# 16 - 87 Tumors of the Liver and Biliary Tree

## 87 Tumors of the Liver and Biliary Tree

Rarely, RET fusions and TRK fusions can be seen in patients with metastatic colorectal cancer. These patients can have tremendous responses to the appropriate RET and TRK inhibitors with marked prolongation of survival. CANCERS OF THE ANUS Cancers of the anus account for 1–2% of the malignant tumors of the large bowel. Anal cancer by convention refers to squamous cell carci nomas arising in the anorectal region. Other types of cancers including melanoma, neuroendocrine cancer, lymphoma, and mesenchymal tumors can arise in these regions but are referred to by their histologic subtype and are not the subject of this chapter. True adenocarcinomas arising from the glands in the anal canal that are distinct from rectal adenocarcinoma can also arise but, for all intents and purposes, are indistinguishable from rectal adenocarcinoma and treated accordingly. Most anal cancers arise in the anal canal, the anatomic area extend ing from the anorectal ring to a zone approximately halfway between the pectinate (or dentate) line and the anal verge. The dentate line can be quite variable in adults but, on average, is 4 cm from the anal verge. Squamous cell carcinomas are characterized as either nonkeratinizing or keratinizing. Older terms such as cloacogenic and basaloid are not used anymore, and these tumors are instead characterized as nonkera tinizing. Outcomes for keratinizing and nonkeratinizing squamous cell carcinoma of the anus are not different. The development of anal cancer is associated with infection by human papillomavirus (HPV), the same virus etiologically linked to cervical and oropharyngeal cancers. The same HPV subtypes associ ated with cervical cancer are seen in anal cancer. The infection may lead to squamous intraepithelial lesions (SILs), which are classified as either low grade (LSIL) or high grade (HSIL). LSILs are associated with non–cancer-causing HPV subtypes, are not considered precancerous, and can spontaneously regress. HSILs are associated with HPV16 and are considered precancerous. Anal cancer risk is increased in both men and women with immunocompromised states including solid organ transplant patients, patients with chronic immunosuppression with glucocorticoids, and patients living with HIV, particularly with low CD4 counts. Anal cancers occur most commonly in middle-aged per sons and are more frequent in women than men. At diagnosis, patients may experience bleeding, pain, sensation of a perianal mass, and pru ritus. Examination of and attention to the inguinal lymph nodes on imaging is important because anal cancers often spread initially to the inguinal region rather than the iliac nodes like rectal cancer. The standard treatment for anal cancers consists of 5-FU, mitomy cin, and concurrent external beam radiation therapy. The majority of patients will experience a complete response to therapy. Some patients will have ongoing resolution of their cancer over the 6 months after completion of therapy. Therefore, the decision about whether a patient has had a complete response to therapy is not

made until after 6 months following chemoradiation. Patients who are considered primarily refractory to chemoradiation or those with locally recurrent disease can be cured with radical resec tion (i.e., APR). In addition to those experiencing a local recurrence, ~10% of patients may experience continued rectal incontinence due to the effects of radiation therapy and undergo a subsequent colostomy. Metastatic anal cancer is considered incurable. It may respond well to carboplatin and paclitaxel. PD-1 antibodies have limited activity in patients with metastatic disease. Acknowledgment Robert J. Mayer contributed to this chapter in the prior edition and material from that chapter has been retained here. ■ ■FURTHER READING André T et al: Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. N Engl J Med 383:2207, 2020. Cercek A et al: PD-1 blockade in mismatch repair-deficient locally advanced rectal cancer. N Engl J Med 386:2363, 2022. Colón-López V et al: Anal cancer risk among people with HIV infec tion in the United States. J Clin Oncol 36:68, 2018.

