15.24.6 Primary and secondary liver tumours 3178

15.24.6 Primary and secondary liver tumours 3178

section 15 Gastroenterological disorders 3178 Graft-versus-host disease The liver is often affected by graft-versus-host disease that may follow allogeneic and solid organ transplantation, especially when large numbers of donor T cells are transplanted (intentionally or in- advertently) which react with major or minor HLA antigens (such as in bowel or liver transplantation). Graft-versus-host disease may present as asymptomatic elevation of liver tests, cholestasis, or an acute hepatitis. Liver involvement usually follows skin and bowel involvement. The liver histology shows lymphocytic infiltration of small bile ducts and apoptosis of epithelial cells. Liver disease in pregnancy This is discussed in Chapter 14.9. Abnormalities of liver function may occur in hyperemesis gravidarum and pre-eclampsia, as well as the liver diseases unique to pregnancy, which include cholestasis of pregnancy, acute fatty liver of pregnancy, and HELLP (haemolysis, elevated liver enzymes, and low platelet count) syndrome. FURTHER READING Babkhanian Z, Donovan JA (2013). Biliary manifestations of systemic disease. Gastrointest Endosc Clin N Amer, 23, 333–46. DeLemos AS, Friedman LS (2013). Systemic causes of cholestasis. Clin Liver Dis, 17, 301–17. Flamm SL (2012). Granulomatous liver disease. Clin Liver Dis, 16, 387–96. Gizard E, et al. (2014). Systematic review: the epidemiology of the hepatobiliary manifestations in patients with inflammatory bowel disease. Aliment Pharmacol Ther, 40, 3–15. Kelly T, Buxbaum J (2015). Gastrointestinal manifestations of cystic fibrosis. Dig Dis Sci, 60, 1903–13. Kosters A, Karpen SJ (2010). The role of inflammation in cholestasis— clinical and basic aspects. Semin Liver Dis, 30, 186–94. Leffler DA, Green PH, Fasano A (2015). Extraintestinal manifestation of celiac disease. Nat Rev Gastroenterol Hepatol, 12, 561–71. Maheshwari A, Thuluvath PJ (2011). Endocrine diseases and the liver. Clin Liver Dis, 15, 55–67. Neuberger J (ed) (2013). The liver in systemic disease. Best Pract

Res Clin Gastroenterol, 27, 469–629. 15.24.6 Primary and secondary liver tumours Graeme J.M. Alexander, David J. Lomas, William J.H. Griffiths, Simon M. Rushbrook, and Michael E.D. Allison ESSENTIALS Benign, as well as malignant tumours arise in the liver. The most important include the following: Hepatocellular carcinoma Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, but with marked geographical variation in incidence; it usually arises on a background of cirrhosis. It is usually asymp- tomatic unless the cancer is advanced. Cross-sectional imaging with contrast with either CT or MRI is sufficient to make a firm diagnosis. Serum α-fetoprotein is elevated in most cases. Historically, tumour biopsy was reserved for indeterminate cases, but molecular analysis may soon guide management of HCC and tumour biopsy to aid this could become the norm. Early diagnosis, perhaps through surveil- lance, increases the proportion of patients that can be considered for curative treatment, including surgical resection, radiofrequency ablation, or liver transplantation. The presence of symptoms denotes a poor prognosis, with less than 10% of patients surviving 3 years. Cholangiocarcinoma Cholangiocarcinoma accounts for 7 to 10% of primary liver malig- nancies. Jaundice is an early feature in those with hilar or extrahepatic tumours, whereas patients with early peripheral intrahepatic tumours are often asymptomatic. The diagnosis of cholangiocarcinoma can be very difficult to make. Tissue from peripheral tumours can be obtained directly by percutaneous biopsy with ultrasonographic or CT guidance, and at endoscopic retrograde cholangiopancreato graphy as brushings or biopsy for tumours of larger-order ducts. Resection results in cure for only a few patients. Palliative approaches include photodynamic therapy, conventional radiotherapy, and high-dose local irradiation. Biliary stents relieve jaundice and may reduce the frequency of episodes of cholangitis. Benign liver tumours Haemangioma, usually an incidental finding, has a prevalence of 2 to 5% in the population. Focal nodular hyperplasia (prevalence 0.4–0.8%) is found predominantly in fertile women and is typically an incidental finding during abdominal imaging. Biopsy is required if there is diagnostic uncertainty and in particular to differentiate from hepatic adenomas, which are also typically incidental findings but may present with abdominal pain and carry risks of spontaneous haemorrhage and malignant transformation. Interventions include surgery, radiofrequency ablation, transarterial embolization, or a combination of each according to location and patient fitness. Secondary liver tumours Secondary tumours may be a presenting feature but more often are found during staging for primary malignancy or during follow- up. Symptoms include abdominal pain and hepatomegaly and later jaundice and ascites. If the primary is not apparent, targeted liver biopsy usually confirms malignancy; immunohistochemical assessment is helpful in determining the source. For most patients with multiple metastases to the liver, the prognosis is poor and treatment palliative. Introduction Several diverse benign and malignant tumours arise in the liver. Benign tumours are relatively common and often incidental; dis- tinction is occasionally challenging and some harbour malignant

 potential. Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy, almost always arising on a background of liver damage, most often manifest as cirrhosis. Early diagnosis and careful patient selection can lead to cure with surgical approaches including liver transplantation. Advances in understanding the molecular mechanisms in- volved in hepatocarcinogenesis are likely to yield novel thera- peutic agents. The prognosis of cholangiocarcinoma remains poor although prospects for earlier diagnosis and curative treatment are improving; intrahepatic cholangiocarcinoma and intermediate

