tumours less than 2 cm in diameter. Its frequency declines as tumour size increases, and fatty changes are rather infrequent in advanced tumours. Metabolic disorders related to hepatocarcinogenesis and insufficient blood supply in the early neoplastic stage have been suggested as a possible mechanism for the development of fatty change in small tumours, but a definite mechanism has not yet been determined.

Bile production. Bile is occasionally observed, usually as plugs in dilated canaluli or pseudoglands. When bile production is prominent, the tumour is yellowish in color and turns green after formalin fixation. Mallory hyaline bodies are intracytoplasmic, irregular in shape, eosinophilic and PAS-negative. They consist of aggregated intermediate filaments and show immunohistochemical positivity with anti-ubiquitin antibodies. Globular hyaline bodies are small, round, homogenous, and strongly acidophilic intracytoplasmic bodies. They are PAS-positive and stain orange to red with Masson trichrome stain. Immunohistochemically, they are often positive for alpha-1-antitrypsin. Pale bodies are intracytoplasmic, round to ovoid, amorphous and lightly eosinophilic. They represent an accumulation of amorphous materials in cystically dilated endoplasmic reticulum, and show distinct immunohistochemical positivity with anti-fibrinogen (1846). They are commonly seen in the fibrolamellar variant of HCC but are also found in the common types of HCC, especially in scirrhous HCC. Ground glass inclusions are rarely observed in tumours of HBsAg-positive patients. They stain with modified orcein, Victoria blue, or aldehyde fuchsin, and show immunohistochemical positivity with anti-HBsAg antibody. They are not seen in tumour casts in the portal vein or in extrahepatic metastases, and most are thought to be HBsAg-positive hepatocytes entrapped in a tumour.

Fibrolamellar HCC
This variant usually arises in non-cirrhotic livers of adolescents or young adults (353). It is rare in Asian and African countries but not so rare in Western countries. The tumour cells grow in sheets or small trabeculae that are separated by hyalinized collagen bundles with a characteristic lamellar pattern. They are large and polygonal and have a deeply eosinophilic and coarsely granular cytoplasm and distinct nuclei. The eosinophilic granularity is due to the presence of a large number of mitochondria. Pale bodies are frequently present, and stainable copper, usually in association with bile, can occasionally be shown.

Undifferentiated carcinoma
Undifferentiated carcinoma is rare, accounting for less than 2% of epithelial liver tumours. There is male preponderance but data on geographical distribution are not available. Localization, clinical features, symptoms and signs, and diagnostic procedures display no difference as compared to hepatocellular carcinoma. Undifferentiated carcinomas are postulated to have a worse prognosis (compared to HCC), although greater case numbers to support this are not available (351, 806).

Grading
According to histological grade, HCC is classified into well differentiated, moderately differentiated, poorly differentiated, and undifferentiated types.

Fig. 8.14 Nodule-in-nodule type of hepatocellular carcinoma. The border between early and advanced components is shown in C.
Well differentiated HCC. This is most commonly seen in small, early-stage tumours less than 2 cm in diameter and is rare in advanced tumours. The lesions are composed of cells with minimal atypia and increased nuclear/cytoplasmic ratio in a thin trabecular pattern, with frequent pseudoglandular or acinar structures and frequent fatty change. In most tumours larger than 3 cm in diameter, well-differentiated carcinoma is observed only in the periphery if at all.

Moderately differentiated HCC. The moderately differentiated type is the commonest in tumours larger than 3 cm in diameter and is characterized by tumour cells arranged in trabeculae of three or more cells in thickness. Tumour cells have abundant eosinophilic cytoplasm and round nuclei with distinct nucleoli. A pseudoglandular pattern is also frequent, and pseudoglands frequently contain bile or proteinaceous fluid.

Poorly differentiated HCC. This proliferates in a solid pattern without distinct sinusoid-like blood spaces, and only slit-like blood vessels are observed in large tumour nests. Neoplastic cells show an increased nuclear/cytoplasmic ratio and frequent pleomorphism, including bizarre giant cells. Poorly differentiated HCC is extremely rare in small early-stage tumours.

Malignant progression of HCC. HCC is known to vary histologically even within a single nodule. From the viewpoint of histological grade, most cancer nodules less than 1 cm in diameter have a uniform distribution of well differentiated cancerous tissues, whereas approximately 40% of cancer nodules 1.0-3.0 cm in diameter consist of more than 2 types of tissue of different histological grades (900). Less differentiated tissues are always located inside, surrounded by well differentiated tumour on the outside. The area of well differentiated neoplasm diminishes as the tumour size increases, and they are completely replaced by less-well-differentiated cancerous tissues when the tumour size reaches a diameter of around 3 cm. When less-well-differentiated areas within a well differentiated tumour nodule are growing expansively, the nodule often has a ‘nodule-in-nodule’ appearance (1275).

Multicentric development of HCC. HCCs frequently occur as multiple intrahepatic nodules. Genetic analysis of HBV integration pattern, chromosomal allele loss, and mutational inactivation of tumour suppressor genes has indicated multicentric independent development of these nodules (1647, 1392). These studies have shown that nodules apparently growing from portal vein tumour thrombi or satellite nodules surrounding a large main tumour represent intrahepatic metastases, whereas other nodules can be considered multicentric HCCs if they satisfy any of the following three criteria: (1) multiple, small early-stage HCCs or concurrent small early-stage HCCs and classical HCCs; (2) presence of peripheral areas of well differentiated HCC in both lesions or in the smaller ones; and (3) multiple HCCs of obviously different histology. Multicentric HCCs are associated with a high rate of tumour recurrence, even after curative resection, making treatment difficult and the prognosis poor. The presence of hyperplastic foci, small-cell dysplasia, an increase in the proliferative activity of non-tumourous liver tissue, or the progression of background liver disease are risk factors for multicentric HCC development (1902, 1859).
Precursor and benign lesions

Early stage HCC and precancerous lesions

Because of remarkable advances in imaging techniques and their widespread availability, increased numbers of small HCCs are detected clinically. Liver transplantation has become common treatment for liver cirrhosis and HCC in highly selected cases. Studies of resected and explant livers have revealed new information about the morphological characteristics of small early-stage HCC and equivocal nodular lesions. The most striking information is that HCC associated with cirrhosis probably evolves from precancerous lesions, and well differentiated HCC further progresses to a less differentiated form (952, 1646, 1882, 1645, 81).

Histological features of small early-stage HCC

Although some small HCCs show features of classical HCCs, most less than 1.5 cm in diameter are vaguely nodular with indistinct margins macroscopically and have a uniform distribution of well differentiated cancerous tissues. They are characterized by increased cell density with increased nuclear/cytoplasmic ratio, increased staining intensity (eosinophilic or basophilic), irregular thin trabecular pattern with a frequent acinar or pseudoglandular pattern, and fatty change (959, 1324). Diffuse fatty change of tumour cells is present in approximately 40% of tumours less than 2 cm in diameter. Many portal tracts are present within the tumour nodule, and tumour cell invasion into some portal tracts can be seen. At the tumour boundary, neoplastic cells proliferate as though they are replacing normal hepatocytes ('replacing growth'), and there is no capsule formation. These small tumours may correspond to 'carcinoma in-situ' or 'microinvasive carcinoma' of the liver. They tend to preserve the underlying liver structures, including portal tracts, receive portal blood supply, and do not show tumour blushing in angiographic examinations. In contrast, classical HCCs, even if small and well differentiated, show tumour blushing without portal flow (1883). Invasion into the stromal tissue can be sometimes identified, but vascular invasion and intrahepatic metastases are exceptional (1942). Moreover, these lesions are locally curable, have a favorable long-term outcome, and can be defined clinically as 'early HCC'.

Adenomatous hyperplasia (dysplastic nodules)

This lesion is characterized by marked enlargement of individual cirrhotic nodules that show thick liver cell plates. Small nodular lesions, most of which are below 1.5 cm in size, have been noticed in the livers of patients with HCCs that have been resected surgically and in explant cirrhotic livers. The nodules show variable atypia but lack features of definite malignancy. Macroscopically, most lesions are vaguely nodular and are not much different from small, well differentiated HCC with indistinct margins; it is almost impossible to distinguish them from cancer on the one hand or from large regenerative nodules on the other hand. Microscopically, they are characterized by a moderate increase in cell density with a slightly irregular trabecular pattern. There are many portal tracts within the nodules but no invasion into the portal tracts. These nodules sometimes contain distinct, well differentiated cancer foci. Many of them gave rise to distinct HCC in clinical follow-up studies (1882, 1645) and are, therefore, considered precancerous lesions. Some of
these nodules contain areas with a marked increase in cell density, a more irregular trabecular pattern, and frequent fatty change, characteristic of well-differentiated HCC but insufficient in extent to warrant such a diagnosis. These foci have been designated adenomatous hyperplasia (1080, 806) or dysplastic nodule (64). Additional terms used for these lesions include macroregenerative nodule, hyperplastic nodule and borderline lesions.

Morphological criteria for the differential diagnosis of adenomatous hyperplasia (dysplastic nodule, low grade), atypical adenomatous hyperplasia (dysplastic nodule, high grade) and early-stage HCC are still under discussion, mainly due to the lack of objective phenotypic or genotypic markers (1080, 64, 805).

Focal liver cell dysplasia (LCD)

Large cell dysplasia. The term liver cell dysplasia (LCD) was first coined by Anthony et al. (73) to describe a change characterized by cellular enlargement, nuclear pleomorphism and multinucleation of liver cells occurring in groups or occupying whole cirrhotic nodules. The change was found in only 1% of patients with normal livers, in 7% of patients with cirrhosis and in 65% of patients with cirrhosis and HCC. There was a strong relationship between LCD and HBsAg seropositivity (73). They concluded that the presence of LCD identified a group of patients at high risk for development of HCC, and that such patients should be followed by serial alpha-fetoprotein determinations.

Small cell dysplasia. Watanabe et al. (2068) have expanded the original definition of LCD to include a 'small cell' variant. The nuclear/cytoplasmic ratio is increased in small cell dysplasia, the ratio being between that of liver cancer and normal hepatocytes. This is in contrast to large cell dysplasia that has normal nuclear/cytoplasmic ratio. Also, multinucleation and large nucleoli are characteristic of large cell dysplasia but not small cell dysplasia. The small dysplastic cells have more of a tendency to form small round foci than large dysplastic cells. On the basis of their morphological and morphometric studies Watanabe et al. (2068) proposed the hypothesis that small cell dysplasia, rather than large cell dysplasia, is the precancerous lesion in man.

Hepatocellular adenoma

A benign tumour composed of cells closely resembling normal hepatocytes, which are arranged in plates separated by sinusoids. On gross examination, adenomas are soft, rounded, yellow or tan masses, often with areas of necrosis, haemorrhage, and fibrosis. A fibrous capsule is uncommon. Lesions are solitary in two-thirds of cases (511). When more than 10 lesions are encountered, a diagnosis of ‘adenomatosis’ has been recommended (511).

Adenoma is histologically composed of benign-appearing hepatocytes arranged in plates one or two cells in thickness (64, 803, 351, 71). Portal tracts are absent; the lesion is supplied by arteries and veins. In most cases, the tumour cells are uniform in size and shape, but occasionally, mild to moderate cytological variation may be seen. Mitotic activity is almost never found. Lipofuscin, fat and clear cell change (due to water or glycogen accumulation) are often present in the cytoplasm. Haemorrhage, infarction, fibrosis, and peliosis hepatis may be seen.

The differential diagnosis may be difficult with small biopsies. Features suggesting hepatocellular carcinoma include mitoses, high nuclear/cytoplasmic ratio, and plates more than 2 cells in thickness. Loss of a normal reticulin pattern is common in HCC whereas it is preserved in hepatocellular adenoma. HCC typically also shows diffuse capillarization using
CD34 immunostain in comparison with hepatocellular adenoma, which is either negative or shows only focal staining. Any evidence of ductular differentiation suggests a regenerative lesion such as focal nodular hyperplasia (FNH). Portal tracts within the peripheral portion of an adenoma may cause confusion.

The clinical setting is an important consideration in differential diagnosis. Most patients have a known risk factor, especially the use of contraceptive or anabolic steroids. Glycogen storage disease has also been associated. A diagnosis of adenoma should be made with caution in the absence of a known cause or in the presence of cirrhosis, where dysplastic nodules, carcinoma, and large regenerative nodules are far more frequent.

**Focal nodular hyperplasia (FNH)**

A lesion composed of hyperplastic hepatic parenchyma, subdivided into nodules by fibrous septa which may form stellate scars. The majority of FNH lesions are asymptomatic. Infarction may lead to abdominal pain but rupture is rare. When more than one FNH lesion is present the patient often has other features suggesting a systemic abnormality of angiogenesis, including hepatic haemangioma, intra-cranial lesions (vascular malformations, meningeoma, astrocytoma), and dysplasia of large muscular arteries (2054, 2055).

Most FNH lesions are solitary, firm, and lobulated nodules (Fig. 8.20). Lesions on the surface of the liver may protrude above the capsule. On cut section, they are circumscribed but not encapsulated, and paler than the surrounding liver. They typically consist of a central stellate scar surrounded by parenchymal nodules. Although most lesions are paler than the surrounding liver, a less common telangiectatic type has prominent blood-filled vascular spaces (64, 2055).

Histologically, FNH has a regular hierarchical structure defined by the arterial supply, which is usually a single artery with several orders of branching. Each terminal branch is located in the center of a 1 mm nodule. The large arteries often have degenerative changes in the media and eccentric intimal fibrosis. The arteries are found in a fibrous stroma without portal veins and usually without ducts. Proliferating ductules are usually present and may be prominent, commonly with visible features of chronic cholestasis (cholate stasis, copper accumulation) and neutrophil infiltration. Nascent FNH is a small region of hyperplasia or dilated sinusoids, recognised in the context of more definite FNH lesions. The rare telangiectatic type of FNH has a similar arterial supply but with markedly dilated sinusoids comprising at least a quarter of the lesion.

The histological differential diagnosis of FNH includes cirrhosis, in which septa contain portal areas, and hepatocellular adenoma. If the ductular component is not sampled, an unequivocal diagnosis may not be possible.