Dekker E et al: Colorectal cancer. Lancet 394:1467, 2019. Eng C et al: Anal cancer: emerging standards in a rare disease. J Clin

Oncol 40:2022. Grothey A et al: Duration of adjuvant chemotherapy for stage III colon cancer. N Engl J Med 378:1177, 2019. Inadomi JM: Screening for colorectal neoplasia. N Engl J Med 376:149, 2017. Long H et al: Pathways of colorectal carcinogenesis. Gastroenterology 158:291, 2020. Petrelli F et al: Prognostic survival associated with left-sided vs right-sided colon cancer. A systemic review and meta-analysis. JAMA Oncol 3:211, 2017. Schrag D et al: Preoperative treatment of locally advanced rectal

cancer. N Engl J Med 389:1631, 2023. Siegel RL et al: Colorectal cancer statistics 2024. CA Cancer J Clin 12:49, 2024. Josep M. Llovet

Tumors of the Liver

and Biliary Tree CHAPTER 87 Tumors of the Liver and Biliary Tree Liver cancer is the sixth most common cancer worldwide, the third leading cause of cancer-related deaths and the leading cause of death among cirrhotic patients. Liver cancer comprises a heterogeneous group of malignant tumors that range from hepatocellular carcinoma (HCC; ~85 cases), intrahepatic cholangiocarcinoma (iCCA; ~10%), and other malignancies, such as fibrolamellar HCC, mixed HCCiCCA, epithelioid hemangiothelioma, and the pediatric cancer hepato blastoma. The burden of liver cancer is increasing globally. HEPATOCELLULAR CARCINOMA ■ ■EPIDEMIOLOGY AND RISK FACTORS Overall, liver cancer accounts for 7% of all cancers (~900,000 new cases each year), and HCC represents 85% of primary liver cancers. The highest incidence rates of HCC occur in Asia and sub-Saharan Africa due to the high prevalence of hepatitis B virus (HBV) infection, with 20–35 cases per 100,000 inhabitants. Southern Europe and now North America have intermediate incidence rates (10 cases per 100,000), whereas Northern and Western Europe have low incidence rates of less than 5 cases per 100,000 inhabitants. In the United States, the incidence of liver cancer is 40,000 cases per year (Fig. 87-1). HCC has a strong male preponderance, with a male-to-female ratio estimated to be 2.5:1. The incidence increases with age, reaching a peak at 65–70 years old. In Chinese and in black African populations (where vertical transmis sion of HBV occurs), the mean age is 40–50 years. By contrast, in Japan mean age in men is now around 75 years. The main risk factors for HCC development are cirrhosis—an asso ciated chronic liver damage caused

by inflammation and fibrosis—of any etiology, chronic infection by HBV or hepatitis C virus (HCV) infection, alcohol abuse, metabolic syndrome, and hemochromatosis (associated to HFE1 gene germline mutations) (Fig. 87-1). Cirrhotic patients represent 1% of the human population, and one-third of them will develop HCC during their lifetime. Long-term follow-up studies have established an annual risk of HCC development of 3–8% in HBV- or HCV-infected cirrhotic patients. HCC is less common (1–2% per year) in cirrhosis associated with alcohol, metabolic dysfunction– associated steatohepatitis (MASH, formerly known as nonalcoholic steatohepatitis or NASH), α1-antitrypsin deficiency, autoimmune hepa titis, Wilson's disease, and cholestatic liver disorders. Predictors of liver cancer development among cirrhotic patients have been associated