hepatocellular–cholangiocarcinoma are increasingly recognized subtypes. Other primary liver malignancies are rare and thus op- timal management, including the role of transplantation, is not well defined. Secondary liver tumours are common. Treatment is palliative except for colorectal metastases, when surgical resection may extend life expectancy, and neuroendocrine tumours where liver-directed therapy and surgical options may provide effective palliation. Hepatocellular carcinoma HCC is the fifth most common cancer worldwide as well as the third most common cause of cancer-related death. Most tumours arise on the background of cirrhosis and typically grow slowly with late spread to extrahepatic sites including adrenals, lymph nodes, lung, and bone. Symptoms may not be apparent until the cancer is already advanced and because of late presentations most deaths occur within 1 year of diagnosis. Selected at-risk patients benefit from enrolment into surveillance programmes where early detection permits a more expansive range of therapeutic options including cure with surgery or radiofrequency ablation. Epidemiology The geographical distribution of HCC worldwide is uneven. More than 80% of cases occur in sub-Saharan and West Africa, China, and Asia. The incidence has always been lower in Western Europe and North and South America. In Taiwan, the introduction of universal vaccination against hepatitis B virus (HBV) has been followed by a substantial reduction in the incidence of HCC. However, the inci- dence of HCC following chronic hepatitis C virus infection is rising in most parts of the world, a rise that will be arrested eventually with the introduction of effective antiviral therapies. HCC is now the fastest-growing cause of cancer-related death in men in Europe, the United Kingdom, and the United States of America; much of this increase is a consequence of nonalcoholic fatty liver disease as a single risk factor or as a cofactor alongside alcohol-related liver disease or chronic viral hepatitis. There is no doubt that many cases labelled as metastatic disease in the past are now attributed more accurately to HCC with the widespread avail- ability of cross-sectional imaging. The main risk for HCC is cirrhosis. Men are at a threefold in- creased risk compared to women. Other risk factors include viral hepatitis, obesity, type 2 diabetes mellitus, the presence and dur- ation of chronic viral hepatitis, excessive alcohol consumption, and smoking. Age is an important risk factor and the incidence rises with each decade. For the minority with HCC arising in the absence of liver injury, males and females are affected equally and the pres- entation is more often in the third and fourth decades. Some cases arise in those with liver disease short of cirrhosis; most of these are a consequence of hepatitis B virus infection acquired in early life; a small number have genetic haemochromatosis; HCC is seen in- creasingly in older men with nonalcoholic fatty liver disease with fibrosis short of cirrhosis. Aetiology and prevention HCC usually occurs in the context of chronic liver injury: 80% of patients worldwide with HCC have cirrhosis, which in most can be attributed to chronic viral hepatitis, alcohol-related or nonalcoholic fatty liver disease. Global prevention of HCC needs to address these risk factors in particular. HCC is the commonest cause of death in haemochromatosis but is uncommon with cirrhosis due to α1-antitrypsin deficiency, Wilson’s disease, autoimmune hepa- titis, or primary biliary cholangitis. Glycogen storage disease type 1a (GSD1a), tyrosinaemia, and acute intermittent porphyria are rare metabolic disorders that predispose to HCC. Many patients with HCC have more than one aetiological risk factor. Hepatitis B virus HBV is the most common cause of HCC worldwide; an estimated 380 million infected individuals harbour a 100-fold increased rela- tive risk of developing HCC. HCC can arise in the absence of cir- rhosis almost certainly because of the combination of chronic liver inflammation in combination with integration of viral DNA into the hepatocyte genome. In areas where HBV is endemic, vertical trans- mission to the fetus or baby results in high rates of chronicity; in low-risk areas, the virus is more likely to be acquired horizontally later in life, when 90% clear infection. Risk factors for HCC among HBV carriers include male sex, cirrhosis,

older age, family history of HCC, Asian or African eth- nicity, and coinfection with hepatitis C or D. Aflatoxin B1, a hepatocarcinogen produced by the aspergillus fungus and pre- sent in stored foods in HBV-endemic areas, has been implicated in susceptibility to HCC via direct disruption of the TP53 tumour- suppressor gene. Higher circulating viral DNA levels are associated with a greater risk of HCC. Conversely, sustained effective antiviral therapy is associated with a reduced risk of HCC. In Taiwan, the introduction of universal vaccination has now been associated with a substantial fall in the incidence of HCC. Hepatitis C virus Hepatitis C virus (HCV) is a leading cause for cirrhosis and HCC development in most countries and plays a particularly important role in Western countries and in Japan where HBV is less common. HCV-infected individuals have a 17-fold increased relative risk of developing HCC. For those who develop HCV-related cirrhosis the annual incidence of HCC thereafter is 1 to 4%. HCC in relation to HCV in the absence of cirrhosis is rare and in most a second risk factor is present. In the West, the peak incidence of HCC related to HCV infection may not yet have been reached, and many infected individuals remain undetected. No vaccine is currently available. However, effective antiviral therapy reduces the risk of HCC and highly effective therapy for most HCV genotypes is now available (although expensive).

section 15 Gastroenterological disorders 3180 Alcohol Alcohol is a well-established risk factor for HCC and acts synergis- tically with chronic viral hepatitis and the many manifestations of insulin resistance. Attempts to reduce per capita alcohol consump- tion would impact favourably on HCC prevalence. Nonalcoholic fatty liver disease Insulin resistance manifest as hypertension, type 2 diabetes mellitus, and a high body mass index are associated with an increased risk of HCC, most likely through evolution to cirrhosis due to nonalcoholic fatty liver disease. Haemochromatosis Patients with haemochromatosis and cirrhosis have up to a 200-fold increased relative risk of HCC, which persists despite iron removal. Iron has a direct mitogenic effect through stimulation of hepatocyte proliferation. Early recognition through screening of those at risk and venesection before the onset of significant fibrosis should re- duce deaths from HCC. Pathogenetic mechanisms Important strides have been made in understanding the molecular biology of HCC development and progression. Alterations of many proteins involved in cell cycle regulation, such as p53 and cyclin/ CDK complex and several intracellular signalling pathways under- going oncogenic activation (specifically Ras/Raf/Mek/Erk, Wnt/ β-catenin and PI3k/Akt/mammalian target of rapamycin (mTOR)) appear key. The role of several growth factors and angiogenic factors in the tissue microenvironment, such as epidermal growth factor (EGF) and vascular EGF, has been confirmed. These pathways may present therapeutic options in the future. Cirrhosis is characterized by decreasing hepatocyte prolifer- ation as regenerative capacity becomes exhausted. A hypothesis for HCC development in the context of hepatocyte senescence in- volves critical telomere shortening which then triggers DNA re- pair mechanisms and chromosomal instability as the first step. Some tumours may originate from a particular subpopulation of stem cells, which persist in the adult liver and are found in portal triads. These ‘oval’ cells retain the potential to proliferate and differ- entiate into either hepatocytes or biliary epithelial cells; they have been implicated in the development of HCC as well as intermediate hepatocellular–cholangiocarcinoma. Clinical features Increasingly, HCC is first identified at imaging, either through screening or liver ultrasonography requested because of a change in clinical circumstance. When symptomatic, HCC may present with the triad of pain in the right upper quadrant, hepatomegaly, and weight loss. Patients presenting with these symptoms usually have large tumours, which are often palpable. Decompensation in any patient with cirrhosis (manifest as worsening ascites, variceal haemorrhage, jaundice, encephalopathy, or a combination of these)