**Nodular regenerative hyperplasia (NRH)**

This condition is characterized by small regenerative nodules dispersed throughout the liver, associated with acinar atrophy with occlusive portal vascular lesions.

The liver has a normal weight and shape with a fine granularity of the capsular surface. The cut surface demonstrates a diffuse nodularity with most nodules measuring 1-2 mm. Occasionally, there are clusters of nodules up to several cm in diameter (64, 2056, 2053). The nodules are paler than the atrophic hepatic parenchyma which surrounds them.

Microscopically, the normal architecture is mildly distorted by widespread atrophy admixed with numerous mononuclear regenerative nodules. The nodules are composed of normal-appearing hepatocytes in plates 1-2 cells wide centered on portal tracts. The atrophic regions have small hepatocytes in thin trabeculae with dilated sinusoids. No significant parenchymal fibrosis is present but numerous small portal veins are obliterated.

Histological diagnosis of NRH depends on the recognition of a nodular architecture in the absence of parenchymal fibrosis. Nodularity may be suspected when there are two adjacent populations of hepatocytes that are normal and atrophic, respectively. This pattern is best appreciated on a reticulin stain. Macro-nodular, incomplete sepal, or regressed cirrhosis commonly have regions with this configuration, especially in livers with healed portal vein thrombosis (1742). These forms of cirrhosis are difficult to exclude in a small biopsy.

**Genetic susceptibility**

Several rare inherited disorders of metabolism are associated with an increased risk of developing HCC.

**Carbohydrate metabolism disorders**

In glycogen storage disease (GSD), especially type 1 (323), HCC can develop within preexisting adenomatous lesions (137). Distinction between benign and malignant tumours is difficult, since GSD-associated HCCs are well differentiated, and atypical lesions (‘nodule within nodule’ pattern and Mallory bodies) are found commonly in GSD-related adenomas (137, 1527). Cirrhosis is never present.
Protein metabolism disorders

In alpha-1-antitrypsin deficiency (A1ATD) (1501), only male A1ATD homozygotes are at high risk for HCC, even in the absence of cirrhosis (473). Further-more, cholangiocarcinomas and combined hepatocellular and cholangiocarcinomas in non-cirrhotic livers of adult patients with heterozygous A1ATD of PiZ type are well documented (2207). HCC occurs in 18%-35% of patients with hereditary tyrosinaemia (2082, 1996). The non-tumourous liver is cirrhotic and often dysplastic (808). HCC has further been reported in 14% of adult-onset cases of hypercitrullinemia in the absence of cirrhosis (1324A).

Disorders of porphyrin metabolism

The prevalence of HCC in porphyria cutanea tarda (PCT) ranges from 7% to 47% (1755, 1073). Almost all HCCs occur in male patients older than 50 years with preexisting cirrhosis and a long-standing history of symptomatic PCT. The involvement of additional risk factors is likely (396). Rarely, PCT evolves as a paraneoplastic syndrome associated with HCC (1389). Other hepatic porphyrinas are occasionally associated with HCC (1073, 53).

Chronic cholestatic syndromes.

HCC may complicate paucity of intrahepatic bile ducts (1028, 99, 898), biliary atresia (2082), congenital hepatic fibrosis (2082), and Byler syndrome (1550).

Metal-storage diseases.

The relative risk for the development of primary liver cancer in inherited haemochromatosis has been calculated as being greater than 200 (181, 1351, 487). HCC develops usually in patients with cirrhosis (403, 951), even after iron depletion (403). Iron-free foci (defined as clear-cut, sublobular, hepatocytic nodules free of iron or having significantly less iron than the surrounding parenchyma) may represent an early step of HCC in genetic haemochromatosis (403). In Wilson’s disease, HCC is present only exceptionally (293).

Hepatic vascular anomalies.

Cases of HCC have been occasionally reported in hereditary haemorrhagic telangiectasia (831) and ataxia-telangiectasia (2083).

Extrahepatic inherited conditions.

Several cases of HCC have been reported in familial adenomatous polyposis of the colon (1000). Occasional cases have also been described in neurofibromatosis, Soto syndrome, and situs inversus (2082). Cases of hepatocellular adenomas and HCC in young patients with Fanconi anaemia have been also described (1033).

Genetics

Clonal expansion and subclonal progression during multistage carcinogenesis

Most HCCs are associated with HBV or HCV infection. Clonal expansion of hepatocytes is initiated during regeneration in damaged livers; a clonal integration pattern of HBV was identified in cirrhotic nodules (2170). Advanced HCCs often emerge as ‘nodule-in-nodule’ HCCs; the early and advanced HCC components of a ‘nodule-in-nodule’ type HCC showed identical integration patterns of HBV (1968, 1647). Ordinary HCCs with increased cell proliferation and neovascularization are subsequently formed.

TP53 mutations

Point and frameshift mutations of the TP53 tumour suppressor gene are frequent in areas with low exposure to aflatoxin B1 (1393). TP53 mutations were most frequent and were clustered in domains IV and V in poorly differentiated HCCs, but were less frequent and equally distributed in domains II to V in well or moderately differentiated HCCs in one study (1393). Analysis of ‘nodule-in-nodule’ type HCC shows that TP53 mutation is associated with the progression of HCC from an early to a more advanced stage (1392, 1391). In areas with high exposure to AFB1, mutation of the third nucleotide in codon 249 of TP53 is frequent (758, 188), suggesting that some TP53 mutations can be fingerprints of past exposure to a given carcinogen (see ‘Aetiology’, above).

HBV X

The HBV X open reading frame is frequently integrated and expressed. HBV X [MLS1] can bind to the C terminus of p53, inhibits its sequence-specific DNA binding and transcriptional activation and suppresses p53-induced apoptosis.
HBV X may affect a wide range of p53 functions and thereby contribute to the molecular pathogenesis of HCCs. HBV X further inhibits nucleotide excision repair [858].

**Oncogenes**

Mutational activation of known oncogenes is rare. Point mutations of the c-KRAS gene and coamplification of the cyclin D1 gene were detected in only 3% (1967) and 11% (1355) of HCCs, respectively. Recent findings, obtained by comparative genomic hybridization of amplified sequences mapped to 11q12, 12p11, and 14q12, may lead to the characterization of new genes involved in hepatocarcinogenesis (1163).

**Wnt pathway and beta-catenin**

In the wingless/Wnt pathway, mutations of the β-catenin gene were detected in 26-41% of HCCs (386, 760). Nuclear accumulation of β-catenin was observed by immunohistochemistry in all HCCs with β-catenin mutations (760). No mutation was detected in mutation cluster region of the APC gene in any of 22 HCCs analysed (760). Deletions on chromosomes 1p, 4q, and 16p were significantly associated with the absence of β-catenin mutation, which suggests that a β-catenin-activating mutation is involved in cases without chromosomal instability (1041).

**Genetic instability and allelic loss**

Frequent allelic losses have been found at loci on 1p, 4q, 5q, 8p, 11p, 13q, 16q, and 17p by restriction fragment length polymorphism analysis (2046, 200, 1970, 2203, 546, 1759, 459, 460). Loss of heterozygosity (LOH) on chromosome 16 was detected in 52% of informative cases (1970). The common deleted region lay between HP (16q22.1) and CTRB (16q22.3-q23.3) loci (1970). These losses occurred more frequently in HCCs with poor differentiation, of large size, and with metastasis, and were not detected in early-stage HCCs (1970). LOH on chromosome 16 may be involved in enhancement of tumour aggressiveness. Recent development of microsatellite markers allows an extensive allelotypic analysis [2171, 163, 1307, 1515, 659, 108]. Detailed deletion mapping revealed that allelic loss at a 1-cM-interval flanked by D4S2921 and D4S2930 loci on 4q35 was frequent in HCCs with poor differentiation and of large size (108). Inactivation of unidentified tumour suppressor genes within this region may contribute to progression of HCCs. Microsatellite instability is another pathway for genetic instability other than chromosomal instability. Only 11% of HCCs had replication errors in one study, and the incidence of replication errors correlated significantly with poor differentiation and portal vein involvement of HCCs (961).

**Cell cycle regulators**

The gene product of p16INK4 binds to cyclin-dependent kinase (CDK) 4 and prevents CDK4 from forming an active complex with cyclin D. p16 protein loss may contribute to both early- and late-stage hepatocarcinogenesis, because it was observed in 22% of early-stage HCCs and occurred approximately twice as often in advanced HCCs as in early-stage HCCs (763). Neither p16 homozygous deletion/mutation nor loss of p16 mRNA expression was observed in HCCs lacking p16 protein (763), suggesting post-transcriptional inactivation. DNA methylation around the promoter region of the p16 gene has been observed in HCCs (1187). Expression of p21WAF1/CIP1 mRNA, a universal CDK inhibitor, was reduced markedly in 38% of HCCs (762). p21 mRNA expression of HCCs with TP53 mutations was significantly lower than that of HCCs with wild-type TP53 (762). p21 expression is regulated predominantly by dependence on TP53 in HCCs. mRNA expression of p27Kip1, another universal CDK inhibitor, was reduced in 52% of HCCs (764).

**Fig. 8.24** Correlation between TP53 mutation at codon 249, dietary exposure to aflatoxin B1, and regional incidence of hepatocellular carcinoma (HCC).

**Fig. 8.25** DNA sequencing autoradiographs of β-catenin mutations in HCC (760).

**Fig. 8.26** Nuclear accumulation of β-catenin protein in neoplastic hepatocytes in a HCC associated with HCV infection (760).
Growth factors

Transforming growth factor-beta (TGF-β) was expressed at a high level in 82% of HCCs and was associated with HBV infection [756]. TGF-β expression could be part of a chain of events by which HBV contributes to the development of HCCs. TGF-β, TGF-β2, and TGF-β3 showed marked mRNA overexpression in HCCs [818, 12]. TGF-β was expressed in both tumour and stroma cells; this suggests that TGF-β may play a role in hepatocarcinogenesis through both autocrine and paracrine pathways [12]. The mannose-6-phosphate / insulin-like growth factor-II receptor (M6P/IGF2R) regulates cell proliferation through interactions with TGF-β and IGF II. A study from the U.S.A. reported LOH at the M6P/IGF2R locus and mutations of the remaining allele were identified in 61% and 55% of HCCs, respectively [2149], while no M6P/IGF2R mutations were detected in HCCs from Japanese patients [2031].

Angiogenic growth factors.

mRNA expression of basic fibroblast growth factor (bFGF) was high in HCCs [1746]. Strong immunoreactivity for bFGF was localised in the progressed HCC component but not in the early-stage component of a nodule-in-nodule HCC [712]. Acquisition by cancer cells of the capacity to produce bFGF could be an important event in the stepwise progression of HCC. Greater mRNA expression of vascular endothelial growth factor (VEGF) was found in 60% of HCCs and was significantly correlated with the intensity of tumour staining in angio-grams. This suggests that VEGF contributes significantly to angiogenesis during hepatocarcinogenesis [1239, 1869].

DNA methylation

DNA methyltransferase (DNMT1) mRNA expression was significantly higher in chronic hepatitis and cirrhotic nodules than in normal livers, and was even higher in HCCs [1863]. Indeed, DNA hypermethylation at D16S32, TAT, and D16S7 loci on chromosome 16 is frequently present even in chronic hepatitis and cirrhotic nodules [885]. The incidence and degree of aberrant DNA methylation increased in HCCs compared with chronic hepatitis and cirrhotic nodules [885]. Aberrant DNA methylation may participate even in the early developmental stages of HCCs by predisposing some loci to allelic loss or silencing specific genes [885].

DNA methylation around the promoter region of the E-cadherin tumour suppressor gene, which is located on 16q22.1, was detected in 46% of chronic hepatitis and cirrhotic nodules and in 67% of HCCs [884]. DNA hypermethylation around the promoter region correlated significantly with reduced E-cadherin expression in HCCs [884]. The HIC-1 (hypermethylated-in-cancer) tumour suppressor gene was identified at the D17S5 locus. DNA hypermethylation at the D17S5 locus was detected in 44% of chronic hepatitis and cirrhotic nodules and in 90% of HCCs [883]. LOH at this locus, which was preceded by DNA hypermethylation, was detected in 54% of HCCs [883]. The HIC-1 mRNA expression level of chronic hepatitis and cirrhotic nodules was significantly lower than that of normal livers, and that of HCCs was even lower [883]. Thus, silencing of tumour suppressor genes by aberrant DNA methylation is a significant event during hepatocarcinogenesis.

Prognosis and predictive factors

The prognosis of patients with HCC is generally very poor, particularly in cases with AFP levels greater than 100 ng/ml at the time of diagnosis, partial or complete portal vein thrombosis, and presence of a TP53 mutation [45, 1861]. Spontaneous regression has been reported rarely. Most studies report a five-year survival rate of less than 5% in symptomatic HCC patients. HCCs are largely resistant to radio- and chemotherapy. Long-term survival is likely only in patients with small, asymptomatic HCC that can be treated by surgical resection, including liver transplantation, or non-surgical methods, including percutaneous ethanol or acetic acid injection and percutaneous radiofrequency thermal ablation.
Intrahepatic cholangiocarcinoma

Definition
An intrahepatic malignant tumour composed of cells resembling those of bile ducts. Intrahepatic (or peripheral) cholangiocarcinoma (ICC) arises from any portion of the intrahepatic bile duct epithelium, i.e. from intrahepatic large bile ducts (the segmental and area ducts and their finer branches) or intrahepatic small bile ducts. Cholangiocarcinoma arising from the right and left hepatic ducts at or near their junction is called hilar cholangiocarcinoma and is considered an extrahepatic lesion.

Epidemiology

Incidence and geographical distribution
ICC is a relatively rare tumour in most populations but second among primary malignant liver tumours; about 15% of liver cancers are estimated to be ICC (61, 2162, 1467). The frequency of ICC among all liver cancers ranges from 5% in males and 12% in females in Osaka, Japan, to 90% in males and 94% in females in Khon Kaen, Thailand (1467, 1471) (Fig. 8.29).