Central Europe Western Europe North America Western Africa Andean Latin America South Latin America ASR (World) per 100,000 ≥8.4 5.8–8.4 4.7–5.8 3.3–4.7 PART 4 Oncology and Hematology Not applicable No data <3.3 FIGURE 87-1 Distribution of hepatocellular carcinoma (HCC) incidence according to geographical area and etiology. HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis. (Reproduced with permission from JM Llovet et al: Hepatocellular carcinoma. Nat Rev Disease Primers 21:76, 2021.) with liver disease severity (platelet count of <100,000/μL, presence of portal hypertension), the degree of liver stiffness as measured by transient elastography, and liver gene signatures capturing the cancer field effect. In terms of attributable risk fraction, HBV infection—a DNA virus that can cause insertional mutagenesis and affects ~300 million people globally—accounts for ~50% of HCC cases globally (60% in Asia and Africa and 20% in the Western world). Among patients with HBV infection, a family history of HCC, HBeAg seropositivity, high viral load, and genotype C are independent predictors of HCC development. HCV infection—an RNA virus that affects ~70 million people—is responsible for ~30% of cases and is the main cause of HCC in Europe and North America. Among patients with HCV infection, HCC occurs almost exclusively when relevant advanced liver damage and fibrosis are present, particularly if associated with HCV genotype 1b. Alcohol consumption and metabolic syndrome due to diabetes and obesity are responsible for ~30% of cases. MASH is the fastest grow ing cause of cirrhosis in developed countries and currently represents ~15–20% of HCC cases in the West. The annual incidence of HCC in MASH-related cirrhosis (1–2%/year) justifies including cirrhotic patients in surveillance programs. Nonetheless, it has to be taken into account that 25–30% of MASH-associated HCCs occur in the absence of cirrhosis. A PNPLA3 polymorphism is strongly associated with fatty and alcoholic chronic liver diseases and HCC occurrence. Finally, other cofactors contributing to HCC development in all etiologies are tobacco, aflatoxin B1 (a fungal carcinogen present in food supplies that induces TP53 mutations), and aristolochic acid contained in Chinese medicine herbs. ■ ■MOLECULAR PATHOGENESIS HCC development is a complex multistep process that starts with precancerous cirrhotic nodules, so-called low-grade dysplastic nodules (LGDN) that evolve to high-grade dysplastic nodules (HGDN) that can transform into early-stage HCC. Molecular studies support the pivotal role of adult hepatocytes as the cell of origin, either by directly transforming to HCC or by de-differentiating into hepatocyte precur sor cells. Alternatively, progenitor cells also give rise to HCC with progenitor markers. Genomic analysis has provided a clear picture of the main drivers responsible for HCC initiation and progression. This tumor results

Eastern Europe Japan East Asia South-East Asia North Africa, Middle East Oceania Etiology HCV Alcohol HBV Southern Africa NASH & other from the accumulation of around 40–60 somatic genomic alterations per tumor, among which 4–8 are considered driver cancer genes. HCC is a

prototypical inflammation-associated cancer, where immune microenvironment and oxidative stress present in chronically damaged livers play pivotal roles in inducing mutations. In preneoplastic HGDN, mutations in telomere reverse transcriptase (TERT) gene (20% of cases) and gains in 8q have been described. Oncogenic transformation occurs upon additional genomic hits. The main molecular drivers of HCC are in the telomerase reverse transcriptase (TERT) promoter (56%), TP53 (27%), and CTNNB1 (26%), all of which are unactionable with molecular therapies. Genes commonly mutated in other solid tumors such as EGFR, HER2, PIK3CA, BRAF, or KRAS are rarely mutated in HCC (<5%) (Table 87-1). Studies assessing copy-number alterations in HCCs have consistently identified: (1) high-level amplifications at 5–10% prevalence containing oncogenes in 11q13 (CCND1 and FGF19) and 6p21 (VEGFA), TERT focal amplification, and homozygous dele tion of CDKN2A; and (2) common amplifications containing MYC (8q gain). Overall, only ~20–25% of HCCs have at least one actionable mutation. Some risk factors have been associated with specific molecu lar aberrations. HBV integrates into the genome of driver genes, such as the TERT promoter, MLL4, and cyclin E1 (CCNE1). Alcohol abuse and HCV infection have been associated with CTNNB1 mutations. TP53 mutations are the most frequent alterations with a specific hotspot of mutation (R249S) in patients with aflatoxin B1 exposure. Molecular and Immune Classes Genomic studies have revealed two molecular subclasses of HCC, each representing ~50% of patients. The proliferative subclass associated with poor outcomes, HBV-related etiologies, and overexpression of α-fetoprotein is enriched by activa tion of Ras, mammalian target of rapamycin (mTOR), and insulin-like growth factor (IGF) signaling and FGF19 amplification. By contrast, the so-called nonproliferative subclass contains a subtype character ized by CTNNB1 mutations and better outcome. Another classification based upon immune status has been proposed. It defines an inflamed HCC class in ~35% of cases (i.e., hot tumors), characterized by immune infiltrate with expression of PD-1/PD-L1, enrichment of T-cell activa tion, and better response to immunotherapies, and a noninflamed class (cold tumors), which includes the excluded subclass associated with activation of pathways related with immune escape (i.e., Wnt signal ing) or absence of T-cell infiltrate. None of this molecular knowledge