should always be considered a possible manifestation of evolution from cirrhosis to HCC. Very rarely the first manifestation is sudden abdominal pain and swelling associated with haemoperitoneum due to tumour rupture, where imaging and analysis of ascitic fluid confirm the diagnosis; angiography is helpful and offers a treatment option through em- bolization. Other liver structures may be involved including, in order of frequency, the portal vein, hepatic veins, and the bile duct. Other rare presentations include haemobilia, pyrexia of unknown origin, and infrequently paraneoplastic manifestations such as poly- cythaemia, hyperthyroidism, hypercalcaemia, and hypoglycaemia. Investigation The diagnosis of HCC is confirmed with a combination of blood tests, various imaging techniques, and histology. Serum markers The α-fetoprotein concentration is the only laboratory test used in routine practice for the diagnosis of HCC. It is a glycoprotein synthesized by fetal liver and maternal plasma concentrations reach a maximum at the end of the first trimester, declining rapidly after birth to adult levels (0–10 ng/ml). Elevated levels are found in about 80% of patients with HCC and tend to be higher in African and East Asian populations (median 10 000 ng/ml) than in those from low- incidence areas (median 1000 ng/ml). This difference may reflect the different stage of disease at diagnosis. Specificity of α-fetoprotein varies according to aetiology and the presence of cirrhosis, but is elevated in most cases. Concentrations of α-fetoprotein above 200 ng/ml in patients with a liver mass are con- sidered diagnostic; the differential diagnosis includes nonseminoma germ cell tumours and hepatoblastoma (in infants). A few cases with elevated levels are reported in families in the absence of disease and attributed to single nucleotide polymorphisms. Serum α-fetoprotein increases with tumour growth and serial measurements showing a steady rise are strongly indicative of HCC, but most patients with HCC without cirrhosis have a normal α-fetoprotein level. A mod- estly raised and fluctuating α-fetoprotein level is common in patients with chronic HCV infection without HCC. The plasma α-fetoprotein level also rises during recovery from severe liver injury and falls with recovery. Other plasma markers, including α-fetoprotein vari- ants, have been considered but have not been adopted into clinical practice. Liver imaging Ultrasonography is inexpensive, safe, can detect HCC as small as 1 cm in diameter, and is the mainstay of screening programmes. HCC is typically hypoechoic (Fig. 15.24.6.1). Further imaging is always required for a definite diagnosis. Sensitivity is operator and patient dependent and is reduced in those with heterogeneous and nodular texture livers or with a high body mass index. In these, screening may best be performed alternating between liver ultrason- ography and MRI of the liver. Liver ultrasonography sensitivity can be improved with microbubble contrast. Doppler ultrasonography can detect tumour vascularity and portal vein flow patency prior to therapeutic intervention. The visibility of a mass during liver ultra-sonography will inform subsequent attempts at biopsy or ablation. Multislice CT is an established imaging modality for the diagnosis and staging of HCC and for planning surgical resection, providing clear definition of critical structures and liver volume measure- ment. The use of intravenous contrast medium allows more detailed characterization: a combination of arterial phase enhancement and portal venous ‘washout’ is almost diagnostic for HCC in lesions over

 2 cm in size in a cirrhotic liver (Fig. 15.24.6.2). Smaller lesions and those with a less typical vascular profile require additional imaging with MRI, which may improve diagnostic certainty. The sensitivity of CT is imperfect; 30% of tumours less than 2 cm in size remain undetected when compared with subsequent explant histology. CT is helpful in demonstrating hepatic features consistent with cirrhosis or portal hypertension and provides important staging information regarding tumour involvement in chest, lymph nodes, peritoneum, adrenals, and macrovascular invasion The sensitivity and specificity of MRI for the

detection of HCC is better than CT, especially for indeterminate lesions at CT and those smaller than 2 cm, but is less informative for extrahepatic staging purposes. A particular advantage is the range of contrast mechan- isms that can detect focal steatosis and restricted water diffusion. Excellent visualization of the hepatic arterial supply can be obtained by selective catheterization at angiography; as the vascular supply for HCC is predominantly arterial, a diagnostic ‘tumour blush’ is seen in most cases. However, angiography is now mainly used for therapy rather than diagnosis. A few HCCs (5–10%) have atypical features as a result of fat or glycogen accumulation or infarction that can alter the imaging char- acteristics. Remaining uncertainty is usually resolved by biopsy of the focal lesion. Without a firm diagnosis, continued surveillance is mandatory. Liver biopsy Histology remains the gold standard for diagnosis, although inter- pretation may be challenging, for example, distinguishing between well-differentiated HCC and severe dysplasia. On microscopic examination, HCC is typically composed of large eosinophilic or clear cells, arranged in trabeculae; intercellular bile is diagnostic when present (Fig. 15.24.6.3). Specific immunohistochemical staining is needed occasionally to distinguish poorly differenti- ated HCC from metastatic disease. Immunohistochemical markers for hepatocytes, such as hepatocyte paraffin 1 and α-fetoprotein, may help where morphology is not characteristic. Biopsy of the Fig. 15.24.6.1 Ultrasonography showing a small (1.4-cm) hypoechoic nodule in the liver (arrow). This finding is suggestive but not diagnostic for HCC and further evaluation with contrast-enhanced CT or MRI is warranted. From Levy AD, Mortele KJ, Yeh BM (eds) (2015). Gastrointestinal imaging. By permission of Oxford University Press. (a) (b) Fig. 15.24.6.2 Hepatocellular carcinoma (arrow) in a cirrhotic liver demonstrating typical arterial enhancement (a) and portal phase washout (b) on CT.

section 15 Gastroenterological disorders 3182 background liver should always be considered as the presence of cir- rhosis both increases the probability of a focal lesion being HCC and has implications for management. Percutaneous biopsy carries a small risk (<2%) of tumour seeding along the tract (relating to needle gauge) and has been avoided by some practitioners prior to curative treatments. Coagulopathy and ascites are additional hazards. For inaccessible lesions of sufficient concern, and where imaging is not diagnostic, laparoscopic biopsy or wedge resection is an alternative. Notwithstanding these issues, histological examination and sta- ging of surgical specimens are important for prognosis in HCC; poor differentiation grade and vascular invasion are strongly associ- ated with tumour recurrence following resection or transplantation. Determining prognosis based on needle-derived specimens is more challenging due to variation of differentiation and vessel involve- ment across the tumour. Dissection of mutations in HCC has highlighted three groups of mutated genes related to aetiological risk factors including CTNNB1 (alcohol), TP53 (HBV), and AXIN1. Further analyses have identi- fied more mutations associated with progression, including TERT, FGF3, FGF4, FGF19, CCND1, TP53, and CDKN2A. Molecular ana- lysis may therefore soon guide management of HCC, and tumour biopsy to aid this could become the norm. Surveillance The value of liver ultrasonographic surveillance for HCC remains contentious, but nevertheless is advised in all or most cirrhotic pa- tients by national and international guidelines. It has been shown to be cost-effective in cirrhosis where the annual risk of HCC exceeds 1.5%. Cirrhosis due to chronic viral hepatitis, alcohol-related and nonalcoholic fatty liver disease, haemochromatosis, and stage 4 pri- mary biliary cirrhosis fulfil that criterion. Incidence data for HCC in cirrhosis due to autoimmune hepatitis and α1-antitrypsin deficiency are less robust. According to international guidelines, HBV carriers considered at increased risk include Asians (men >40 years, women >50 years), Africans (from adulthood), those with a family history of HCC, and older white men with active disease. With HCV infection, surveil- lance can be limited