The highest incidence of ICC is found in areas of Laos and North and Northeast Thailand suffering from endemic infection with the liver fluke, Opisthorchis viverrini. In 1997, the age standardized incidence of ICC in Khon Kaen (Thailand) was 88 per 100,000 in males and 37/105 in females (1467, 1471). About 90% of the histologically confirmed cases of liver cancer in Khon Kaen are ICC, and almost all the ICC cases were found to be related to chronic O. viverrini infection (2006, 2007). In the Clonorchis sinensis endemic area in Korea, there is also a high incidence of liver cancer with truncate incidence rates (35-64 years group) of 75 per 100,000 in males and 16 per 100,000 in females (23). About 20% of liver cancers in Pusan, Korea, are ICC (871).

Time trends
In both endemic and non-endemic areas, there have been no significant changes in the incidence of ICC in recent years (61). It is less than 10 years since O. viverrini drug therapy was initiated; since it probably takes 30 years for ICC to complicate opisthorchiasis, the trends of ICC are probably not likely to change in the next decade (2007, 2009).

Age and sex distribution
Patients with ICC are elderly, with no clear sex differences. ICC occurs at rather older ages than hepatocellular carcinoma (HCC) in most clinical series (1419).

Aetiology

Although many aetiological factors have been characterized, the cause of ICC remains speculative in many cases.

Parasites
Clonorchis sinensis parasitizes the bile ducts of millions of individuals in the Far East, particularly China and Korea (1467). Early reports from Hong Kong have shown that 65% of patients with ICC were infected by C. sinensis (747). However, the incidence of C. sinensis infection in the general population was also similarly high at that time (308). ICC from this cause appears to less frequent in recent years. By contrast, infection of O. viverrini is continuing in Northeast Thailand, and...
the evidence for the role of opisthorchiasis in the induction of ICC is compelling (2009, 2008). Carcinogenesis is probably related to the length and severity of infection, the host’s immune response, and other variables such as ingestion of dietary carcinogens, for example nitrosamines. In northeast Thailand, several carcinogenic N-nitroso compounds and their precursors exist at low levels in the daily diet (1230). In addition, endogenous nitrosamine formation by liver fluke infection has been reported (1673). Both exogeneous and in situ nitrosamine formation may lead to DNA alkylation and deamination (1346). It seems that the presence of parasites induces DNA damage and mutations as a consequence of the formation of carcinogens/free radicals and of cellular proliferation of the intrahepatic bile duct epithelium.

**Hepatolithiasis**

Hepatolithiasis (recurrent pyogenic cholangitis), which is not uncommon in the Far East, is also associated with ICC (1857, 1321). It is frequently observed in clonorchiasis (746) but not in opisthorchiasis. Most of these cases are associated with calcium bilirubinate stones; a few cases with cholesterol stones have also been reported. Patients with intrahepatic stones and ICC have a significantly longer duration of symptoms and a higher frequency of previous biliary surgery.

**Inflammatory bowel disease and primary sclerosing cholangitis**

Patients with primary sclerosing cholangitis (PSC) and ulcerative colitis (UC) have a predisposition to develop colorectal neoplasia and also bile duct carcinoma, including ICC (672, 1993, 194, 2078).

**Epstein-Barr virus (EBV) infection**

Rare examples of ICC have a lymphoepitheliomatous, undifferentiated pattern. Clonal EBV has been found in such cases (757, 2025).

**Non-biliary cirrhosis**

There are several reports of ICC arising in non-biliary cirrhosis, particularly hepatitis virus-related liver cirrhosis (2159, 1940). HCV is frequent in such cases and ICC is usually of a smaller, mass-forming type. Such ICC and combined hepatocellular-cholangiocarcinomas share apomucin profiles (1669), suggesting that these two tumours have a similar or common histogenesis, or that ICC associated with cirrhosis might be the result of exclusive proliferation of the cholangiocellular component of the combined type. Genotypes of hepatitis B and C viruses have been shown in cholangiocarcinoma cells (2049, 1787).

**Deposition of Thorotrast**

Thorotrast is a radioactive α-particle emitter that was widely used as a radiopaque intra-arterial contrast medium between 1930 and 1955. ICC has been recorded in many patients with prior exposure to Thorotrast. The data suggest that the chronic alpha-irradiation may be the causative factor, with latent periods ranging from 25 to 48 years.

**Biliary malformations and other lesions**

ICC may arise rarely in solitary unilocular or multiple liver cysts, congenital segmental or multiple dilatation of the bile ducts (Caroli disease), congenital hepatic fibrosis, and von Meyenburg complexes (736, 2165).

**Clinical features**

The site of the tumour, its growth pattern and the presence or absence of stricture or obstruction of the biliary tree are responsible for the variable clinical features of ICC.

**Symptoms and signs**

General malaise, mild abdominal pain and weight loss are frequent clinical symptoms. When the carcinoma infiltrates the hilar region, jaundice and cholangitis become manifest. ICCs, particularly those arising from the small bile ducts, may go unnoticed until they have attained a large size. The liver is enlarged to a lesser extent, ascites is less common, and signs of portal hypertension are absent or minimal. Patients with unrelieved obstruction of the intrahepatic large bile ducts may die from complications, e.g. liver failure or sepsis.

**Imaging**

Advanced cases of ICC show mixed growth and spreading patterns with intrahepatic metastases. Computerized tomography (CT) images of ICC usually show a lobulated or fused hypodense space-occupying lesion with peripheral enhancement, probably due to central hypocellular dense fibrosis. Secondary dilated ducts around the tumour are detectable by CT and ultrasonography. A focal area of carcinoma involving the bile duct wall is identifiable by spiral CT. Endoscopic retrograde, transhepatic or magnetic resonance cholangiography is a useful adjunct for the identification of the level of biliary obstruction and secondary bile duct dilatation. ICCs at relatively early and surgically resectable stages are classifiable into three representative types of growth patterns (1080), and these patterns, which are evaluable by imaging studies, can be useful for the preoperative staging of.

**Fig. 8.30 Ultrasonography of an intrahepatic cholangiocarcinoma. A hyperechoic mass is present in a dilated bile duct.**
tumour extent and for designing the surgical procedure. The mass forming type is an expansile nodule and is the most common. The tumour borders between the cancerous and noncancerous portions are relatively clear. The contrast enhanced CT scan shows a low-density tumour with peripheral ring-like increased density. The periductal-infiltrating type, which is usually associated with biliary stricture, is relatively common. The tumour exhibits diffuse infiltration along the portal pedicle, which resembles hilar or extrahepatic bile duct carcinoma. The contrast enhanced CT demonstrates a small cancerous enlargement of the portal pedicle, or a mass central to the dilated peripheral ducts. The anatomical location of the involved ducts can be evaluated by caliber changes or the rigidity of the bile duct on high-quality cholangiographic images. The intraductal growth type (intraductal papillary cholangiocarcinoma) is less common. These tumours are confined within the dilated part of an intrahepatic large bile duct, with no or mild extension beyond the bile duct walls. Some tumours of this type of ICC might have arisen from biliary papillomatosis after malignant transformation. Marked localized dilatation of the affected duct is detectable by ultrasound or CT. Cholangiography shows filling defects in the biliary tract, due to polypoid tumours and mucin.

**Macroscopy**

ICC can arise from any portion of the intrahepatic bile duct epithelium (61, 1418). Lesions are gray to gray-white, firm and solid, although some tumours show intraductal growth, sometimes with polyp formation. Typical tumours consist of variably sized nodules, usually coalescent. Portal tract infiltration is also seen. Central necrosis or scarring are common, and mucin may be visible on the cut surfaces. ICC cases involving the hepatic hilum are hardly distinguishable from hilar cholangiocarcinoma, and such cases show cholestasis, biliary fibrosis, and cholangitis with abscess formation. ICC is not often noted in a non-cirrhotic liver.

**Tumour spread**

ICC shows direct spread into the surrounding hepatic parenchyma, portal pedicle and bile duct. Intrahepatic metastases develop in nearly all cases at a relatively advanced stage. Vascular invasion is a frequent histological finding relatively early, suggesting the development of early metastasis. The incidence of metastases in regional lymph nodes is higher than in HCC. Blood-borne spread occurs later, to the lungs in particular; other sites include bone, adrenals, kidneys, spleen, and pancreas.
On rare occasions, the tumour shows extensive intraluminal spread of bile ducts throughout the liver. The tumour cells can also infiltrate into the peribiliary glands of the intrahepatic large bile ducts and their conduits. It may be difficult to distinguish this lesion from reactive proliferated peribiliary glands histologically.

**Histopathology**

Most ICCs are adenocarcinomas showing tubular and/or papillary structures with a variable fibrous stroma (326). There is no dominant histological type of ICC in cases associated with liver flukes or hepatolithiasis when compared to those in non-endemic areas.

**Adenocarcinoma**

This common type of ICC growing in the hepatic parenchyma and portal pedicle reveals a significant heterogeneity of histological features and degree of differentiation. At an early stage, a tubular pattern with a relatively uniform histological picture is frequent. Cord-like or micro-papillary patterns are also seen. The cells are small or large, cuboidal or columnar, and can be pleomorphic. The nucleus is small and the nucleolus is usually less prominent than that of HCC. The majority of cells have a pale, eosinophilic or vacuolated cytoplasm; sometimes, the cells have a clear and abundant cytoplasm or resemble goblet cells.

ICC arising from the large intrahepatic bile ducts shows intraductal micropapillary carcinoma and in situ like spread along the biliary lumen. Once there is invasion through the periductal tissue, the lesion may be well, moderately, or poorly differentiated adenocarcinoma, with considerable desmoplasia and stenosis or obliteration of the bile duct lumen.

Infrequently, a papillary tumour growing in the duct lumen is supported by fine fibrovascular cores. Cholangio-carcinoma arising from the intrahepatic peribiliary glands (1914) mainly involves these glands, sparing the lining epithelial cells at an early stage.

An abundant fibrous stroma is an important characteristic of ICC. Activated perisinusoidal cells (myofibroblasts) are incorporated into the tumour, producing extracellular matrix proteins that lead to fibrosis (1913). Usually, the central parts of the tumour are more sclerotic and hypocellular, while the peripheral parts show more actively proliferating carcinoma cells. On rare occasions, the tumour cells are lost in a massive hyaline stroma, which may be focally calcified.

The secretion of mucus in one form or another can be demonstrated in the majority of tumours by mucicarmine, diastase-PAS and Alcian blue staining. Mucus core (MUC) proteins 1, 2, and 3 are detectable in the carcinoma cells (1264, 1670). ICC cells can immunoreexpress cytokeratins 7 and 19, CEA, epithelial membrane antigen, and blood group antigens. Bile may be present occasionally in ICC as a result of destruction of the bile ducts or entrapment of non-neoplas-
Intrahepatic cholangiocarcinoma


Lymphoepithelioma-like carcinoma. Two cases of undifferentiated lymphoepitheliomatous lesions with adenocarcinoma have been reported (757, 2025). In these cases, EBV-coded nuclear RNAs were demonstrable.

Clear cell variant. This lesion is characterized by distinct overgrowth of clear cells in an acinar or tubular pattern. The tumour cells are PAS reactive and diastase resistant, indicating the presence of mucin.

Mucoepidermoid carcinoma. This variant resembles the tumour arising in salivary glands.

Differential diagnosis

Hepatocellular carcinoma. Some ICCs grow in a cord-like pattern reminiscent of the trabeculae of HCC. The cords are always separated by a connective tissue stroma rather than by sinusoids; canaliculi and bile are also absent. Almost all
ICCs are diffusely positive for cytokeratin 7 and 19, whereas only a few cases of HCC are positive. The hepatocyte antigen (Dako) is expressed by HCC but not by ICC.

**Metastatic carcinoma.** ICC cannot be distinguished histologically from metastatic adenocarcinoma of biliary tract or pancreatic origin. Occasionally, dysplastic changes in neighbouring bile ducts suggest intrahepatic origin. In addition, diffuse expression of cytokeratin 20 favours metastatic adenocarcinoma, particularly from colon [1141]. While cytokeratin 7 is common in ICC, it is not so common in metastatic carcinoma.

**Sclerosing cholangitis.** Periductal spread of ICC may be difficult to distinguish from sclerosing cholangitis, particularly when only biopsy material is available. The most important criteria for the diagnosis of malignancy are severe cytological atypia, random and diffuse infiltration of the duct wall by the neoplastic cells, and perineural invasion.

**Grading**

ICCs can be graded into well, moderately, and poorly differentiated adenocarcinoma according to their morphology. In the case of the common type of adenocarcinoma, well-differentiated lesions form relatively uniform tubular or papillary structures, moderately differentiated tumours show moderately distorted tubular patterns with cribriform formations and/or a cord-like pattern, while the poorly differentiated show severely distorted tubular structures with marked cellular pleomorphism.

**Precursor and benign lesions**

**Biliary intraepithelial neoplasia (dysplasia)**

This is characterized by abnormal epithelial cells with multilayering of nuclei and micropapillary projections into the duct lumen [2078, 1322]. The abnormal cells have an increased nuclear/cytoplasmic ratio, a partial loss of nuclear polarity, and nuclear hyperchromasia. They are divisible into low-grade and high-grade lesions. Some peribiliary glands may also be dysplastic. Cell kinetic studies have disclosed proliferative activity of intraepithelial neoplasia between that of hyperplasia and ICC, and telomerase activity is demonstrable in both intraepithelial and invasive carcinoma [1915, 1440]. Carcinoembryonic antigen (CEA) is focally detectable in biliary intraepithelial neoplasia and more so in carcinoma [1322]. These findings support the concept of a hyperplasia–dysplasia–carcinoma sequence in the biliary tree [1989]. In liver fluke infestations, the bile ducts first show desquamation of the epithelial lining with subsequent hyperplasia, periductal fibrosis, inflammation and goblet cell metaplasia [2008, 913]. The neoplastic transformation from hyperplasia in bile ducts to ICC through dysplastic changes is demonstrable in opisthorchiasis. In hepatolithiasis, the findings are those of cholangitis, with proliferation of the biliary epithelial lining and peri-biliary glandular cells, and multiple foci of biliary intraepithelial neoplasia [1323]. Hyperplasia and intraepithelial neoplasia of the duct epithelium in livers with Thorotrust-deposition and congenital biliary anomalies may be also related to the development of ICC [1626, 2165]. It has been reported in patients with PSC that biliary intraepithelial neoplasia could evolve from papillary hyperplasia [2078, 1107]. However, recent experience at orthotopic liver transplantation of PSC has detected hardly any in situ or invasive neoplastic foci.