TABLE 87-1 Molecular Aberrations Common in Hepatocellular Carcinoma (HCC)a PATHWAY TARGET PREVALENCE (%) Mutations Telomere stability TERT promoter

p53/cell cycle control TP53 ATM RB1

Wnt/β-catenin signaling CTNNB1 AXIN1

Chromatin remodeling ARID1A ARID2 KMT2A KMT2C

Ras/PI3K/mTOR pathway RPS6KA3 TSC1/TSC2

Oxidative stress NFE2L2 KEAP1

High-level focal amplifications VEGF signaling VEGFA

FGF signaling FGF19

Cell-cycle control CCND1 protein

Target with homozygous deletion TP53/cell-cycle control CDKN2A TP53 Retinoblastoma 1

Wnt/β-catenin signalling AXIN1

aRecurrent mutations, focal amplifications, or homozygous deletions in HCC based on next-generation sequencing analyses. has yet been translated into actual clinical benefits for any specific molecularly based subgroups, and thus, precision oncology is still an unmet goal of therapy. ■ ■PREVENTION AND EARLY DETECTION Prevention Primary prevention of HCC can be achieved by vac cination against HBV and effective treatment of HBV and HCV infec tion. Universal vaccination against HBV infection is associated with a significant decrease of the incidence of HCC. Nowadays, HBV vaccina tion is recommended to all newborns and high-risk groups, following World Health Organization guidelines, and people with risk factors for acquiring HBV infection, such as health workers, travelers to areas where HBV infection is prevalent, injecting drug users, and people with multiple sex partners. Effective antiviral treatments for patients with chronic HBV infection— achieving undetectable viral titers (circulating HBV-DNA)—result in 50–80% risk reduction of HCC development. Treatment of HCV with direct-acting antiviral agents (DAAs) yields >90% sustained virological response (SVR) rates after 12 weeks of treatment, thus significantly reducing HCC occurrence. Once cirrhosis is established, the incidence of HCC is lower for patients with SVR than for those with active viral disease, although they continue to have persistent HCC risk. Clinical practice guidelines recommend coffee consumption as a preventive strategy in patients with chronic liver disease. Aspirin, statins, and metformin have shown preventive effects but are not yet recommended as formal chemopreventive strategies. Surveillance Surveillance programs aim to reduce cancer-related mortality. This is usually achieved through early detection that enhances the applicability and cost-effectiveness of curative therapies. U.S. and European guidelines recommend surveillance for patients at high risk for HCC on the basis of cost-effectiveness analyses.

Surveillance is recommended for cirrhotic patients owing to any cause, those with HCV-related advanced fibrosis, and patients with chronic HBV infection if Asian aged >40 years, African aged

> 20 years, family history of HCC, or patients with sufficient risk by risk scores such as PAGE-B. In terms of liver dysfunction, the presence of advanced cirrhosis (Child-Pugh class C) prevents potentially curative therapies from being employed, and thus surveillance is not recom mended. As an exception, patients on the waiting list for liver trans plantation, regardless of liver functional status, should be screened for HCC in order to detect tumors exceeding conventional criteria and to define priority policies for transplantation.

Ultrasonography every 6 months with serum α-fetoprotein (AFP) levels is the recommended method of surveillance. It has a sensitivity of ~65% and a specificity of >90% for early detection. A shorter followup interval (every 3–6 months) is recommended when a nodule of <1 cm has been detected. Computed tomography (CT) and magnetic resonance imaging (MRI) are not recommended as screening tools due to lack of data on accuracy, high cost, and possible harm (i.e., radiation with CT). Contrast-enhanced MRI can be considered in patients with obesity and