to those with advanced fibrosis or cirrhosis. For surveillance of HCC, liver ultrasonography repeated every 6 months has a sensitivity of 65–80% with a specificity exceeding 90%; the standard 6-month interval is based on average tumour doubling times. α-Fetoprotein alone is inadequate as a screening test as it lacks sensitivity, though is typically used in conjunction with ultrasonography. Management Cure is the goal, but extended survival is now reported with many approaches. Several treatment options are available; increasingly, therapeutic approaches are used in combination or sequentially. HCC is distinguished from almost all cancers by the absolute need to consider underlying liver function. Many patients with HCC will die from liver failure as part of the natural course of cirrhosis or ex- acerbated by treatment focused on HCC. Liver transplantation, sur- gical resection, and radiofrequency ablation all have the potential for cure and should be considered as first-line therapies. In general, transarterial chemoembolization (TACE)/embolization (TAE) is considered palliative with survival benefit, but for small lesions may occasionally be curative. A role for systemic internal radiotherapy has not yet been established. Sorafenib is targeted specifically at those with more advanced HCC; other tyrosine kinase inhibitors have proved disappointing. Cytotoxic drugs are considered ineffective. Sirolimus and analogues undoubtedly affect HCC beneficially, but a precise role for mTOR inhibitors has yet to be established. Surgical resection There are two important factors: patient fitness for surgery and tech- nical feasibility. Operative mortality is low with careful patient se- lection and laparoscopic approaches reduce risk further. Assuming cardiovascular fitness, the best candidates are those without cir- rhosis with a single tumour, or those with cirrhosis with minimal portal hypertension and well-preserved liver function. Selection of patients with cirrhosis should be restricted to those in Child–Pugh class A and a hepatic venous pressure gradient less than 12 mmHg. Survival in such cases reaches 70% at 5 years. The risk of hepatic de- compensation rises in those falling outside those criteria, with 50% survival in the presence of portal hypertension and 30% with jaun- dice. Increasingly, the estimated residual volume is another factor in selecting those most likely to survive surgery. Microscopic analysis of the whole tumour provides a clear indication of the likelihood of recurrence. Even after successful surgery there remains a significant risk that a new primary might develop. It can be difficult to distinguish recurrent disease from a new pri- mary. Early recurrence is usually due to dissemination prior to sur- gery, whereas later recurrence is more likely to be the result of de novo tumour development. Recurrence is associated with microvascular invasion, the maximal rate of proliferation, and the presence of satel- lite nodules, rather than the size of the lesion per se, although larger lesions are more likely to have adverse features. Surgical resection after spontaneous rupture of HCC is often essential if haemorrhage is not arrested by TAE. Liver transplantation Transplantation confers a significant long-term survival benefit for patients with cirrhosis, curing both the tumour and the underlying liver disease, but is not without risk. Donor shortage has restricted selection to those with predicted survival comparable to non-HCC indications. The Milan criteria (single tumour ≤5 cm or up to three tumours ≤3 cm) predict a 70% 5-year survival and 10% recurrence rate. Patients awaiting transplantation usually undergo palliative Fig. 15.24.6.3 Biopsy specimen from a well-differentiated HCC showing eosinophilic cells arranged in a trabecular pattern with pseudoglandular formation and bile plugs.

 therapy with TACE/TAE or radiofrequency ablation on the waiting list, but current waiting times result in a 25% dropout rate due to tumour growth after 12 months. Local management decisions will differ regarding priority for HCC on the liver transplant waiting lists. Extension of the Milan (or similar) criteria is considered fre- quently, which reflects observations that not all larger tumours ex- hibit ‘bad biology’ while some very small

tumours recur soon after liver transplantation. In some transplant centres, patients with larger tumours that respond well to local therapy are considered for liver transplantation. Better methods to predict tumour behaviour, inde- pendent of size, are still required. It is not unusual for HCC recurrence after liver transplantation to be extrahepatic, reflecting preoperative seeding. For these, treat- ment decisions are specific to the circumstance. Recent observations support the early observations that post-transplantation immuno- suppression with the mTOR inhibitor sirolimus reduces or delays tumour recurrence. Explant histology can be used to identify those at greater risk of recurrence and a need for increased surveillance. Ablative therapy Ablation is undertaken for tumours usually less than 3 cm in size. Several approaches are used, including radiofrequency, microwave, laser, high-intensity focused ultrasonography, or freezing, aiming to destroy the tumour and the local penumbra. For small lesions these treatments can be curative, but the reassurance of seeing the excised tumour under the microscope is absent. Whether a small lesion is ablated or resected will depend on lo- cation and patient fitness. Tumours in contiguity with vascular structures or the liver capsule may be less suited to ablation. Liver ultrasonography or CT is needed to guide placement for therapy and ablation cannot be undertaken unless the mass is seen clearly with these modalities. The procedure can be undertaken laparoscopic- ally or as an adjunct to surgery when there is a second less access- ible lesion. The procedure is followed very occasionally by abscess formation at the site of the tumour. Tumour tracking up the needle used for therapy has been reported. Post-treatment images reveal an avascular region following successful therapy. Survival after radiofrequency ablation is 75% at 3 years, similar to that for surgical resection of small tumours; for larger tumours mor- tality and recurrence rates increase exponentially with size. Embolization therapies: TACE and selective internal radiation therapy TACE is considered for more extensive disease where surgical ap- proaches or ablation are not applicable. It often needs to be repeated and this is safe provided it remains effective and liver function is ad- equate. TACE involves injection of a chemotherapeutic agent (typ- ically doxorubicin bound to beads) into hepatic arterial branches supplying the tumour, followed by embolic occlusion. Infarction and necrosis ensue since tumours derive 95% of their blood supply from the hepatic artery. To avoid extensive infarction of neighbouring liver tissue, portal vein patency is essential. Although cure is very rare, up to 60% of patients respond and tumour progression is delayed with a 20 to 60% improvement in 2-year survival. A postembolization syndrome of abdominal pain and fever is common, indicating tu- mour necrosis. There is a real risk of abscess formation so antibiotic prophylaxis is recommended. The most worrisome complication is the development of liver decompensation in those with borderline liver function prior to the procedure, hence careful assessment is es- sential; patients with jaundice or ascites rarely do well. The best can- didates have preserved liver function without vascular involvement or extrahepatic spread. Although TAE, which is used by many, achieves similar objective responses, only TACE has shown survival benefit in recent meta- analysis. Selective internal radiation therapy is similar in concept except that radioactive yttrium bound to beads designed to lodge in tumour capillaries is injected. The role for this approach in relation to other modalities has not yet been established. Chemotherapy HCC is considered resistant to chemotherapy and there is no benefit from systemic therapy. Responses to cytotoxic drugs, typically doxorubicin, are limited and hampered by side effects. Tamoxifen, octreotide, pravastatin, and gemcitabine have not shown any impact on survival. Agents targeting particular molecular pathways have not ful- filled early or theoretical promise with the exception of sorafenib, a multikinase inhibitor that reduces proliferation and angiogenesis. Randomized controlled trials in patients with cirrhosis without liver decompensation show a small survival benefit, but many are in- tolerant of the associated side effects. Radiotherapy