**Biliary papillomatosis**

Dilated intrahepatic and extrahepatic bile ducts are filled with papillary or villous excrencences, which microscopically are papillary or villous adenomas with delicate fibrovascular stalks covered with a columnar or glandular epithelium [806, 351]. They are soft and white, red or tan. In some cases, there are variable degrees of cellular atypia and multilayering of nuclei. Occasionally, foci of in situ or invasive carcinoma are encountered [1340].

**Von Meyenburg complex (biliary microhamartoma)**

The lesions are small, up to several mm in diameter. They are usually multiple and
are adjacent to a portal area. Within a fibrous or hyalinized stroma, they present as irregular or round ductal structures that appear somewhat dilated and have a flattened or cuboidal epithelium. The lumina contain proteinaceous or bile-stained secretion. These lesions carry little or no malignant potential [736, 673].

**Bile duct adenoma (BDA)**

BDA is usually single and subcapsular, and is white and well circumscribed but non-encapsulated. BDA is usually less than 1 cm in size, and is composed of a proliferation of small, normal appearing ducts with cuboidal cells that have regular nuclei and lack dysplasia [44]. These ducts have no or little lumen and can elaborate mucin. Their fibrous stroma shows varying degrees of chronic inflammation and collagenization. Enclosed in the lesion are normally spaced portal tracts. They are considered to be a focal reaction to injury.

BDA and peribiliary glands share common antigens, suggesting a common line of differentiation [136]. Occasionally, BDA contains periductular endocrine cell clusters [1384].

In addition, there are several atypical BDA with a neoplastic nature. Biliary adenofibroma is characterized by a complex tubulocystic biliary epithelium without mucin production, together with abundant fibroblastic stromal components [1972]. Its expansive growth, and foci of epithelial tufting, cellular atypia and mitoses favor a neoplastic process.

**Intrahepatic peribiliary cysts**

In chronic advanced liver disease and biliary anomalies, and also in normal livers, multiple cysts may be seen around the intrahepatic large bile ducts [1319, 1320]. They are visible by ultrasound or CT. These cysts are derived from peribiliary glands and should be differentiated from ICC clinically and histologically.

**Diffuse and multifocal hyperplasia of peribiliary glands**

Diffuse, severe, macroscopically recognizable dilatation and hyperplasia of the peribiliary glands of intrahepatic and extrahepatic bile ducts is a rare condition [1319, 437]. Some ducts may be cystically dilated. Lack of familiarity with this lesion could lead to an erroneous diagnosis of a well-differentiated cholangiocarcinoma. It occurs in apparently normal livers and also in acquired liver diseases.

**Molecular genetics and genetic susceptibility**

Mutations of the RAS and TP53 genes are the most common genetic abnormalities identified in ICC. The incidence of KRAS mutations ranges from 100% and 60% among British [1054] and Japanese patients respectively [1878, 1402], to 4% among Thai patients [1510]. Taiwanese and Korean patients show an intermediate frequency [1037, 887]. The most frequently mutated position in the KRAS...
gene is codon 12 involving GGT (glycine) to GAT (aspartic acid). Less frequent mutations have been identified in codon 13, involving GGT (glycine) to GAT (aspartic acid) and codon 61, involving CAA (glutamine) to CAC (histidine) [1402, 1969, 1511].

TP53 mutations occur between exons 5 to 8, the most common change being G to A transitions [887, 1511, 907, 1848]. The mutations are random with no specific hot spot, being mostly missense mutations and less frequently nonsense mutations [887]. p53 protein is immunohistochemically detectable in carcinoma cells in more than 70% of ICC cases.

KRAS and TP53 mutations correlate with the gross morphology of ICC [1969, 1401]; a higher prevalence of KRAS gene alterations is found in the periductal and spicular forming infiltrating subtype compared to the slower growing, non-invasive mass-forming type. TP53 mutations are prominent in the mass-forming type of ICC.

TP53 and KRAS mutations correlate with the variable incidence of KRAS mutations in different populations of ICC may reflect different aetiologies. O. viverrini infection and increased consumption of nitrates and nitrites are contributing factors in Thailand where the incidence of KRAS abnormalities is low [2025, 1446]. Overexpression of c-erbB-2 occurs in one fourth to about two thirds of carcinoma of the biliary tract, and may be used as a phenotypic marker for neoplastic transformation [1912]. Membranous expression of E-cadherin, alpha-catenin, and beta-catenin is reduced in a majority of ICC and this down-regulation correlates with ICC at high-grade [91]. Overexpression of MET, the receptor for hepatocytes growth factor, occurs in ICC and correlates with tumour differentiation, being poorly expressed in poorly differentiated tumours [1912]. It also correlates with the markedly increased proliferation indices seen in precancerous glands and cholangiocarcinoma. Biliary epithelial cells are continuously exposed to genotoxic insults such as chronic inflammation and hydrophobic bile acids, predisposing to oncogenic mutations. Progression to malignancy may be due, in part, to failure in activating apoptosis and deleting cells with genetic damages [263]. The anti-apoptotic protein bcl-2, is overexpressed in ICC [281] and telomerase activity is detectable in carcinoma cells of almost all ICC cases.

**Prognosis and predictive factors**

Early detection of ICC is difficult, and the overall prognosis after resection is poor compared with that of HCC. Lymph node spread, vascular invasion, positive margins and bilobar distribution are associated with a high recurrence rate and a poor prognosis. One study found the 5-year survival rate was 39% in patients with mass-forming tumours and 69% for intraductal tumours while no patients with mass-forming plus periductal-infiltrating tumours survived > 5 years [2161]. Histologically, squamous cell or sarcomatous elements and mucinous variants confer a poor prognosis [1312, 1313]. Patients with well differentiated ICC seem to survive longer than those with moderately or poorly differentiated ones. A few cases of well differentiated ICC with bland features resembling bile duct adenoma show a good prognosis [522]. MUC 2 protein expression is relatively frequent in well differentiated ICC, suggesting a somewhat more favourable prognosis [1915].

Lymph node metastasis is a significant prognostic factor [2160]. The 5-year survival rate in patients with lymph node metastases is significantly lower than that in patients without lymph node metastasis (51%). In liver fluke-associated ICC, survival after right hepatectomy is better than after left hepatectomy, and is not associated with tumour size [1990]. In addition, multiple tumour masses have a poor prognosis. Concomitant hepatolithiasis prevents precise diagnosis preoperatively, and precipitates biliary sepsis. Long-term post-surgical survival of patients with stone-containing ICC compared to ICC alone is controversial [291, 1849]. ICC found in non-biliary cirrhosis is usually detectable as a small nodule during follow-up of hepatitis virus-related cirrhosis, and is treatable with hepatectomy [2159].
Combined hepatocellular and cholangiocarcinoma

**Definition**
A rare tumour containing unequivocal elements of both hepatocellular and cholangiocarcinoma that are intimately admixed.

This tumour should be distinguished from separate hepatocellular carcinoma and cholangiocarcinoma arising in the same liver (605). Such tumours may be widely separated or close to each other (‘collision tumour’).

**Epidemiology**
This tumour type comprises less than 1% of all liver carcinomas. There are similar geographical distribution differences as for hepatocellular carcinoma and a similar age and sex distribution.

**Tumour spread and staging**
Some studies have found a higher frequency of lymph node metastasis compared with HCC.

**Macroscopy**
Gross inspection does not show significantly different morphology compared to hepatocellular carcinoma. In tumours with a major cholangiocarcinomatous component with fibrous stroma, the cut surface is firm.

**Histopathology**
Combined hepatocellular and cholangiocarcinoma is the term preferred for a tumour containing both hepatocellular and distinct or separate cholangiocarcinoma. The presence of both bile and mucus should be sought in the combined tumour. This category should not be used for tumours in which either form of growth is insufficiently differentiated for positive identification.

Hepatocytes preferentially express cytokeratins 8 and 18 and, like duct epithelial cells, cytokeratins 7 and 19. However, the different patterns of expression are not as clear-cut in these tumours. For practical purposes, demonstration of bile canaliculi by polyclonal CEA (mixed biliary glycoproteins) combined with Hep Par immunoeexpression is sufficient for the diagnosis of a hepatocellular carcinomatous component, and that of neutral epithelial mucin by the PAS-diastase reaction for the diagnosis of a cholangiocarcinomatous component (1046, 1456, 667).

**Prognostic factors**
Some authors have reported patients with combined hepatocellular and cholangiocarcinoma having a worse prognosis as compared with patients with HCC.

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**Fig. 8.42** Combined hepatocellular carcinoma and cholangiocarcinoma arising in non-cirrhotic liver tissue in a patient with heterozygous Piz type alpha-1 antitrypsin deficiency. **A** Pale, homogeneous cut surface. **B** Microscopic, showing glandular areas.

**Fig. 8.43** Combined hepatocellular and cholangiocarcinoma. **A** Microtrabecular HCC and cholangiocarcinoma with desmoplastic response. **B** Border zone between HCC and cholangiocarcinoma.
Bile duct cystadenoma and cystadenocarcinoma

Definition
A cystic tumour either benign (cystadenoma) or malignant (cystadenocarcinoma), lined by epithelium with papillary infoldings that may be mucus-secreting or, less frequently, serous. Lesions arise from ducts proximal to the hilum of the liver. They differ from tumours that arise in cystic congenital malformation and in parasitic infections and hepatolithiasis.

Epidemiology
Bile duct cystadenoma and cystadenocarcinoma are rare. Cystadenoma is seen almost exclusively in females, with cystadenocarcinoma appearing equally in males and females. The average age of patients is 50-60 years.

Clinical features
Patients often present with abdominal pain and mass. A few patients have jaundice. Elevated serum levels of tumour marker CA 19-9 may occur. Imaging techniques show multilocular cystic tumour(s), occasionally with tiny papillary folds in the cystic wall.

Macroscopy
The cysts are usually multilocular and typically range from 5 to 15 cm diameter. In cystadenocarcinoma, a large papillary mass may occur as well as solid areas of grey-white tumour in a thickened wall.

Tumour spread and staging
Cystadenocarcinomas show intrahepatic spread and metastasis to regional lymph nodes in the hepatoduodenal ligament. Distant metastases occur most frequently in the lungs, the pleura and the peritoneum. Staging is performed according to the TNM Classification of liver tumours.

Histopathology
Cystadenomas are usually multilocular and are well defined by a fibrous capsule, which may contain smooth muscle fibres. The contents of the locules are either thin, opalescent or glairy fluid, or mucinous semisolid material. Two histological variants are recognized. The mucinous type is more common and is lined by columnar, cuboidal, or flattened mucus-secreting epithelial cells resting on a basement membrane; polypoid or papillary projections may be present. About 5% of the tumours reveal neuroendocrine differentiation, as identified by expression of chromogranin and synaptophysin. Subjacent to the basement membrane is a cellular, compacted mesenchymal stroma, which in turn is surrounded by looser fibrous tissue. This mesenchymal component is seen only in females and has been likened to ovarian stroma. The stromal cells express vimentin, and there are many cells that express smooth muscle actin. A xan-
thogranulomatous reaction, with foam cells, cholesterol clefts and pigmented lipofuscin-containing macrophages, may be present in the cyst wall. The *serous* type consists of multiple, small locules lined by a single layer of cuboidal cells with clear cytoplasm containing glycogen. The cells rest on a basement membrane but are not surrounded by the mesenchymal stroma typical of the mucinous variety. Squamous metaplasia may also occur.

*Cystadenocarcinoma* are usually multilocular and contain mucoid fluid. Malignant change may not involve all of the epithelium lining the cyst; it is usually multifocal. The tumours are so well defined that complete removal can usually be achieved with good prognosis. Differentiation from intrahepatic bile duct cystadenoma depends on the demonstration of cytological (particularly nuclear) atypia, mitosis, and invasion of the underlying stroma.

Some bile duct cystadenocarcinomas may be misdiagnosed as bile duct cystadenomas because insufficient sampling results in tumour morphology showing no cytological features of malignancy or invasion of the underlying stroma (351, 809, 1268, 2096).

**Prognostic factors**

The prognosis of patients with biliary duct cystadenocarcinomas is good if a curative resection is possible. The course of patients with unresectable tumours seems to be better than of patients with cholangiocarcinoma (71).
Hepatoblastoma

Definition
A malignant embryonal tumour with divergent patterns of differentiation, ranging from cells resembling fetal epithelial hepatocytes, to embryonal cells, and differentiated tissues including osteoid-like material, fibrous connective tissue and striated muscle fibers.

Epidemiology
Hepatoblastoma is the most frequent liver tumour in children. Four percent of hepatoblastomas are present at birth, 68% in the first two years of life and 90% by five years of age. Only 3% are seen in patients over 15 years of age. A recent increase in the incidence of tumours in infants with birth weights below 1500 grams has been reported (776, 777, 1899). There is a male predominance of 1.5:1 to 2:1, but no racial predilection.

Localization
Hepatoblastomas occur as a single mass in 80% of cases, involving the right lobe in 57%, the left lobe in 15% and both lobes in 27% of patients (1838). Multiple masses, seen in the other 20% of cases, may occur in either or both lobes.

Clinical features
Hepatoblastomas are often noted by a parent or physician as an enlarging abdomen in the infant that may be accompanied by weight loss or anorexia. Less frequently nausea, vomiting, and abdominal pain are present. Jaundice is seen in 5% of cases. Rarely, tumour cells may produce human chorionic gondotrophin, leading to precocious puberty with pubic hair, genital enlargement and deepening voice, noted most prominently in young boys.

Hepatoblastoma is accompanied by anemia in 70% of cases and by thrombocytosis in 50%, with platelet counts exceeding 800 x 10^9/L in nearly 30% of cases (1717). Alpha fetoprotein (AFP) is elevated in about 90% of patients at the time of diagnosis. The levels of AFP parallel the course of the disease, falling to normal levels after complete removal of the tumour and rising with recurrence of the lesion. AFP levels may be normal or only slightly elevated with small cell undifferentiated hepatoblastoma. Caution must be taken in evaluating the levels of AFP in younger infants since the 'adult' level of AFP (< 25ng/mL) is not reached until approximately six months of age. Other laboratory abnormalities can include elevated levels of serum cholesterol, bilirubin, alkaline phosphatase, and aspartate aminotransferase (10).