fatty liver, where visualization with ultrasound is subopti mal. The accuracy of other serum biomarkers proposed, such as des-γ carboxyprothrombin (DCP) and the L3 fraction of AFP (AFP-L3), in early detection is not known. CHAPTER 87 Despite the fact that surveillance is cost-effective in HCC, the global implementation of such programs is estimated to engage ~50% of the target population in Europe and ~30% in the United States. Public health policies encouraging the implementation of such programs could lead to an increase in early tumor detection. Tumors of the Liver and Biliary Tree Diagnosis HCC is generally diagnosed at early or intermediate stages in Western countries but at advanced stages in most Asian (except Japan) and African countries. A surveillance program yields detection of early HCC in 70–80% of cases. At these stages, the tumor is asymptomatic, and diagnosis can be made by noninvasive (radiological) or invasive (biopsy) approaches. Without surveillance, HCC is discovered either as a radiological finding or due to cancerrelated symptoms. If symptoms are present, the disease is already at an advanced stage, with a median life expectancy of <1 year. Symptoms include malaise, weight loss, anorexia, abdominal discomfort, or signs related to advanced liver dysfunction. NONINVASIVE (RADIOLOGICAL) DIAGNOSIS Patients enrolled in a surveillance program are diagnosed by identification of a new liver nodule on abdominal ultrasound. Noninvasive criteria can only be applied to cirrhotic patients and are based on imaging techniques obtained by four-phase multidetector CT scan (four phases are unen hanced, arterial, venous, and delayed) or dynamic contrast-enhanced MRI. A flowchart of diagnosis and recall policy recommended by U.S. and European guidelines is summarized in Fig. 87-2. In nodules >1 cm or with AFP ≥20 ng/mL or rising AFP, multiphasic contrast-enhanced CT or MRI is recommended. Using these techniques, the typical hall mark of HCC consists of vascular uptake of the nodule in the arterial phase with washout in the portal venous or delayed phases. This radio logical pattern captures the hypervascular nature characteristic of HCC and has a diagnostic specificity of ~95–100%, making a biopsy unnec essary. The Liver Imaging Reporting and Data System (LI-RADS) has been proposed as a way of classifying radiological findings. Essentially, nodules >10 mm visible on multiphase exams are assigned category codes reflecting their relative probability of being benign, HCC, or other hepatic malignant neoplasm. LI-RADS-1 lesions have a 0% prob ability of HCC, whereas lesions assigned to the LI-RADS-4 category are likely to be an HCC in 60–70% of cases and repeated imaging within 3–6 months or biopsy is recommended. Finally, LI-RADS-5 lesions have a ~95% probability of being HCCs. LI-RADS-M category comprises lesions that have malignant radiological features but are only HCC in ~35% of cases. Nodules <1 cm in size are unlikely to be HCC and would be very difficult to diagnose, and thus ultrasound follow-up at 3–4 months is recommended. Contrast-enhanced ultrasound (CEUS) and angiography

Mass/Nodule on US

> 1 cm, AFP ≥20 ng/mL or rising AFP <1 cm Repeat US at 3–6 mos Growing/changing pattern 1 positive technique HCC radiological hallmark or LI-RADS 5* Stable LI-RADS 4 LI-RADS 3 Use alternative imaging PART 4 Oncology and Hematology Inconclusive *Hallmark of HCC: Contrast uptake in arterial phase and washout in venous or delayed phase **Consider a second biopsy in case of inconclusive FIGURE 87-2 Recall diagnosis schedule for HCC (EASL). EASL, European Association for the Study of Liver Disease; HCC, hepatocellular