HCC is also considered resistant to radiotherapy, but some tumours respond well and it has proved useful for local and bone metastases. Prognosis Symptomatic presentation carries a poor prognosis; less than 10% of patients survive 3 years. Surveillance programmes, however, identify one-third of patients at an early stage when curative treat- ment is possible. Estimating prognosis depends on tumour stage, liver function, and overall health. Several staging systems have been proposed and are in clinical use, although none has been adopted universally. The Barcelona Clinic Liver Cancer system links tumour stage and Child–Pugh status with treatment strategy to optimize prognosis. Fibrolamellar hepatocellular carcinoma This rare variant presents in individuals in or around the third decade. Risk factors are not apparent, cirrhosis is not found, and the α-fetoprotein level is not elevated. The tumour tends to grow slowly; regional lymph node metastases are common. Histology is charac- teristic and reveals dense fibrotic bands surrounding eosinophilic tumour cells. The prognosis is much better than for HCC, probably because of slow growth in a young patient in the absence of liver injury, so regeneration is prompt. Although recurrence is common after resection, patients often do well with repeated surgery for liver masses and/or affected nodes. Hepatoblastoma This primary hepatic malignancy occurs in children, mostly under 3 years of age. The optimal treatment approach of resection combined

section 15 Gastroenterological disorders 3184 with chemotherapy achieves 5-year survival of 80%. Transplantation is an effective rescue therapy. Cholangiocarcinoma This is an epithelial malignancy of the biliary tree, which on anatomical grounds is separated into intrahepatic or extrahepatic and the latter then divided into hilar and lower duct tumours. Cholangiocarcinoma is less common than HCC and comprises around 7 to 10% of primary liver malignancies. The prognosis is poor unless detected very early, usually fortuitously. Epidemiology and aetiology Cholangiocarcinoma occurs most commonly in the sixth and sev- enth decades, is much more common in men, and twice as common in Asians. The incidence of intrahepatic cholangiocarcinoma ap- pears to be increasing worldwide. The highest reported incidence is in northern Thailand, due to endemic biliary infection with the trematode Opisthorchis viverrini. A high incidence is also seen in Korea where a similar infection with the fluke Clonorchis sinensis is prevalent. Other risk factors for the intrahepatic variant include oriental fibrocholestatic hepatitis, primary sclerosing cholangitis, Epstein–Barr virus, HCV infection, and exposure to Thorotrast (thorium dioxide which was used as contrast for angiographic pro- cedures between 1930 and the 1950s). The developmental abnormal- ities Caroli’s disease, congenital hepatic fibrosis, and von Meyenburg complexes are also associated with an increased risk of intrahepatic cholangiocarcinoma. Extrahepatic cholangiocarcinoma is associated with primary scler- osing cholangitis, abnormal anatomy at the choledochopancreatic junction, choledochal cysts, and infection by either C. sinensis or O. viverrini. Pathogenesis Most of the aetiological factors associated with cholangiocarcinoma induce chronic inflammation within the biliary tree, for example, age, cholelithiasis, smoking, alcohol consumption, developmental abnormalities of the biliary tree, parasitic biliary infection, and primary sclerosing cholangitis. Chronic inflammation stimulates inducible nitric oxide and free radical production in bile duct epi- thelial cells. These processes in turn induce oxidative DNA damage and telomere shortening with resultant loss or gain of critical genes involved in cellular control. Methylation of tumour suppressor pro- moters and cholangiocyte resistance to apoptosis are thought to be relevant to oncogenesis. Pathology Cholangiocarcinoma is an adenocarcinoma with a prominent stromal reaction. Histological variants include adenosquamous, signet cell, sarcomatous, clear cell, and lymphoepithelial. Three contrasting growth patterns have been applied to both intrahepatic and extrahepatic cholangiocarcinoma: mass-forming, periductal- infiltrative, and intraductal. Mass-

forming is the commonest mode of presentation of intrahepatic cholangiocarcinoma; tumours are often large, up to 15 cm in diameter. The margin is typically well circumscribed and lobulated and central necrosis may be present. Multicentricity is common, probably because of the propensity of the tumour to in- vade adjacent peripheral branches of the portal vein. Mass-forming tumours arising from extrahepatic ducts tend to be smaller, typically less than 2 cm. Periductal-infiltrative cholangiocarcinoma is most common at the hilum (Fig. 15.24.6.4), growing along the bile ducts and there- fore elongated, spiculated, or branchlike. These tumours are difficult to detect radiologically. Most intraductal cholangiocarcinomas are papillary adeno- carcinomas comprising innumerable frond-like proliferative columnar epithelial cells with slender fibrovascular cores. The tumours are usually small, sessile, or polypoid, often spreading superficially along the mucosal surface, often resulting in multiple tumours (papillomatosis) along the biliary tree. Occasionally, a large mass occludes the bile duct; some tumours produce profuse amounts of mucin akin to pancreatic intraductal papillary mu- cinous tumours. Clinical features With peripheral intrahepatic masses, patients present with upper abdominal pain, anorexia, malaise, and weight loss. Jaundice is an early feature of hilar tumours. Hepatomegaly is usual and spleno- megaly may occur in the context of a secondary biliary cirrhosis due to prolonged obstruction. Investigation A confident diagnosis of cholangiocarcinoma can be very difficult to make. Liver function tests are typically cholestatic with eleva- tion of plasma bilirubin and alkaline phosphatase concentrations. α-Fetoprotein concentrations are usually normal or only slightly raised. Carbohydrate antigen (CA)-19-9, a glycoprotein secreted by bile duct cells, is used as a tumour marker but has poor sensitivity and specificity. In patients with primary sclerosing cholangitis, a CA19-9 level over 100 U/mL is 80% specific for the presence of a superimposed cholangiocarcinoma. Depending on location, cross-sectional imaging or magnetic res- onance cholangiopancreatography (MRCP) may be helpful but not diagnostic. Mass-forming intrahepatic cholangiocarcinoma often reveals persistent peripheral enhancement on contrast-enhanced Fig. 15.24.6.4 Histological slide of resection margin following surgical resection of hilar cholangiocarcinoma showing neurovascular invasion, predictive of a poor outcome. Reproduced from Kerr DJ, Haller DG, van de Velde CJH, Baumann M (2016). Oxford Textbook of Oncology, 3rd edition with permission from Oxford University Press.

 CT imaging (Fig. 15.24.6.5). For extrahepatic hilar tumours, MRCP demonstrates first- and second-order duct involvement; a mass may be evident which is hypointense on T1-weighted imaging, but hyperintense on T2-weighted imaging. The differential diagnosis of hilar lesions includes inflammatory pseudotumour and metastasis. A periductal-infiltrative tumour appears on MRCP as a concentric irregular thickening of the bile duct with an abrupt calibre change (Fig. 15.24.6.6). An intraductal neoplasm may be visualized as an enhancing mass confined to the lumen of the bile duct. In all three, the ducts peripheral to the tumour may appear dilated with associ- ated atrophy of the liver. Percutaneous transhepatic cholangiography may help if prox- imal involvement of the biliary tree cannot be determined at MRCP and then used to drain segments prior to surgery. Endoscopic retrograde cholangiopancreatography with brush cytology and biopsy, or choledochoscopy, may assist in the diagnosis of a ma- lignant biliary stricture. Cytological analyses of specimens for an- euploidy by digital image analysis or for chromosomal alterations using fluorescence in situ hybridization improves diagnostic ac- curacy considerably but are not available routinely. Endoscopic ultrasonography-guided fine needle aspiration of hilar masses can achieve a sensitivity and specificity for malignancy of 89% and 100%, respectively. This technique can also be used to identify ma- lignant lymph nodes. Positron emission tomography imaging may be a useful adjunct