Imaging
Computed tomography (CT) shows single or multiple masses within the liver, which in 50% of cases display calcification (1233). Magnetic resonance imaging (MRI) along with CT can help differentiate hepatoblastoma from infantile haemangioendothelioma, mesenchymal hamartoma, and hepatocellular carcinoma by demonstrating cystic or vascular features peculiar to each lesion (1999). MRI may also be used to characterize epithelial and mesenchymal components of hepatoblastoma (1533).

Macroscopy
Hepatoblastomas vary in size from 5 to 22 cm in diameter and from 150 to 1,400 g in weight. Single and multiple lesions may be well circumscribed, the edge of the lesion being separated from the normal liver by an irregular pseudocapsule. Pure fetal hepatoblastomas have the tan-brown colour of normal liver, while mixed hepatoblastomas display a variety of colours from brown to green to white. The lesions are often nodular and bulge from the cut surface. Areas of necrosis and haemorrhage are usually present and may appear as soft or gelatinous, brown to red tissue (1837).

Tumour spread
At clinical manifestation, 40-60% of hepatoblastomas are either very large or involve both lobes to the extent that they are considered unresectable (1839). Preoperative chemotherapy, however, reduces the size of the lesion in nearly 85% of these patients to a size that renders it resectable. Tumour spread includes local extension into the hepatic...
Histopathology

Hepatoblastomas display a distinct variety of histological patterns that may be present in varying proportions. Some tumours are composed entirely of uniform fetal epithelial cells or small undifferentiated cells, while others contain a variety of tissue types including hepatic fetal epithelial and embryonal cells, fibrous connective tissue, osteoid-like material, skeletal muscle fibers, nests of squamous epithelial cells, and cells with melanin pigment.

Pure fetal epithelial differentiation

Accounting for nearly one third of cases, the fetal epithelial pattern is composed of thin trabeculae of small cuboidal cells resembling the hepatocytes of the developing fetal liver. These cells contain a small round nucleus with fine nuclear chromatin and an indistinct nucleolus. The cytoplasm varies from finely granular to clear, reflecting variable amounts of glycogen and lipid which can impart a ‘light and dark’ pattern to the lesion when viewed at lower magnifications. Canalliculi may be seen between hepatocytes of the 2-3 cell layer trabeculae, but only rarely is bile stasis present. In biopsies taken before preoperative chemotherapy, foci of extramedullary haematopoiesis (EMH) composed of clusters of erythroid and myeloid precursors may be present in the sinusoids (2023). Sinusoids are lined by endothelial and Kupffer cells which show a more diffuse staining with UEA-1 and anti-CD34 than the focal staining of the sinusoidal endothelial cells of normal liver (1630). The fetal phenotype has been significantly associated with both diploid DNA nuclear content and low proliferative activity assessed by flow cytometry and PCNA labeling index (1640).

Combined fetal and embryonal epithelial

Approximately 20% of cases display a pattern combining fetal epithelial cells and sheets or clusters of small, ovoid to angulated cells with scant amounts of dark granular cytoplasm surrounding a nucleus with increased nuclear chromatin. The cells display little cohesiveness but may cluster into pseudorosette, glandular or acinar structures. These small, round, blue cells resemble the blastemal cells seen in nephroblastomas, neuroblastosomas and other ‘embryonal’ tumours in children. While often intermixed with the fetal epithelial cells, the foci of embryonal cells, which are devoid of glycogen and lipid, can be identified by their absence of staining with PAS or oil red-O stains. Mitotic activity is more pronounced in the embryonal areas, and associated with a low TGF-alpha expression. EMH, in the absence of preoperative chemotherapy, may also be noted (925).

Macrotabecular

In about 3% of cases of fetal or fetal and embryonal epithelial hepatoblastomas, areas containing broad trabeculae (6-12 or more cells in thickness) are present. These macrotabeculae are composed of fetal and embryonal epithelial cells and a third, larger cell type characterized by more abundant cytoplasm and larger nuclei. Although the trabeculae resemble those seen in the pseudoglandular type of hepatocellular carcinoma, the cells display only mild hyperchromasia and anisocytosis, and mitotic activity is low. The term ‘macrotabecular’ is applied to only those cases in which macrotabeculae are a prominent feature of the lesion. If only an isolated focus is present, the

| Table 8.03 Staging of Hepatoblastoma according to the Children’s Cancer Study Group (CCSG) classification. |
|-------------------|-------------------------|
| Stage I           | Complete resection      |
| Stage II          | Microscopic residual    |
|                   | Negative nodal          |
|                   | involvement             |
|                   | No spilled tumour       |
| Stage III         | Gross residual or       |
|                   | Nodal involvement or    |
|                   | Spilled tumour          |
| Stage IV          | Metastatic disease      |

Table 8.04 Clinical syndromes, congenital malformations and other conditions that have been associated with hepatoblastoma.

- Absence of left adrenal gland
- Acardia syndrome
- Alcohol embryopathy
- Beckwith-Wiedemann syndrome
- Beckwith-Wiedemann syndrome with opsonocytopenia
- Bilateral talipes
- Budd-Chiari syndrome
- Cleft palate, macroglossia, dysplasia of ear lobes
- Cystathioninuria
- Down syndrome, malrotation of colon, Meckel diverticulum, pectum excavatum, intrathoracic kidney, single coronary artery
- Duplicated ureters
- Fetal hydrops
- Gardner syndrome
- Goldenhar syndrome – oculoauriculovertebral dysplasia, absence of portal vein
- Hemihyper trophy
- Heterotopic lung tissue
- Heterozygous α1-antitrypsin deficiency
- HIV or HBV infection
- Horseshoe kidney
- Hypoglycaemia
- Inguinal hernia
- Isosexual precocity
- Maternal clomiphene citrate and Pergonal
- Meckel diverticulum
- Oral contraceptive, mother
- Oral contraceptive, patient
- Osteoporosis
- Persistent ductus arteriosus
- Polyposis coli families
- Prader-Willi syndrome
- Renal dysplasia
- Right-sided diaphragmatic hernia
- Schinzel-Geidion syndrome
- Synchronous Wilms tumour
- Trisomy 18
- Type 1a glycogen storage disease
- Umbilical hernia
- Very low birth weight

Hepatoblastoma 185
classification is based on the epithelial or mixed epithelial/mesenchymal components present.

**Small cell undifferentiated**
Hepatoblastomas composed entirely of noncohesive sheets of small cells resembling the small blue cells of neuroblastoma, Ewing sarcoma, lymphoma, and rhabdomyosarcoma are called small cell undifferentiated hepatoblastomas and amount to about 3% of the tumours. This type is believed to represent the least differentiated form of hepatoblastoma [602].

While often difficult to identify as hepatic in origin, the presence of small amounts of glycogen, lipid and bile pigment, along with cytoplasmic cytokeratin, helps separate this lesion from metastatic small cell tumours. The cells are arranged as solid masses with areas of cellular pyknosis and necrosis and high mitotic activity. Sinusoids are present but decreased in amount compared to the fetal epithelial pattern, and there is pronounced intracellular expression of extracellular matrix proteins and large numbers of fibers immunoreactive for collagen type III [1629].

Mixed epithelial and mesenchymal
The largest number of hepatoblastomas (44%) display a pattern combining fetal and embryonal epithelial elements with primitive mesenchyme and mesenchymally derived tissues. Of these mixed tumours, 80% have only immature and
mature fibrous tissue, osteoid-like tissue and cartilaginous tissue, in addition to the epithelial cells. The other 20% contain additional elements.

The mesenchymal elements of the ‘simple’ mixed tumour are interspersed with the fetal and embryonal epithelial elements. The primitive mesenchymal tissue consists of a light myxomatous stroma containing large numbers of spindle-shaped cells with elongate nuclei. The cells may display a parallel orientation with collagen fibers and cells resembling young fibroblasts. More mature fibrous septa with well differentiated fibroblasts and collagen may also be seen.

Islands of osteoid-like tissue composed of a smooth eosinophilic matrix containing lacunae filled with one or more cells are the hallmark of the mixed lesion. Rarely, they are the only ‘mesenchymal’ component noted in a predominantly fetal epithelial hepatoblastoma. In fact, the ‘osteoid’ material is positive for alpha 1-antitrypsin, alpha 1-antichymotrypsin, alpha fetoprotein, carcinoembryonic antigen, chromogranin A, epithelial membrane antigen, vimentin and S-100 protein, suggesting an origin from epithelial cells {10, 2058, 1629}. The cells within the lacunae, while ‘osteoblast-like’ with angulated borders, abundant eosino-philic cytoplasm and one or more round or oval nuclei, may in some areas blend with adjacent areas of embryonal epithelial cells, further supporting their epithelial origin. Cartilaginous material may also be present.

**Mixed with teratoid features**

In addition to the features noted in the ‘simple’ mixed epithelial/mesenchymal hepatoblastoma, about 20% of lesions will display additional features, including striated muscle, bone, mucinous epithelium, stratified squamous epithelium, and melanin pigment {1839}. These tissues may occur separately or be admixed with others. It is important to differentiate these teratoid features from a true teratoma, which does not contain fetal and embryonal epithelial hepatoblastoma areas. There is, however, a single case report of a discrete cystic teratoma contiguous to a hepatoblastoma {331}.

**Staging**

These is no official TNM classification for hepatoblastoma but a TNM-type system has been proposed {332}. The Children’s Cancer Study Group (CCSG) classification is widely used. While 40-60% of patients are considered inoperable at the time they are first seen and 10-20% have pulmonary metastases, preoperative chemotherapy and transplantation for the more extensive lesions have resulted in resectability for nearly 90% of cases.

**Precursor lesions and benign tumours**

Precursor lesions of hepatoblastoma have not been identified, but hepatoblastoma must be differentiated from other liver tumours and pseudotumours that occur in the same age period. Infantile haemangioendothelioma, the most commonly occurring benign tumour of the liver, is seen almost exclusively in the first year of life and presents as an asymptomatic mass or, less frequently, as congestive heart failure due to rapid shunting of blood through the liver {1708}. MRI and arteriography are helpful in establishing the diagnosis. Mesenchymal hamartoma, another benign lesion, occurs during the first 2-3
years of life and presents as a rapidly enlarging mass due to accumulation of fluid within cysts formed in the mesenchymal portion of the lesion [1841]. CT and MRI are useful in defining the cystic nature of the lesion. Focal nodular hyperplasia and nodular regenerative hyperplasia may be seen in the first few years of life but are more common in older children [1839]. Hepatocellular adenoma is rarely seen in the first 5-10 years of life, but may be difficult to differentiate from a pure fetal epithelial hepatoblastoma.

Genetic susceptibility
Congenital anomalies are noted in approximately 5% of patients (Table 8.04) and include renal malformations such as horseshoe kidney, renal dysplasia and duplicated ureters, gastrointestinal malformations such as Meckel diverticulum, inguinal hernia and diaphragmatic hernia, and other disparate malformations such as absent adrenal gland and heterotopic lung tissue. Other syndromes with an increased incidence of hepatoblastoma include Beckwith-Wiedemann syndrome, trisomy 18, trisomy 21, Acardia syndrome, Goldenhar syndrome, Frader Will syndrome, and type 1a glycogen storage disease [1585]. Hepatoblastoma and familial adenomatous polyposis (FAP) are associated due to germline mutation of the adenomatous polyposis coli (APC) gene. FAP kindreds include patients with hepatoblastoma who have an APC gene mutation at the 5’ end of the gene [267, 578]. Alterations in APC have also been noted in cases of hepatoblastoma in non-familial adenomatous polyposis patients [1390].

Molecular genetics
Cytogenetic abnormalities include trisomy for all or parts of chromosome 2, trisomy for chromosome 20 and loss of heterozygosity (LOH) for the telomeric portion of 11p (11p15.5). The material lost on 11p is always of maternal origin [43]. LOH has also been observed on the short and long arms of chromosome 1 with a random distribution of parental origin for chromosome arm 1p and a paternal origin for chromosome arm 1q [970]. TP53 overexpression has been described in several cases, but TP53 mutations in exons 5 to 9 are infrequent [1406]. Increased copy numbers of c-met and K-sam proto-oncogenes and cyclin D1 genes have been described in a case of hepatoblastoma in an adult patient [977]. The presence of oval cell antigen has been demonstrated in hepatoblastomas, which supports the stem cell origin of these tumours [1631].
Prognosis and predictive factors
Prognosis is directly affected by the ability to resect the lesion entirely, i.e. to attain Stage I or II following the initial surgery [332, 446, 648, 2024]. Chemotherapy and transplantation have allowed resectability in 90% of cases, increasing the overall survival to 65-70%.

Survival in Stage I is nearly 100% and Stage II survival approaches 80%. AFP levels are useful in predicting outcome by observing their response to surgery and chemotherapy [1997]. AFP levels of 100 to 1,000,000 ng/mL at initial diagnosis are associated with a better prognosis than if they are < 100 or > 1,000,000ng/mL. Other factors positively influencing prognosis include tumour confined to one lobe, fetal epithelial growth pattern, and multifocal dissemination (rather than unifocal growth pattern in the liver with distant metastases and vascular invasion) [2022].
Lymphoma of the liver

A. Wotherspoon

Definition
Primary lymphoma of the liver is defined as an extranodal lymphoma arising in the liver with the bulk of the disease localized to this site. Contiguous lymph node involvement and distant spread may be seen but the primary clinical presentation is in the liver, with therapy directed to this site.

Epidemiology
Primary lymphoma of the liver is rare [796]. It is mainly a disease of white middle aged males [1043, 1217] although an occasional case has been reported in childhood [1557]. Most are B-cell lymphomas. Primary hepatosplenic T-cell lymphomas have a different distribution. Patients are almost always male (M:F approximately 5:1) but are usually younger with a mean age of 20 years (range 8-68 years) [334]. In contrast to primary lymphoma, secondary liver infiltration is a frequent occurrence, being present in 80-100% of cases of chronic leukaemia, 50-60% of cases of non-Hodgkin lymphoma and approximately 30% of cases of multiple myeloma [2042, 261].