> carcinoma. (Modified with permission from EASL. J Hepatology 69:182, 2018.) are less accurate for HCC diagnosis. Positron emission tomography (PET) scan performs poorly for early diagnosis. AFP levels ≥400 ng/dL are highly suspicious but not diagnostic of HCC according to guidelines. PATHOLOGICAL DIAGNOSIS Pathological diagnosis is required: (1) in patients without cirrhosis, (2) if radiology is not typical in at least one of two imaging techniques (CT and MRI), and (3) for a LI-RADS-4 lesion. Biopsy has not been used as the gold standard in clinical prac tice, although with the advent of molecular therapies, some guidelines advocate obtaining tissue samples in the setting of all research stud ies in HCC, even if radiological criteria are met. Sensitivity of liver biopsies ranges between 70 and 90% for all tumor sizes but decreases to <50% in tumors 1–2 cm in size. The risk of complications, such as tumor seeding and bleeding, after liver biopsy is ~2–3%. Biopsies should be assessed by an expert hepatopathologist. The use of special stains may help to resolve diagnostic uncertainties. Positive staining in two of four markers (glypican 3 [GPC3], glutamine synthetase, heat shock protein 70 [HSP70], and clathrin heavy chain) is highly specific for HCC. Additional staining can be considered to detect progenitor cell features (K19 and epithelial cell adhesion molecule [EpCAM]) or assess neovascularization (CD34). A negative biopsy does not elimi nate the diagnosis of HCC. A second biopsy is recommended in case of inconclusive findings or growth or change in enhancement pattern identified during follow-up (Fig. 87-2). ■ ■TREATMENT Overview The landscape of management of HCC has substan tially changed during the last decade. For early stages, resection, liver transplantation, and local ablation have substantially improved life expectancy, with median overall survival (OS) times beyond 5 years (Fig. 87-3). Adjuvant therapy with atezolizumab plus bevacizumab improves recurrence-free survival in patients at high risk of recurrence undergoing resection or ablation. For intermediate stages, transarterial chemoembolization (TACE) has improved the natural history of 16

Four-phase contrast-enhanced CT or Multiphasic contrast-enhanced/or gadoxetic-enhanced MRI Yes HCC Biopsy** Benign or non-HCC malignant months to ~30 months, and when combined with durvalumab plus bevacizumab, it improves progression-free survival. Systemic drugs for advanced tumors (atezolizumab plus bevacizumab, durvalumab plus tremelimumab, sorafenib, lenvatinib, regorafenib, cabozantinib, and ramucirumab) have improved median survivals from 8 months to even beyond 19 months in front-line and to 10 months in second-line treatment (Fig. 87-3). Staging Systems and Treatment Allocation Staging systems are aimed at stratifying patients according to prognostic factors and out come and allocating the best available therapies according to evidence. The most accepted staging system is the Barcelona Clinic Liver Cancer (BCLC) Classification, which is endorsed by U.S. and European clinical practice guidelines (Fig. 87-3). This staging system defines five prog nostic subclasses and allocates specific treatments for each stage. The BCLC staging system has been externally validated by numerous stud ies. It is an evolving system that allows incorporation of new therapies and treatment-dependent variables as new evidence emerges. Several treatments improve survival in HCC, and thus have been incorporated in the

therapeutic algorithm: surgical resection, liver transplanta tion, radiofrequency (RF) ablation, microwave, chemoembolization, and systemic therapies (atezolizumab-bevacizumab, durvalumab plus tremelimumab, sorafenib, lenvatinib, regorafenib, cabozantinib, and ramucirumab). The BCLC assigns each patient to a given treatment allocation. Treatment stage migration is also applied by this scheme, meaning that if patients are not candidates for the selected therapy, the next effective therapy at more advanced stages can be given. In HCC, three parameters are relevant for defining treatment strat egy: tumor status, cancer-related symptoms, and liver dysfunction. The BCLC staging captures all three variables and allocates patients to treatments according to evidence. Since >80% of patients have two diseases, HCC and cirrhosis, a clear measurement of liver dysfunction should be in place. The prognosis of chronic liver disease is com monly assessed using the Child-Pugh score, which uses five clinical

Hepatocellular carcinoma Very early (BCLC 0) Early (BCLC A) Stages Stratification Treatment

- Single nodule ≤2 cm
- Child-Pugh A, ECOG 0
- Single or ≤3 nodules ≤3 cm
- Child-Pugh A-B, ECOG 0 2–3 nodules ≤3 cm Solitary Yes Optimal surgical candidate No Yes Transplant candidate No Transplantation (LT) Ablation First choice# Second choice## Ablation Resection Systemic therapy* Best supportive care Downstaging LT TACE (TARE, SBRT) Extended criteria LT (TARE) Resection Expected outcomes Median OS: 10 yr Transplantation;