for diagnosis; laparoscopy can detect occult peritoneal spread. Management and prognosis For peripheral tumours, the main treatment approach is resection with prospect of cure, although results are generally disappointing. Poor prognostic factors include a preoperative CA19-9 concentration greater than 1000 U/mL, multifocal disease, liver capsule invasion, regional lymph node metastases, and mass-forming or periductal infiltrative histology. Extrahepatic tumours of the distal duct should be considered for a Whipple's procedure. Hilar tumours may be suitable for curative resection with an extended hemihepatectomy with anastomosis of a jejunal Roux loop to a hilar bile duct. Contraindications to surgery include bilateral involvement of second-order radicles and portal vein or hepatic artery encasement contralateral to the resection side. Despite surgical advances, the median 5-year survival for hilar tu- mours following resection is around 20% and controlled trials of ad- juvant chemotherapy are needed. More commonly, curative excision is not possible, and the aim is to establish biliary drainage. A stent (a) (b) Fig. 15.24.6.5 Parenchymal cholangiocarcinoma on CT: (a) unenhanced, (b) portal phase. Note the delayed central enhancement (arrow) and overlying capsular retraction typical of a fibrotic lesion. Fig. 15.24.6.6 Maximum intensity projection of three-dimensional MRCP demonstrates intrahepatic biliary dilatation and a stricture of the common hepatic duct due to a hilar cholangiocarcinoma (arrows).

section 15 Gastroenterological disorders 3186 can be placed through the growth endoscopically or via a percutan- eous transhepatic route to relieve jaundice and possibly reduce the frequency of episodes of cholangitis. Unilateral self-expanding metal stent placement has been shown to be effective and cost-effective if survival is expected to exceed 6 months. MRCP may assist optimal stent positioning. Photodynamic therapy may prolong survival. Conventional radiotherapy and high-dose local irradiation within the biliary tree with an iridium-192 wire may produce symptomatic relief. If bil- iary drainage can be achieved by these procedures, survival for 1 to 2 years is not unusual. In most countries, liver transplantation is not considered for cholangiocarcinoma as historical data indicate a high level of re- currence and related mortality. However, long-term survival has been reported in highly selected cases with unresectable hilar cholangiocarcinoma, based on high-dose neoadjuvant radiotherapy (external and internal) with chemosensitization and operative sta- ging to exclude patients with regional lymph node metastases, with 5-year post-transplantation survival of greater than 80%. Vascular complications were more common than expected and such findings need to be replicated before adoption. Malignant vascular tumours Angiosarcoma Angiosarcoma of the liver is a rare, aggressive primary tumour, often multifocal, which may arise in a cirrhotic liver. About 200 new cases are reported worldwide annually. Peak incidence is in the sixth and seventh decades and men are affected more commonly than women. In 75% of cases there is no recognized cause. There are associations with arsenic, vinyl chloride, and Thorotrast. Angiosarcoma is re- ported in workers in the vinyl chloride industry; strict safety regu- lations have been introduced but new cases still present because of the long latent period. Long-term androgen use, haemochroma- tosis, and von Recklinghausen disease (neurofibromatosis type 1) are other associations. Vinyl chloride-associated tumours are associated with TP53 mutations, while KRAS2 mutations are associated with Thorotrast-related and sporadic angiosarcoma. Patients may present with symptoms of hepatic venous outflow obstruction (abdominal pain and ascites) akin to the Budd–Chiari syndrome; 15% present with an acute abdominal crisis following tu- mour rupture and 15% present with splenomegaly and pancytopenia. A few present with metastases to lung, spleen, or bone marrow. Signs of high-output cardiac failure may be present; ascites may be blood stained after spontaneous haemoperitoneum. Disseminated intravas- cular coagulation may be associated (Kasabach–Merritt syndrome). On CT and MRI these

tumours demonstrate a variety of appear- ances, although most have focal hypodense areas, often haemor- rhagic, which demonstrate arterial enhancement with intravenous contrast (Fig. 15.24.6.7). A typical reticular pattern due to previous Thorotrast accumulation may be evident on CT, and vascular lakes may be observed on angiography. Diffuse infiltration may give rise to a nonspecific heterogeneous appearance of the liver. Liver biopsy is diagnostic in 25% of percutaneous and 65% of open procedures, the latter is preferred due to the risk of bleeding. Histology shows typical spindle or pleomorphic tumour cells with eosinophilic cytoplasm growing along the vascular lumen. The growth and blockage of sinusoids is associated with sinusoidal con- gestion and then liver cell atrophy. These cells are derived from vas- cular structures so express CD34 (Fig. 15.24.6.8). If Thorotrast or vinyl chlorides are the cause there may be considerable periportal and subcapsular fibrosis. Curative resection is rarely possible and chemotherapy is unproven. Hepatic epithelioid haemangioendothelioma This rare malignant tumour of vascular endothelial origin runs a clinical course resembling low-grade angiosarcoma. It is usually multifocal and slow growing. Patients are more often female and pre- sent in the fifth decade with right upper quadrant pain. Histological appearances are characteristic, with a spindle lesion infiltrating hepatocyte plates and hepatic veins. Immunohistochemistry using the vascular marker CD34 helps confirm the diagnosis. Resection is associated with a 5-year survival of 75% but may be unfeasible technically and recurrence is common. Transplantation is under- taken in a few, highly selected cases, but with an unpredictable out- come since recurrence is hard to predict. There is no proven role for chemotherapy. Benign liver tumours Haemangioma This is the most common benign tumour of the liver found in 2 to 5% of the general population with female preponderance; le- sions are often multiple. Histology, which is needed rarely, reveals multiple, large blood-filled spaces, lined by endothelial cells, with varying degrees of hyalinization and fibrosis. Cavernous haem- angioma refers to lesions larger than 4 cm which are fed by hepatic arterial branches and have a slow internal circulation. Haemangiomas are usually discovered incidentally during abdominal imaging. Larger tumours can cause abdominal symp- toms from mass affect and have been reported to cause portal hypertension, haemobilia, caval thrombosis, and a consumptive coagulopathy (Kasabach–Merritt syndrome). Spontaneous or traumatic ruptures have also been reported. Fig. 15.24.6.7 Portal phase CT examination demonstrating multiple focal hepatic and splenic lesions with vascular elements in an aggressive angiosarcoma.