Aetiology
A proportion of cases are associated with hepatitis C virus infection with and without mixed cryoglobulinaemia [390, 56, 1257, 90, 371, 1625, 311]. Other lymphomas have been reported arising within a background of hepatitis B virus infection [1441, 1183]. HIV infection [1680, 1516] and primary biliary cirrhosis [1535].

Clinical features
The most frequent presenting symptoms are right upper abdominal/epigastric pain or discomfort, weight loss and fever [1043, 1217]. Most cases are solitary or multiple masses within the liver which may be misdiagnosed as a primary liver tumour or metastatic cancer [1043, 1217]. Some cases have been reported with diffuse infiltration of the liver associated with hepatomegaly but without a discrete mass, simulating hepatic inflammation [668].

Hepatosplenic T-cell lymphomas present with hepatosplenomegaly, usually without peripheral lymphadenopathy and without lymphocytosis. There is almost always thrombocytopenia and most patients are anaemic. Liver function tests are usually abnormal with moderate elevation of levels of transaminases and alkaline phosphatase. Serum lactate dehydrogenase level may be very high [334].

Histopathology

B-cell lymphoma
The majority of primary hepatic lymphomas are of diffuse large B-cell type with sheets of large cells with large nuclei and prominent nucleoli. Phenotypically these characteristically express the pan B-cell markers CD20 and CD79a. Occasional cases of Burkitt lymphoma have been described [759] in which the morphology is typical of Burkitt lymphoma encountered elsewhere in the digestive tract. Immunohistopathologically the cells express CD20, CD79a and CD10. They are generally negative with antibodies to bcl-2 protein. Low-grade B-cell lymphomas of MALT type have also been described. These are characterized by a dense lymphoid infiltrate within the portal tracts. The atypical lymphoid cells have centrocyte-like cell morphology and surround reactive germinal centres. Lymphoepithelial lesions are formed by the centrocyte-like cells and the bile duct epithelium, and these may be highlighted by staining with anti-cytokeratin antibodies. Nodules of normal liver may be entrapped within the tumour. The cells express pan-B-cell markers CD20 and CD79a and are negative for CD5, CD10 and CD23. There is no expression of cyclinD1 [797, 1143, 923]. Secondary involvement of the liver by chronic lymphocytic leukaemia and B-cell non-Hodgkin lymphoma tends to show a distribution involving the portal triads although nodular infiltration may also be seen with non-Hodgkin lymphoma and multiple myeloma [2042].

Hepatosplenic T-cell lymphoma
This is characterized by infiltration of the sinusoids by a monomorphic population of medium sized cells with a moderate amount of eosinophilic cytoplasm. The nuclei are round or slightly indented with moderately dispersed chromatin and contain small, usually basophilic, nucleoli. There may be mild sinusoidal dilation and there are occasional pseudo-peliotic lesions. Perisinusoidal fibrosis may be present. Portal infiltration is variable. A similar sinusoidal pattern of infiltration is seen in the spleen and bone marrow both of which are usually involved by the lymphoma at diagnosis [486, 334]. The cells are usually immunoreactive for CD2, CD3, CD7 and the cytotoxic granule related protein TIA-1. There is usually no expression of CD5. The majority of cases are CD4+/CD8+ although some are CD4-/CD8+ [486, 334]. A CD4+ variant has been described very infrequently [771]. There is variable expression of CD16 and CD56. All cases are negative for βF1 and positive with antibodies for the T-cell receptor δ.

Genetics
Hepatosplenic T-cell lymphoma exhibits rearrangement of the T-cell receptor γ gene. EBV sequences have not been detected [334]. Cytogenetic studies have shown isochromosome 7q in a number of cases and in some this has been present as the sole cytogenetic abnormality [524, 48].

Prognosis
The prognosis of primary hepatic lymphoma is generally poor. Chemotherapy or radiotherapy alone has been reported to be ineffective but combination modalities, including surgery in resectable cases, can give relatively good results [1043, 1217]. Hepatosplenic T-cell lymphomas are very aggressive, with a mean survival of 1 year [334] although the CD4+ subtype may be associated with a slightly longer survival [771].
Mesenchymal tumours of the liver

Definition
Benign and malignant tumours arising in the liver, with vascular, fibrous, adipose and other mesenchymal tissue differentiation.

ICD-O codes
ICD-O codes, terminology, and definitions largely follow the WHO ‘Histological Typing of Soft Tissue Tumours’ (2086).

Imaging
Imaging studies establish the presence of a space-occupying lesion or lesions in the liver, and may provide a diagnosis or differential diagnosis (1565). Biopsy of a mass is, however, needed for a definitive diagnosis (806).

Mesenchymal hamartoma
Mesenchymal hamartoma is a ‘tumour malformation’ that develops in utero. It accounts for 8% of all liver tumours and pseudotumours from birth to 21 years of age, but during the first two years of life it represents 12% of all hepatic tumours and pseudotumours, and for 22% of the benign neoplasms (1839). It usually manifests in the first two years of life and there is a slight male predominance. Lesions involve the right lobe in 75% of cases, the left lobe in 22% and both lobes in 3%. Presentation is typically with abdominal swelling, but rapid accumulation of fluid in the tumour can cause sudden enlargement of the abdomen (1841). Macroscopically, it is usually a single mass that can attain a large size (up to 30 cm or more). Mesenchymal hamartoma has an excellent prognosis after resection. The fate of untreated lesions is not known but there is no convincing evidence of malignant transformation.

Histopathology. This tumour-like lesion is composed of loose connective tissue and epithelial ductal elements in varying proportions. Grossly, the cut surfaces exhibit solid, pink-tan areas and cysts containing a clear fluid. Histologically, the connective tissue is typically loose and oedematous with a matrix of acid mucopoly-

Fig. 8.61 Mesenchymal hamartoma. A Cut surface shows cysts and tan-white tissue. B Mixture of bile ducts, mesenchymal tissue and blood vessels. C Bile ducts display a ductal plate malformation; the primitive mesenchymal tissue consists of loosely arranged stellate cells. In addition to blood vessels, the tumour also contains liver cells (top). D Fluid accumulation in the mesenchymal mimics lymphangioma, but the spaces lack an endothelial lining.

Table 8.05
Presentation of mesenchymal tumours of the liver.

<table>
<thead>
<tr>
<th>Mode of Presentation</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic (incidental finding)</td>
<td>Any</td>
</tr>
<tr>
<td>Upper abdominal mass +/- hepatomegaly</td>
<td>Mesenchymal hamartoma, cavernous haemangioma</td>
</tr>
<tr>
<td>Sudden increase in size of tumour</td>
<td>Febrile illness with weight loss</td>
</tr>
<tr>
<td>Acute abdominal crisis from rupture</td>
<td>Inflammatory pseudotumour, embryonal sarcoma, angiosarcoma</td>
</tr>
<tr>
<td>Budd-Chiari syndrome</td>
<td>Cavernous haemangioma, angiosarcoma, epithelioid haemangioendothelioma</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Epithelioid haemangioendothelioma</td>
</tr>
<tr>
<td>Cardiac tumour syndrome</td>
<td>Infantile haemangioendothelioma</td>
</tr>
<tr>
<td>Consumption coagulopathy</td>
<td>Embryonal sarcoma</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>Cavernous haemangioma, infantile haemangioendothelioma</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>Solitary fibrous tumour</td>
</tr>
<tr>
<td>Liver failure</td>
<td>Epithelioid haemangioendothelioma, inflammatory pseudotumour</td>
</tr>
<tr>
<td>Obstructive jaundice</td>
<td>Epithelioid haemangioendothelioma, angiosarcoma</td>
</tr>
<tr>
<td>Lung metastases</td>
<td>Inflammatory pseudotumour</td>
</tr>
</tbody>
</table>
saccharide, or it is collagenous and arranged concentrically around the ducts. Fluid accumulation leads to separation of the fibres with formation of lymphangioma-like areas and larger cavities. The epithelial component consists of bile ducts that may be tortuous and occasionally dilated. The ducts often are arranged in a ductal-plate-malformation pattern. Islets of liver cells without an acinar architecture may be present. Numerous arteries and veins are scattered throughout, as are foci of extramedullary haematopoiesis.

Infantile haemangioendothelioma

This lesion is defined as a benign tumour composed of vessels lined by plump endothelial cells, intermingled with bile ducts, that are set in a fibrous stroma. Infantile haemangioendothelioma accounts for about one fifth of all liver tumours and pseudotumours from birth to 21 years of age. It usually presents in the first two years of life, when it represents 40% of all tumours and pseudotumours and 70% of the benign ones [1839]. It occurs more frequently in females (63%) than in males. Infantile haemangioendothelioma is a localized ‘tumour malformation’ that develops in utero. There may be a variety of associated congenital anomalies, including hemihypertrophy and Cornelia de Lange syndrome. Patients may develop congestive heart failure or consumption coagulopathy, with or without an abdominal mass [397, 1708], and about 10% have haemangiomas of the skin.

Grossly, infantile haemangioendothelioma forms a single large mass (55%) or involves the entire liver by multiple lesions (45%). The single tumours have a maximum diameter up to 14 cm while the multiple lesions are often less than a centimeter. The large, single lesions are red-brown or red-tan, often with haemorrhagic or fibrotic centers and focal calcification. The small lesions appear spongy and red-brown on sectioning.

Histopathology. Lesions are composed of numerous small vascular channels lined by plump endothelial cells usually arranged in a single layer, but multilayering and tufting can occur. The vessels are supported by a scanty fibrous stroma that may be loose or compact. Larger cavernous vessels with a single layer of flat endothelial cells are often present in the centre of the larger lesions; these vessels may undergo thrombosis with infarction, secondary fibrosis and calcification. Other characteristic features of infantile haemangioendothelioma are small bile ducts scattered between the vessels, and foci of extramedullary haematopoiesis. Endothelial cells in the tumour express Factor VIII-related antigen and CD34.

Prognosis. Infantile haemangioendothelioma has an overall survival of 70%; adverse risk factors include congestive heart failure, jaundice and the presence of multiple tumours (1708). Single tumours are generally resected although some 5-10% undergo spontaneous regression. Hepatic artery ligation or transcatheter embolization are other therapeutic modalities. There are occasional reports of transformation of infantile haemangioendothelioma to angiosarcoma [1708].

Cavernous haemangioma

This is the most frequently occurring benign tumour of the liver. The reported incidence varies from 0.4 to 20%, the highest figure being the result of a thorough prospective search (892). It is more frequent in females, and occurs at all ages but is least common in the paediatric age group. Although it usually presents in adults, it is thought to be a hamartomatous lesion. It is known to increase in size or even rupture during pregnancy, and also may enlarge or recur in patients on oestrogen therapy. Consumption coagulopathy may occur. Cavernous
Haemangiomas are not known to undergo malignant change. Only large symptomatic tumours (‘giant’ haemangiomas) that can replace most of the liver. They are usually single, and soft or fluctuant. When sectioned they partially collapse due to the escape of blood and have a spongy appearance. Recent haemorrhages, organized thrombi, fibrosis and calcification may be seen.

**Histopathology.** Lesions are typically composed of blood-filled vascular channels of varied size lined by a single layer of flat endothelial cells supported by fibrous tissue. Thrombi in various stages of organization with areas of infarction may be present, and older lesions show dense fibrosis and calcification. In sclerosed haemangiomas, most or all of the vessels are occluded and sometimes are only demonstrable by stains for elastic tissue.

**Angiomyolipoma**
The lesion is defined as a benign tumour composed of variable admixtures of adipose tissue, smooth muscle (spindled or epithelioid), and thick-walled blood vessels. The age range of angiomyolipoma is from 30-72 years, with a mean of 50 years [1373]. It is seen equally in males and females [604]. A small number are associated with tuberous sclerosis. Angiomyolipomas are usually single, with 60% located in the right lobe, 30% in the left lobe, 20% in both lobes and 8% in the caudate lobe [1373]. They are sharply demarcated but not encapsulated, fleshy or firm and, when sectioned, with a homogeneous yellow, yellow-tan or tan appearance, depending on their content of fat.

**Histopathology.** Angiomyolipomas are composed of adipose tissue, smooth muscle and thick-walled, sometimes hyalinized blood vessels in varying proportions. Morphologically and phenotypically they are believed to belong to a family of lesions characterized by proliferation of perivascular epithelioid cells [2197]. The smooth muscle is composed of spindle-shaped cells arranged in bundles, or larger more rounded cells with an ‘empty’ (glycogen-rich) cytoplasm or an eosinophilic, epithelioid appearance. The nuclei of the spindle cells are elongated with blunt ends, but the larger smooth muscle cells can have large, hyperchromatic nuclei with prominent nucleoli. The microscopic appearances are extensively varied and may imitate several malignant tumours, e.g. leiomyosarcoma, malignant fibrous histiocytoma and hepatocellular carcinoma [1971]. A characteristic feature of angiomyolipoma is the presence of extramedullary haematopoiesis. The smooth muscle cells contain variable quantities of melanin and express the melanoma markers HMB-45 and Melan-A. They also express muscle specific actin and smooth muscle actin.
Solitary fibrous tumour
Solitary fibrous tumour has an age range from 32-83 years (mean, 57 years) (1270). Its aetiology is unknown. Lesions vary considerably in size, from 2-20 cm in diameter (1270). They arise in either lobe and are occasionally pedunculated. The external surface is smooth and the consistency firm. They are sharply demarcated but not encapsulated. Gross sections show a light tan to almost white colour with a whorled texture. Histopathology: Solitary fibrous tumour often shows alternating cellular and relatively acellular areas. The cellular areas consist of bundles of spindle cells arranged haphazardly or in a storiform pattern. There is a well-developed reticulin network. In some cases the cells are arranged around ectatic vessels in a hae-mangiopericytoma-like pattern. Nuclei of the spindle cells are uniform and lack pleomorphism, but these tumours may undergo malignant change as evidenced by the presence of foci of necrosis, prominent cellular atypia, and mitotic activity in the range of 2-4 mitoses/10 hpf (1270, 514). The relatively acellular areas of solitary fibrous tumour contain abundant collagen bundles with thin, stretched-out tumour cells. The tumour cells characteristically express CD34.