> 6 yr for resection/ablation FIGURE 87-3 Staging system and therapeutic strategy. BCLC classification comprises five stages that select the best candidates for therapies according to evidence-based data. Patients with asymptomatic early tumors (stages 0 -A) are candidates for radical therapies (resection, transplantation, or local ablation). Asymptomatic patients with multinodular HCC (stage B) are suitable for transcatheter arterial chemoembolization (TACE), whereas patients with advanced symptomatic tumors and/or an invasive tumoral pattern (stage C) are candidates to receive systemic therapies. End-stage disease (stage D) includes patients with poor prognosis that should be treated by best supportive care. BCLC, Barcelona Clinic Liver Cancer; DDLT, deceased donor liver transplantation; EASL, European Association for the Study of Liver Disease; ECOG, Eastern Cooperative Oncology Group Performance Status; EORTC, European Organisation for Research and Treatment of Cancer; GRADE, grading of recommendations assessment, development, and evaluation; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; OS, overall survival; PEI, percutaneous ethanol injection; RF, radiofrequency ablation; TACE, transcatheter arterial chemoembolization. (Modified with permission from JM Llovet et al: Molecular pathogenesis and systemic therapies for hepatocellular carcinoma. Nature Cancer 3:386, 2022.) *Around 70–80% of patients are expected to receive this regimen #Based on high level evidence studies. ##Based on low or moderate level of evidence studies. measures—total

> bilirubin, serum albumin, prothrombin time, ascites severity, and hepatic encephalopathy grade—to classify patients into one of three groups (A–C) of predicted survival rates. In brief, ChildPugh class A reflects well-preserved liver function, Child-Pugh class B moderate liver dysfunction, and Child-Pugh class C severe liver dys function. Other measurements of liver dysfunction, such as the Model for End-Stage Liver Disease (MELD) score or the albumin-bilirubin score, are not integrated in this staging system. Performance status is assessed by Eastern Cooperative Oncology Group (ECOG) scale (a 5-point scale where higher numbers indicate greater disability), and presence of cancer-related symptoms (ECOG 1–2) is considered a sign of advanced stage. Considering all these prognostic/predictive variables and evidencebased treatment efficacy, five BCLC stages have been defined (Fig. 87-3). Patients with liver-only neoplastic disease, no symptoms (ECOG 0), and mild to moderate liver dysfunction (Child-Pugh A-B) can be clas sified as very early (stage 0), early (stage A), or intermediate (stage B) stage depending on tumor size and number. Very early HCC (BCLC 0) is defined by single tumors ≤2 cm (if pathology is available, the tumors should be well-differentiated with absence of microvascular invasion or satellites). Early HCC (BCLC A) includes either single tumors or a

Intermediate (BCLC B) Advanced (BCLC C) Terminal (BCLC D)

- Portal invasion, N1, M1
- Child Pugh A-B, ECOG 1–2
- Multinodular
- Child-Pugh A-B, ECOG 0
- Child Pugh C
- ECOG >2 TACE candidate No Yes CHAPTER 87 Chemoembolization (+ systemic therapies) Tumors of the Liver and Biliary Tree Median OS ~26–30 mo mPFS: 15 mo 1st line: ~16–19 mo 2nd line: 13–15 mo 3rd line: 8–12 mo Median OS 3–6 months maximum of three nodules of ≤3 cm in diameter. Intermediate stage (BCLC B) is defined by all other liver-only tumors. Conversely, HCC is considered at advanced stages (BCLC C) when patients present with cancer-related symptoms (ECOG 1–2) or tumors with macrovascular invasion (of any type, including branch, hepatic, or portal vein), lymph node involvement, or extrahepatic spread. Finally, end-stage disease (BCLC D) is considered in cases of severe impairment of quality of life or severe cancer-related symptoms (ECOG 3–4) or severe liver dysfunction (Child-Pugh C). Around 40% of patients are diagnosed at stages 0 and A and hence are eligible for potentially curative therapies, resection, transplantation, or local ablation. These treatments provide median survival rates of 60 months and beyond, which are in sharp contrast with outcomes of 36 months reported in historical controls (Fig. 87-3, Table 87-2). Adjuvant therapy with atezolizumab plus bevacizumab is recom mended in patients after resection or local ablation who are at high risk of recurrence. Patients at intermediate stage (stage B) with preserved liver function have a documented natural history of around 16 months. These patients benefit from TACE, as reported in two randomized studies and one meta-analysis and achieve an estimated survival of 25–30