 The typical appearance on ultrasonography is a well-circumscribed, uniform hyperechoic mass. MRI is a more sensitive and specific mo- dality, demonstrating a lesion that is hypointense on T1-weighted imaging and hyperintense on T2-weighted views. Dynamic imaging shows nodular peripheral enhancement with progressive centripetal ‘fill-in’ and retention of contrast in the portal phase (Fig. 15.24.6.9). Occasionally biopsy is required to confirm diagnosis in larger lesions where typical features are not present. Usually no treatment is required and patients can be given re- assurance. Large symptomatic haemangiomas can be managed by surgical resection or embolization. Avastin has been reported to shrink such masses. Liver transplantation has been performed on rare occasions when resection is impossible and symptoms are intractable. Focal nodular hyperplasia Focal nodular hyperplasia (FNH) is the second most common benign tumour of the liver, with a prevalence of 0.4 to 0.8%. It is nine times more prevalent in women than men and usually pre- sents in the third or fourth decades. Tumours are often multiple and occasionally reach a considerable diameter, but most often are under 5 cm in size. The oral contraceptive pill does not in- duce FNH formation, but oestrogens promote FNH growth and vascularity. Histology shows a central large fibrous septum containing a branch of the

hepatic artery, which divides in a star-shaped manner and is not accompanied by either the portal vein or bile duct. Within the central ‘stellate scar’ there is bile ductular pro- liferation surrounded by polyclonal nodular hyperplasia of the hepatic parenchyma giving a pseudobiliary cirrhotic pattern. The hyperplastic response of the hepatic parenchyma may be driven by angiopoietins released from the hepatic artery branch, or in response to a hyperperfusion injury. The less common, recently recognized ‘telangiectatic’ variant is now classified as an adenoma. FNH is usually detected on ultrasonography but requires further characterization. On MRI the lesion demonstrates (a) (b) (c) (d) Fig. 15.24.6.9 Typical hepatic haemangioma on MRI with high signal on (a) heavily T2-weighted imaging; (b) low signal on T1-weighted imaging; (c) peripheral nodular arterial enhancement; and (d) progressive infilling and persisting enhancement on delayed imaging. (a) (b) Fig. 15.24.6.8 Biopsy specimen from an angiosarcoma showing irregular cells with pleomorphic and hyperchromatic nuclei infiltrating the sinusoids and terminal hepatic vein branches ((a) haematoxylin and eosin; (b) stained for CD34).

section 15 Gastroenterological disorders 3188 homogeneous signal intensity with the central scar hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging (Fig. 15.24.6.10a). In 80% of lesions less than 3 cm in size, a cen- tral scar may not be visible. With administration of contrast medium, avid arterial enhancement occurs around the scar (if present) and the lesion then becomes isointense in the portal phase. With delayed imaging, the central scar may become hyperintense. Hepatobiliary contrast media such as gadoxetic acid (Primovist) typically accumu- late in FNH lesions on delayed imaging, which may help discrimin- ation from adenomas that do not retain the agent (Fig. 15.24.6.10b). If the imaging techniques are not diagnostic, targeted biopsy usually confirms the diagnosis. The prognosis is excellent and malignant change has not been recorded. For women on the oral contraceptive pill where FNH appears likely, but biopsy is not straightforward, a surveillance ap- proach with cessation of oestrogen use may provide reassurance. Hepatic adenoma Hepatic adenoma is 10 times less common than FNH and rare in men, with a female-to-male ratio of 4:1, and they share CT and MRI features of hepatic arterial enhancement and isointensity in the venous phase. Hepatic adenoma may be multiple, and it is not un- usual to find both FNH and adenoma in the same liver. The presence of more than 10 adenomas defines hepatic adenomatosis. The incidence of adenomas among long-term users of the oral contraceptive pill is approximately 4 per 100 000 and increases with length of contraceptive use. In women who do not use oral contra- ceptives, or have used them for less than 2 years, the incidence is 1 per million. Adenomas may increase in size in pregnancy and shrink with suspension of oestrogen use, and often become undetectable following the menopause. A few cases arise due to genetic predisposition. Patients with GSD1a may develop inflammatory hepatic adenoma, especially men and those aged over 25 years. Adenoma expressing HNF-1α may be associated with a family history of maturity-onset diabetes mellitus of the young type 3 (MODY 3). Most are associated with somatic variants including inflammatory/telangiectatic with muta- tions in gp-130, previously classified as telangiectatic FNH, HNF-1α positive, and β-catenin positive. The incidence of adenoma is also increased in patients with type 2 diabetes mellitus, haemochroma- tosis, acromegaly and in men using anabolic steroids. On microscopic examination, adenomas consist of trabeculae of mature-appearing hepatocytes with absent portal tracts and Kupffer cells, though arterial branches are present. Genetic mutations have been identified which correlate with distinct biological phenotypes. Biallelic HNF1A mutations define adenomas with marked steatosis, a lack of both cytological abnormalities and inflammatory infil- trates, and a very low risk of malignant transformation. Mutations resulting in β-catenin (CTNNB1) activation are present in 15%

of cases and are associated with a higher risk of transformation into HCC. A third group of adenomas has been defined by the absence of known mutations but the presence of inflammatory infiltrates and features such as sinusoidal dilatation, ductular reaction, and cytological abnormalities. Such ‘telangiectatic’ adenomas, origin- ally called telangiectatic FNH, are thought to have a higher risk of bleeding and may harbour malignant potential. Mutations in the IL6ST gene encoding gp130, activating the interleukin-6 pathway, have been associated with most of these lesions. A fourth group comprises adenomas without known mutations or inflammatory infiltrates. Hepatic adenoma is typically an incidental finding but may present with abdominal pain, which may be severe and associ- ated with cardiovascular compromise, in which case spontaneous rupture and haemorrhage should be considered (Fig. 15.24.6.11). The main risks, which make the distinction between adenoma and FNH important clinically, are spontaneous haemorrhage and malignant transformation, and for both complications the risk is linked to size, such that tumours with a diameter greater than 5 cm should be considered for intervention. The risk of haemorrhage is greater with telangiectatic tumours, while malignant transform- ation is seen more often with GSD1a or with β-catenin-expressing adenomas. CT imaging of complex adenomas may demonstrate an area of haemorrhage and occasionally internal fat or calcification, making the appearances relatively nonspecific. More typical le- sions demonstrate homogeneous enhancement in the hepatic arterial phase with lesions becoming isoattenuating in the portal venous phase. With MRI, adenomas are hyperintense or isointense (a) (b) Fig. 15.24.6.10 Delayed ‘hepatobiliary’ phase imaging on MRI following gadoxetic acid administration demonstrates typical accumulation in (a) focal nodular hyperplasia (arrow) but nonspecific low signal in other lesions such as (b) adenoma (arrow).