Inflammatory pseudotumour
This lesion is defined as a benign, non-neoplastic, non-metastasizing mass composed of fibrous tissue and proliferated myofibroblasts, with a marked inflammatory infiltration, predominantly plasma cells (318). The mean age at presentation of inflammatory pseudotumour of the liver is 56 years (range, 3-77) (438); it is commoner in males (70%) than in females (1270). Inflammatory pseudotumours are solitary (81%) or less often multiple (19%) (1275) and usually intrahepatic, but some can involve the hepatic hilum. About half of the solitary tumours are located in the right lobe. They vary in size from 1 cm to large masses involving an entire lobe, and are firm, tan, yellow-white or white. Some inflammatory pseudotumours are probably the residuum of a resolved bacterial abscess, while others may be related to Epstein-Barr virus infection (82, 318). Histopathology: The lesions are similar to those occurring in other sites. They are composed of inflammatory cells in a stroma of interlacing bundles of myofibroblasts, fibroblasts, and collagen bundles. The majority of inflammatory cells are mature plasma cells, but lymphocytes (and occasional lymphoid aggregates or follicles), as well as eosinophils and neutrophils, may be present. Macrophages, sometimes showing xanthomatous changes, occasional granulomas and, rarely, phlebitis involving portal vein branches or outflow veins, may be seen.

Lymphangioma and lymphangiomatosis
Lymphangioma is a benign tumour characterized by multiple endothelial-lined spaces that vary in size from capillary channels to large, cystic spaces containing lymph. The vascular spaces are lined by a single layer of endothelial cells, though papillary projections or tufting may be seen. The cells rest on a basement membrane and the supporting stroma is usually scanty. Clear, pink-staining lymph fills the lymphatic channels. Hepatic lymphangiomatosis, often accompanied by lymphangiomatosis of the spleen, skeleton, and other tissues, may represent a malformation syndrome. Diffuse lymphangiomatosis involving the liver and multiple organs is associated with a poor prognosis. Single lesions have been successfully resected.

Pseudolipoma
Pseudolipoma is believed to represent an appendix epiploica attached to the Glisson capsule after becoming detached from the large bowel (1609). Lesions are usually a small, encapsulated mass of fat located in a concavity on the surface of the liver, the fat typically showing necrosis and calcification (891).

Focal fatty change
Focal fatty change of the liver is characterized by multiple, contiguous acini showing macrovesicular steatosis of hepatocytes, with preservation of acinar architecture (804). About 45% of cases of a series of focal fatty change occurred in patients with diabetes mellitus (632).

Embryonal sarcoma
A malignant tumour composed of mesenchymal cells that, by light microscopy, are undifferentiated. Embryonal sarcoma (‘undifferentiated’ sarcoma) comprises 6% of all primary hepatic tumours in childhood (2082). It usually occurs between 5 and 20 years of age (1840). Rarely, cases have occurred in middle and even old age. The incidence in males and females is equal (1840). Embryonal sarcoma is of unknown aetiology, although one patient had a past history of prenatal exposure...
Mesenchymal tumours

to phenytoin (148). Symptoms include abdominal enlargement, fever, weight loss, and nonspecific gastrointestinal complaints (1840). Rarely, the tumour invades the vena cava and grows into the right atrium, mimicking a cardiac tumour (561).

**Macroscopy.** Embryonal sarcoma is usually located in the right lobe of the liver, and varies from 10-20 cm in diameter. It is typically well-demarcated but not encapsulated. Gross sections reveal a variegated surface with glistening, solid, grey-white tumour tissue alternating with cystic, gelatinous areas and/or red and yellow foci of haemorrhage or necrosis.

**Histopathology.** Embryonal sarcoma is composed of malignant stellate or spindle cells that are compactly or loosely arranged in a myxoid stroma. Tumour cells often show prominent anisokaryosis with hyperchromasia; giant cells that may be multinucleated are seen in many cases. A characteristic feature is the presence of eosinophilic globules of varied size, sometimes many per cell, in the cytoplasm. They are PAS-positive, resist diastase digestion, and express alpha-1 antitrypsin, though the larger globules may only be immunoreactive at the periphery. Entrapped bile ducts and hepatocellular elements are often present in the peripheral areas of these tumours. The spindle, stellate and giant cells typically show no morphological evidence of differentiation, but immunohistochemical studies in a few cases have demonstrated widely divergent differentiation into both mesenchymal and epithelial phenotypes, probably from a primitive stem cell (1460).

**Prognosis.** Until recently the prognosis of embryonal sarcoma has been very poor, with a median survival of less than one year after diagnosis (1840). The survival has greatly improved in the last several years with some patients living five or more years after combined modality therapy (surgical resection, radiotherapy, and chemotherapy).

**Kaposi sarcoma**

This lesion is defined as a tumour composed of slit-like vascular channels, spindle cells, mononuclear inflammatory cells, with an admixture of haemosiderin-laden macrophages.

Kaposi sarcoma involves the liver in 12-25% of fatal cases of the acquired immunodeficiency syndrome (AIDS), but is not known to contribute significantly to its morbidity and mortality. In patients with AIDS, it is aetiologically related to HHV-8 infection (276, 1367). It involves portal areas but can infiltrate the adjacent parenchyma for short distances, and is characterized grossly by irregular, variably-sized, red-brown lesions scattered throughout the liver. Histologically, lesions resemble those occurring in other sites with spindle cells showing elongated or ovoid, vesicular nuclei with rounded ends and inconspicuous nucleoli. Eosinophilic, PAS-positive globules may be seen in the cytoplasm. The tumour cells are separated by slit-like vascular spaces. Aggregates of haemosiderin granules may be present. The spindle cells express endothelial cell markers (CD31, CD34).

**Epithelioid haemangioendothelioma**

A tumour of variable malignant potential that is composed of epithelioid or spindle cells growing along preformed vessels or forming new vessels.

Epithelioid haemangioendothelioma presents between 12 and 86 years (mean 47 years) (807, 1150). Its overall incidence is unknown, but more are reported in females (61%) than in males (39%) (807, 1150). Risk factors are not known; the

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**Fig. 8.68** Kaposi sarcoma. A Multiple dark brown lesions centered in large portal areas. B, C Spindle cells and slit-like vascular spaces.

**Fig. 8.69** Epithelioid haemangioendothelioma. There is extensive destruction of liver cell plates. Note the intracellular vascular lumina (arrow).
suggestion of a relationship to oral contraceptive use has not been validated (1270). Epithelioid haemangioendothelioma causes systemic symptoms (weakness, malaise, anorexia, episodic vomiting, upper abdominal pain, and weight loss) and hepato-splenomegaly (807, 1150). Some patients develop jaundice and liver failure. Uncommon modes of presentation include the Budd-Chiari syndrome (2040) or portal hypertension.

**Macroscopy.** Macroscopically, lesions are usually multifocal; ill-defined lesions scattered throughout the liver vary from a few millimeters to several centimeters in greatest dimension. They are firm, tan to white on sectioning, and often have a hyperaemic periphery; calcification may be evident grossly.

**Histopathology.** The tumour nodules are ill-defined, and often involve multiple contiguous acini. In actively proliferating lesions the acinar landmarks, such as terminal hepatic venules (THV) and portal areas, can be recognized despite extensive infiltration by the tumour. The cells grow along preexisting sinusoids, THV, and portal vein branches, and often invade Glisson capsule. Growth within the acini is associated with gradual atrophy and eventual disappearance of liver cell plates. Intravascular growth may be in the form of a solid plug, or a polypoid or tuft-like projection. Neoplastic cell are either ‘dendritic’, with spindle or irregular shapes and multiple interdigitating processes, ‘epithelioid’, with a more rounded shape and an abundant cytoplasm, or ‘intermediate’. Nuclear atypia and mitoses are mainly observed in the epithelioid cells. Cytoplasmic vacuoles, representing intracellular vascular lumens, are often identified and may contain erythrocytes. The tumour cells synthesize factor VIII-related antigen (von Willebrand factor), which can be demonstrated in the cytoplasm or in the neoplastic vascular lumens. Other endothelial cell markers, such as CD31 and CD34, are also positive.

The stroma can have a myxoid appearance due to an abundance of sulphated mucopolysaccharide. Reticulin fibres surround nests of tumour cells. Basement membrane can be demonstrated around the cells by the PAS stain, as well as ultrastructurally and immunohistochemically. Variable numbers of smooth muscle cells surround the basement membrane.

As the lesions evolve they are associated with progressive fibrosis and calcification. Eventually, tumour cells (and indeed, the vascular nature of the lesion) may be difficult if not impossible to recognize in the densely sclerosed areas. Needle biopsy specimens taken from such areas often pose diagnostic problems. The histopathological differential diagnosis includes angiosarcoma and cholangiocarcinoma. Angiosarcoma is much more destructive than epithelioid haemangioendothelioma, obliterates acinar landmarks and results in cavity formation. Cells of cholangiocarcinoma are arranged in a tubular or glandular pattern, and often produce mucin; the cells are cytokeratin positive and do not express endothelial cell markers.

**Prognosis.** The clinical outcome of epithelioid haemangioendothelioma is unpredictable, with some patients having a fulminant course and others surviving many years with no therapy. A recent study (1150) showed a correlation between high cellularity of the tumour with a poor clinical outcome. Successful treatment includes resection, when feasible, and liver transplantation.

**Angiosarcoma**

A malignant tumour composed of spindle or pleomorphic cells that line, or grow into, the lumina of preexisting vascular spaces, such as liver sinusoids and small veins. Worldwide, about 200 cases of angiosarcoma are diagnosed annually (848, 59). During the period 1973-87, the SEER database of the US National Cancer Institute contained 6,391 histologically-confirmed primary liver cancers; of these only 65 (1%) were angiosarcomas (252). The peak incidence is in the 6th and 7th decades of life. The male to female ratio is 3:1 (1085). 75% of angiosarcomas of the liver have no known aetiology (484). The remainder have been linked to prior administration of Thorotrast (a radioactive material containing thorium dioxide, that was used as an angiography contrast medium from the 1930s to the early 1950s), exposure to vinyl chloride monomer (VCM) or inorganic arsenic, and the use of androgenic-anabolic steroids (484). Patients with angiosarcoma present in one of several ways: 61% have symptoms referable to the liver (e.g. hepatomegaly, abdominal pain, ascites); 15% have an acute abdominal crisis due to haemoperitoneum from rupture of the tumour; 15% have splenomegaly, often with pancytopenia; and 9% present due to distant metastases (804). The prognosis of angiosarcoma is very poor, with most patients dying within 6 months of diagnosis.

**Macroscopy.** Angiosarcoma typically affects the entire liver. Grayish-white...
tumour alternates with red-brown haemorrhagic areas. Large cavities with ragged edges, filled with liquid or clotted blood, may be present. A reticular pattern of fibrosis is seen in cases related to prior exposure to Thorotrast.

**Histopathology.** Tumour cells grow along preformed vascular channels (sinusoids, THV and portal vein branches). Sinusoidal growth is associated with progressive atrophy of liver cells and disruption of the plates, with formation of larger vascular channels and eventually the development of cavities of varied size. These cavities have ragged walls lined by tumour cells, sometimes with polypoid or papillary projections, and are filled with clotted blood and tumour debris. Reti-
Culin fibres and, less often, collagen fibres support the tumour cells. Perithelial cells, reactive for alpha-smooth muscle actin, may also be present. The tumour cells are sometimes packed solidly in nodules that resemble fibrosarcoma. The cells of angiosarcoma are spindle-shaped, rounded or irregular in outline, and often have ill-defined borders. The cytoplasm is lightly eosinophilic, and nuclei are hyperchromatic and elongated or irregular in shape. Nucleoli can be small, or large and eosinophilic. Large, bizarre nuclei and multinucleated cells may be seen, and mitotic figures are frequently identified. The spindled cells have ill-defined outlines, a lightly eosinophilic cytoplasm, and vesicular nuclei with blunt ends. Factor VIII-related antigen can be identified in tumour cells immunohistochemically. Other useful markers include CD31 and CD34; the former is believed to be the most sensitive immunostain (1224).

Invasion of THV and portal vein branches leads to progressive obstruction of the lumen, and readily explains the frequently encountered areas of haemorrhage, infarction, and necrosis. Haematopoietic activity is observed in the majority of tumours. Cases related to Thorotrast and vinyl chloride monomer are often associated with considerable periportal and subcapsular fibrosis. Thorotrast deposits are readily recognized in reticuloendothelial cells, in connective tissue of portal areas, in Glisson capsule, or in the walls of THV. The deposits are coarsely granular and refractile, and in an H&E-stained section they have a pink-brown hue. They are readily visualized by scanning electron microscopy, and thorium can be definitively identified by energy dispersive X-ray microanalysis (804).

Genetics. Analysis of six hepatic angiosarcomas associated with VCM exposure found three TP53 mutations, all A:T → T:A transversions, which are otherwise uncommon in human cancers (728). Another study of 21 sporadic angiosarcomas not associated with vinyl chloride exposure found TP53 mutations to be uncommon, thus supporting previous evidence of the carcinogenic potential of chloroethylene oxide, a metabolite of VCM (1776). A high rate of KRAS-2 mutations has been found in both sporadic and Thorotrast-induced angiosarcomas of the liver (1542). Malignant mesenchymal tumours other than angiosarcoma may have cytogenetic aberrations similar to those of soft tissue tumours (513, 1812).

Carcinosarcoma
This neoplasm is defined as a malignant tumour containing an intimate mixture of carcinomatous (either hepatocellular or cholangiocellular) and sarcomatous elements; such lesions have also been called ‘malignant mixed tumour’ of the liver. Carcinosarcoma should be distinguished from carcinomas with foci of spindled epithelial cells and from the rare true ‘collision’ tumours.
Secondary tumours of the liver

P.P. Anthony
P. DeMatos

Definition
Malignant neoplasms metastasized to the liver from extrahepatic primary tumours.