 on T1-weighted imaging and often slightly hyperintense on T2- weighted imaging (Fig. 15.24.6.12). These appearances can be indistinguishable from FNH when no central scar is present. The MRI demonstration of fat within the lesion may help identify the HNF1A variant. It is suggested that lesions larger than 5 cm should be con- sidered for resection because of the risk of bleeding or malignant transformation.
A conservative approach involves discontinuation of the oral contraceptive pill or androgens, which may reduce tu- mour size, weight loss with attention to insulin resistance, and sur- veillance imaging. Interventions include surgery, radiofrequency ablation, TAE, or a combination of each according to location and patient fitness. Smaller lesions may grow after resection of a large lesion. Spontaneous haemorrhage can often be controlled with TAE. Inhibitors of β-catenin are being sought for targeted therapy. Lymphangioma Lymphangiomas consist of dilated lymphatic channels that compress normal liver parenchyma. Often these occur as part of multisystem disease affecting bone, brain, soft tissues, and lung. Typically, using MRI, multiple cystic areas in the liver are seen that do not enhance with contrast. Angiomyolipoma While common in the adrenals and kidneys, these lesions can be found in the liver and are associated in 6 to 10% of cases with tu- berous sclerosis. Mesenchymal hamartoma This lesion is more common in males and usually manifests within the first 2 years of life. Patients usually present with progressive (a) (b) Fig. 15.24.6.11 CT image of an acutely presenting spontaneous adenoma rupture. Unenhanced imaging demonstrates hyperdense blood clot ((a) and (b), star) with low-attenuation fluid anteriorly. This fails to enhance following contrast administration (b) whereas the focal arterial enhancement posteriorly ((b), arrow) indicates the underlying adenoma. (a) (b) (c) (d) Fig. 15.24.6.12 Multiple adenomas (arrows) demonstrating subtle signal variation on (a) T2-weighted MRI; (b) T1-weighted imaging; (c) homogeneous arterial enhancement (arrows); and (d) isointensity on

portal phase imaging.

section 15 Gastroenterological disorders 3190 abdominal swelling. Structurally, the tumour is composed of mixed endodermal and mesodermal components in a connective tissue stroma. Surgical resection is the treatment of choice. Biliary cystadenoma This cystic lesion usually occurs in middle-aged women. Papillary infolding is characteristic on ultrasonography or CT. Malignant potential is recognized and distinction from cystadenocarcinoma on radiology alone is difficult. Cystic aspiration for diagnosis is un- helpful and complete excision is required to avoid recurrence. Secondary liver tumours The liver is a common site for metastases, which thrive on the rich blood supply and favourable milieu for tumour growth. Secondaries are often discovered as part of the staging process for primary malig- nancy (synchronous) or during follow-up (metachronous) or indeed may be the initial presentation. Liver function tests may be normal, but the alkaline phosphatase level usually rises with increased tu- mour mass. Symptoms include abdominal pain; with extensive infil- tration, jaundice and ascites may occur and presentation with acute liver failure is reported. If a primary tumour is not apparent, tar- geted liver biopsy under ultrasonography usually confirms malig- nancy and an immunohistochemical panel for antigens may point to the origin. For most primary cancers with liver involvement, the prognosis is poor and treatment palliative. However, there are notable excep- tions such as colorectal and neuroendocrine tumours. A quarter of patients with colorectal cancer have liver metastases at presenta- tion with a median survival untreated of between 6 and 9 months. Hepatic resection in appropriate candidates where the primary has been resected achieves 30 to 40% 5-year survival, with cure in some patients. The liver remnant must be adequate and disease should be preferably unilobar. The role of adjuvant chemotherapy is un- clear, nor is it clear if there is benefit from synchronous resection of primary and secondary disease. Portal vein embolization of the tumour-affected lobe has become a standard method for increasing the size of the liver remnant to reduce the risk of decompensation. Innovative approaches include downstaging the tumour using systemic chemotherapy to within criteria for resection, the same no- tion applies with systemic internal radiotherapy, hepatic arterial infusion of chemotherapy, targeted therapies against EGF recep- tors, and combining radiofrequency ablation with surgery to pre- serve liver volume. None of these modalities has been subject to randomized study. Neuroendocrine tumours typically grow slowly and are therefore more amenable to therapy even when multifocal within the liver. Directed therapies such as surgical debulking, embolization, TACE, and ablation have been shown to improve symptoms and slow pro- gression although survival benefit is unproven. Sirolimus, somato- statin analogues, and targeted agents against vascular EGF activity also appear efficacious. For carcinoid tumour, where the primary has been removed and there is no evidence of extrahepatic disease, survival after liver transplantation approaches 70% at 5 years with recurrence-free survival nearer 50%. Gastrointestinal stromal tumours are also slow growing and metastasize to the liver and good control can be achieved using a combination of surgical resection and tyrosine kinase inhibitors. FURTHER READING Bioulac-Sage P, et al. (2008). Benign and malignant vascular tumors of the liver in adults. Semin Liver Dis, 28, 302–14. Bioulac-Sage P, et al. (2019). Snapshot summary of diagnosis and management of hepatocellular adenoma subtypes. Clin Res Hepatol Gastroenterol, 43, 12–9. Bruix J, Reig M, Sherman M (2016). Evidence-based diagnosis, sta- ging, and treatment of patients with hepatocellular carcinoma. Gastroenterology, 150, 835–53. Chow FC, Chok KS (2019). Colorectal liver metastases: an update on multidisciplinary approach. World J Hepatol, 11, 150–72. Garrot C, Stuart K (2007). Liver-directed therapies for metastatic neuroendocrine tumours. Hematol Oncol Clin North Am, 21, 545–60. Habib A, et al. (2015). Transarterial approaches to primary and sec- ondary hepatic malignancies. Nat Rev Clin

Oncol, 12, 481–9. Ito F, et al. (2009). Hilar cholangiocarcinoma: current management. Ann Surg, 250, 210–18. Khan AS, Dageforde LA (2019). Cholangiocarcinoma. Surg Clin North Am, 99, 315–35. Kulke MH, et al. (2019). Real-world treatment patterns and clinical outcomes in advanced gastrointestinal neuroendocrine tumors
(GI NET): a multicenter retrospective chart review study. Oncologist, pii, doi: 10.1634/theoncologist.2018-0519. Lazar DC, et al. (2019). Malignant hepatic vascular tumors in adults: characteristics, diagnostic difficulties and current management. World J Clin Oncol, 10, 11–35. Llovet JM, Bruix J (2003). Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization im- proves survival. Hepatology, 37, 429–42. Llovet JM, et al. (1999). Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis, 19, 329–38. Maluf D, et al. (2005). Hepatic angiosarcoma and liver transplant- ation: case report and literature review. Transplant Proc, 37, 2195–9. Mazzaferro V, et al. (1996). Liver transplantation for treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med, 334, 693–9. Nault JC, et al. (2013). High frequency of telomerase reverse- transcriptase promoter somatic mutations in hepatocellular car- cinoma and preneoplastic lesions. Nat Commun, 4, 2218. Pilati C, et al. (2014). Genomic profiling of hepatocellular adenomas reveals recurrent FRK-activating mutations and the mechanisms of malignant transformation. Cancer Cell, 25, 428–41. Rebouissou S, et al. (2009). Frequent in-frame somatic deletions ac- tivate gp130 in inflammatory hepatocellular tumours. Nature, 457, 200–4. Woodall CE, et al. (2008). Hepatic malignant epithelioid hemangio endothelioma: a case report and review of the literature. Am Surg, 74, 64–8. Zucman-Rossi J, et al. (2015). Genetic landscape and biomarkers of hepatocellular carcinoma. Gastroenterology, 149, 1226–39.

Revision #1
Created 2026-01-22 16:38:50 UTC by Omar Ayman
Updated 2026-01-22 16:38:50 UTC by Omar Ayman