Epidemiology
In Europe and North America, metastases predominate over primary hepatic tumours in a ratio of 40:1 (130, 1517). In Japan the ratio is 2.6:1 (1517). In South-East Asia and sub-Saharan Africa, primary hepatic tumours are more common than metastases (1909) owing to the high incidence of hepatocellular carcinoma, a shorter life span (common extrahepatic carcinomas affect older age groups) and the low incidence of certain tumour types (e.g. carcinomas of the lung and colorectum). Autopsy studies in the USA and Japan have shown that about 40% of patients with extrahepatic cancer have hepatic metastases (351, 1517).

Aetiopathogenesis
The liver has a rich systemic (arterial) and portal (venous) blood supply, providing a potentially abundant source of circulating neoplastic cells. Circulating tumour cell arrest is controlled by Kupffer cells in the sinusoids (881, 121) and may be enhanced by growth factors such as transforming growth factor alpha (TGFα) (385), tumour necrosis factor (TNF) (1431), and insulin-like growth factor-1 (IGF-1) (1091). As tumour deposits enlarge, they induce angiogenesis using native sinusoidal endothelium; this enhances their chances of survival and is often macroscopically evident (1919). Most metastases from unpaired abdominal organs reach the liver via the portal vein, and from other sites via the systemic arterial circulation. Lymphatic spread is less common and extension to the liver via the periportal fluid is rare (351). Cirrhosis provides some relative protection against seeding by secondary tumours (1983, 1211). It has also been suggested that metastasis is rare in fatty livers (676), but excess alcohol consumption apparently enhances hepatic metastases (1140).

In the majority of cases, metastases to the liver are a manifestation of systemic, disseminated disease. Colorectal carcinoma, neuroendocrine tumours, and renal cell carcinoma are exceptions as these neoplasms sometimes produce isolated, even solitary deposits (1517).

Fig. 8.74 Secondary tumours in the liver. A Metastatic colon carcinoma showing umbilication and hyperemic borders. B Metastatic small cell carcinoma of lung forming innumerable small nodules. C, D Metastatic large intestinal carcinoma, cut surfaces. E Metastatic gastric adenocarcinoma, cut surface. F A metastasis lies adjacent to a Zahn infarct.

Origin of metastases
The majority of secondary liver neoplasms are carcinomas, involvement by lymphomas is next and sarcomas are uncommon. The order of frequency by primary site in Western populations is: upper gastrointestinal tract (stomach, gallbladder, pancreas); 44-78%; colon: 56-58%; lung: 42-43%; breast: 52-53%; oesophagus: 30-32% and genito-urinary organs: 24-38% (130, 1517, 351). Carcinomas of the prostate and the ovaries preferentially spread to the lymph nodes and the spine, and to the peritoneal cavity, respectively. Hodgkin and non-Hodgkin lymphomas may involve the liver in up to 20% of cases on presentation and 55% at autopsy (1620, 826). Sarcomas are much less common but 6% had hepatic metastases at presentation (mostly intra-abdominal leiomyosarcomas) in one study (833).
while 34% had hepatic metastases at autopsy in another [1517]. In a study of randomly selected liver biopsies from England and Wales [852], the commonest histological type of metastasis was adenocarcinoma (39%), followed by carcinoma not otherwise specified (36%); the rest were undifferentiated small cell carcinoma, other special types of carcinoma, and lymphomas.

Clinical features
Symptoms and signs
Hepatic metastases produce clinical manifestations in about two-thirds of cases and they generally reveal themselves through symptoms referable to the liver. Afflicted patients often present with ascites, hepatomegaly or abdominal fullness, hepatic pain, jaundice, anorexia, and weight loss. Constitutional symptoms, such as malaise, fatigue, and fever may be present. On examination, nodules or a mass are felt in up to 50% of the cases, and a friction bruit may be heard on auscultation. Unfortunately, symptomatic presentation is associated with bulky, rapidly progressive tumours with a poor prognosis [2035]. Rarely, patients present with fulminant hepatic failure, obstructive jaundice, or intraperitoneal haemorrhage. Functioning neuroendocrine tumours produce syndromes of hormonal excess. ‘Carcinomatous cirrhosis’ with jaundice, ascites, and bleeding varices due to diffuse infiltration of the liver, usually by metastatic breast carcinoma, has been described [174].

Laboratory studies
The alkaline phosphatase (ALP) and serum glutamic-oxaloacetic transaminase (SGOT) levels, although non-specific, are elevated in approximately 80% and 67% of patients respectively, and most likely represent the effects of hepatic parenchymal infiltration by tumour and of generalized wasting. Elevated lactic dehydrogenase (LDH) levels are relatively specific for the presence of metastatic melanoma. Tests of synthetic function, e.g. serum albumin levels and the prothrombin time, may be normal despite extensive metastatic involvement. Alpha-fetoprotein (AFP) levels may be slightly to moderately elevated but very high concentrations are more consistent with a diagnosis of hepatocellular carcinoma [904]. Carcinoembryonic antigen (CEA) levels, which are raised in as many as 90% of patients with metastases from colorectal carcinoma, can be useful in monitoring patients after primary tumour resection. However, CEA levels do not correlate well with prognosis [2043, 1821].

Imaging
Ultrasound (US) can identify tumours measuring 1-2 cm in size, can differentiate solid from cystic lesions, and provide guidance for percutaneous needle biopsy. However, it provides poor anatomical definition and frequently misses smaller lesions. Computed tomography (CT), using both contrasted and non-contrast images, can also serve as a screening tool. The administration of intravenous contrast permits the detection of tumours as small as 0.5 cm in diameter [1763]. Most metastases display decreased vascularity in comparison to the surrounding hepatic parenchyma and appear as hypodense defects. Tumours that are hypervascular (e.g. melanoma, carcinoids and some breast cancers) or calcified (e.g. colorectal carcinoma) are better delineated by noncontrast views. Magnetic resonance imaging (MRI) is more sensitive than CT in the detection of hepatic tumours and can demonstrate additional lesions, too small to be seen on CT. Positron emission tomography (PET) can detect metastatic disease in the liver and elsewhere. Using 2-(18)fluoro-2-deoxy-D-glucose (F-18 FDG), a radiolabeled glucose analogue, PET highlights metabolically active tissues. Through co-registration with anatomical studies like CT or MRI, viable malignant tumours can be differentiated from benign or necrotic lesions [54]. CT arterial portography performed preoperatively, and intraoperative ultrasound are associated with the highest sensitivities [1796]. The former is capable of detecting lesions as small as 15 mm, although a false positive rate of...
17% has been reported (1795). Its success relies on the fact that tumours are not fed by portal vein blood, so that metastases appear as filling defects. The latter, capable of detecting lesions 2-4 mm in diameter delineates the anatomical location of tumours in relationship to major vascular and biliary structures and provides guidance for intraoperative needle biopsies. It is the definitive step in determining resectability at the time of exploratory laparotomy or laparoscopy.

Angiography use has declined in recent years. It remains useful for defining vascular anatomy for planned hepatic resections, selective chemotherapy, chemoblation, or devascularization procedures, for assessing whether there is metastatic involvement of the portal venous system and/or hepatic veins, and for differentiating between benign vascular lesions, such as haemangiomas and metastases, when other imaging studies have yielded equivocal results.

**Macroscopy**

The distribution of metastases from colorectal carcinoma was found to be homogenous, regardless of the primary site of origin (1695) but in another study, it was suggested that right sided cancers predominantly metastasize to the right lobe of the liver and left sided cancers to both lobes (1749).

Metastases are nearly always multinodular or diffusely infiltrative, but may rarely be solitary and massive (e.g. from colorectal and renal cell carcinomas). Umbilication (a central depression on the surface of a metastatic deposit) is due to necrosis or scarring and is typical of an adenocarcinoma from stomach, pancreas or colorectum. A vascular rim around the periphery is often seen. Highly mucin secreting adenocarcinomas appear as glistening, gelatinous masses whilst well differentiated keratinizing squamous cell carcinomas are granular. Metastatic carcinoid tumours can form pseudocysts (401). Haemorrhagic secondary deposits suggest angiosarcoma, choriocarcinoma, carcinoma of thyroid or kidney, neuroendocrine tumour, or vascular leiomyosarcoma. Some diffusely infiltrating carcinomas (e.g. small cell carcinoma), lymphomas and sarcomas may have a soft, opaque ‘fish flesh’ appearance. Metastatic breast carcinoma in particular can produce an intensely fibrous, granular liver (‘carcinomatous cirrhosis’) either before (174) or after (1693) treatment. Calcification of secondary deposits is a feature of colorectal carcinoma but it is seldom excessive and has no effect on prognosis (653). Metastatic melanoma is often, but not always, of a brown-black colour. Secondary tumours may appear in the liver long after the removal of the primary.

**Histopathology**

Liver biopsy samples can be obtained by percutaneous or transjugular routes with or without imaging techniques for guidance, as a wedge during laparotomy, or a fine needle can be used to aspirate material for cytology. Each of these methods has advantages and drawbacks but a guided percutaneous needle biopsy producing a core of liver for histology is the one most frequently used. It produces a tissue sample that is usually adequate for all purposes, including the use of special stains, immunohistochemistry and molecular biological techniques. Touch preparations for cytology can also be prepared from needle cores before fixation and may provide an instant diagnosis (1523).

**Differential diagnosis**

Hepatocellular carcinoma can usually be distinguished from metastatic tumours by its trabecular structure, sinusoids, lack of stroma, bile production, absence of mucin secretion, and the demonstration of bile canaliculi by polyclonal CEA antisera, which is specific for a liver cell origin. Other useful immunophenotypic features in this differentiation are the presence of liver export proteins (albumin, fibrinogen, alpha-1-antitrypsin), the cytokeratin pattern, and the expression of Hep Par 1 antigen (1046). Metastatic tumours that often mimic hepatocellular carcinoma are adrenal cortical and renal cell carcinomas. Amelanotic melanoma may also cause difficulties but it is easily identified by positive immunostaining for S100 protein and HMB45.

The distinction between primary cholangiocarcinoma and metastatic adenocar-
cinomas is much more difficult and may be impossible [351]. Cholangiocarcinoma may take on any of the histological patterns of an adenocarcinoma; it is usually tubular but may be mucinous, signet-ring, papillary, cystic, or undifferentiated. Mucin secretion and production of CEA are nearly always demonstrable in both primary and secondary adenocarcinomas. Metastases from many sites form similar patterns. However, small tubular or tubulo-papillary glands frequently derive from the stomach, gallbladder and extrahepatic biliary tree, and a signet-ring cell appearance suggests a gastric primary. Perhaps the easiest pattern to recognize as metastatic in origin is that exhibited by adenocarcinomas of the colon and rectum, which nearly always show glands of variable size and shape that are lined by tall columnar cells and contain debris within the lumen. Metastases from the colorectum frequently have well defined edges whereas those from other glandular sites tend to be more diffuse. Colorectal metastases are also frequently necrotic and may show calcification [653].

The presence of carcinoma-in-situ in intrahepatic bile ducts in the vicinity of an adenocarcinoma is evidence that it is a cholangiocarcinoma. However, this may be mimicked by intrabiliary ductal growth of metastatic colonic adenocarcinoma (1593). Analysis of cytokeratin expression may be useful in the distinction of primary and metastatic gastrointestinal adenocarcinomas. The former express cytokeratins 7 and 19 but not 20, whereas the latter are negative for 7 and positive for 20 [1141].

Carcinoma of the breast often produces a diffuse sinusoidal infiltrate that on imaging studies may mimic cirrhosis and, indeed, may be associated with splenomegaly, ascites and oesophageal varices (174); sclerosis following systemic chemotherapy may exaggerate this effect. Metastases from the breast may be identified by the combined use of zinc-α2-glycoprotein, gross cystic disease fluid protein 15 and oestrogen receptor (283). However, occult breast carcinoma presenting with metastases is rare and most patients with liver involvement have a past history of a primary tumour.

Most hepatic metastases from the lung in clinical practice are undifferentiated small cell carcinomas, characteristically producing an enlarged liver due to diffuse or miliary spread. The primary tumour may still be small, asymptomatic and undetected. Squamous cell and adenocarcinomas will metastasize to the liver but their existence is usually known already. The same applies to squamous cell carcinomas of the oesophagus and cervix. Squamous cell carcinomas of the head and neck seldom involve the liver. Neuroendocrine/islet cell/carcinoid tumours are easily identified by their organoid nesting pattern, uniform cytology and vascularity, and positive immunostaining for chromogranin, synaptophysin and neuron specific enolase; islet cell tumours also produce specific hormones such as insulin, glucagon, gastrin, vasoactive intestinal peptide and somatostatin, which either give rise to clinical syndromes or can be demonstrated in the blood or tumour tissue. Most sarcomas that metastasize to the liver are gastrointestinal stromal tumours that are positive for CD34 and c-kit, or leiomyosarcomas of the uterus that may be positive for desmin or muscle-specific actin. Some carcinomas, notably of the kidney, may be sarcomatoid in their morphology. Many haematological malignancies, e.g. leukaemias, myeloproliferative disorders and both Hodgkin and non-Hodgkin lymphomas, involve the liver. Leukaemias tend to produce diffuse sinusoidal infiltrates. Hodgkin and high-grade non-Hodgkin lymphomas produce tumour-like masses, while low-grade non-Hodgkin lymphomas produce diffuse portal infiltrates.

Rare secondary tumours include those from the thyroid, prostate, and gonads. The diagnosis can be confirmed by the immunohistochemical demonstration of thyroglobulin, prostate specific antigen and AFP and βHCG, respectively. A triad of histological features, namely proliferating bile ducts, leukocytes and focal sinusoidal dilatation, is found in the liver adjacent to space-occupying lesions. Their presence in a core biopsy suggests the possibility of a metastatic deposit missed by the biopsy needle. Three lesions, bile duct adenoma, sclerosed haemangioma, and larval granuloma may resemble metastatic tumours at laparotomy.

Prognosis
In most cases, disseminated disease is present which precludes surgical intervention. Due to recent improvements in imaging techniques, more metastatic carcinomas are being diagnosed early, providing the possibility of surgical resection in a greater number of patients. When curative resection is feasible, 5-year survival can be as high as 40%; without surgical therapy, median survivals of less than 12 months should be expected [1817].