months. Combination of durvalumab plus bevacizumab with TACE

TABLE 87-2 Summary of Key Results of Randomized and Cohort Studies in the Management of Hepatocellular Carcinoma (HCC) TREATMENT OF EARLY AND INTERMEDIATE STAGE HCC TREATMENTS HCC STAGE TREATMENT ARMS OUTCOMES (OS) Treatments for early HCC Resection Early Optimal (single nodule; no portal hypertension) 5-year: 50–70% Suboptimal (multinodular or portal hypertension) 5-year: 35–55% Resection + adjuvant Early Adjuvant atezolizumab + bevacizumab vs surveillance 12-month RFS: 78 vs 65% Liver transplantation Early Milan (1 nodule <5 cm, 2–3 nodules ≤3 cm, no MVI, no EHS) 5-year: 70–80% Early/intermediate Downstaged (1 nodule ≤6.5 cm, ≤3 nodules ≤4.5 cm and total diameter ≤8 cm, no MVI, no EHS) Ablation Early RFA Median: 50–60 months Treatments for intermediate HCC Transarterial therapies Intermediate TACE Median: 20–32 months Median PFS: 8 months Locoregional + systemic Intermediate TACE + durvalumab + bevacizumab Median PFS: 15.2 months TREATMENT OF ADVANCED STAGE HCC STUDY NAME TREATMENT MEDIAN OS, MONTHS (HR 95% CI) MEDIAN PFS, MONTHS (HR 95% CI) ORR mRECIST/RECIST First-line therapies IMbrave150 Atezolizumab + bevacizumab 19.2 vs 13.5 (HR 0.66, 0.452–0.85) 6.9 (HR 0.65, 0.53–0.81) 35.4%/29.8% HIMALAYA Durvalumab + tremelimumab 16.4 (HR 0.78, 0.65–0.93) 3.7 (HR 0.90, 0.77–1.05) NA/20% PART 4 Oncology and Hematology SHARP Sorafenib 10.7 (HR 0.69, 0.55–0.87) 10.7 (HR 0.69, 0.55–0.87) NA/2% REFLECT Lenvatinib 13.6 (HR 0.92, 0.79–1.06) 7.4 (HR 0.66, 0.57–0.77) 24.1%/18.8% Second-line therapies RESORCE Regorafenib 10.6 (HR 0.63, 0.5–0.79) 3.1 (HR 0.46, 0.37–0.56) 11%/7% CELESTIAL Cabozantinib 10.2 (HR 0.76, 0.63–0.92) 5.2 (HR 0.44, 0.36–0.52) NA/4% REACH-2 Ramucirumab 8.5 (HR 0.71, 0.53–0.95) 2.8 (HR 0.45, 0.34–0.6) NA/5% Abbreviations: CI, confidence interval; EHS, extrahepatic spread; HCC, hepatocellular carcinoma; HR, hazard ratio; mRECIST, modified Response Evaluation Criteria in Solid Tumors; MVI, microvascular invasion; NA, not available; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RFA, radiofrequency ablation; TACE, transarterial chemoembolization. has shown benefits in progression-free survival compared with TACE alone. Patients progressing on TACE or at advanced stage (stage C) benefit from systemic treatments. First-line therapy for advanced HCC includes atezolizumab plus bevacizumab or durvalumab plus tremelimumab. Both combinations were superior to sorafenib in phase 3 trials. In patients with contraindications for immunotherapies, both sorafenib or lenvatinib are recommended Three additional targeted therapies have shown to improve survival compared to placebo in patients with HCC progressing on sorafenib: regorafenib, cabozantinib, and ramucirumab (only in patients with AFP >400 ng/mL). Therefore, these treatments have been adopted by guidelines and incorporated into the treatment algorithm. Patients with end-stage disease (BCLC D) should be considered for nutritional and psychological support and proper management of pain. Although the BCLC establishes validated stages and treatment assignment according to evidence, clinical practice is not always aligned with this classification. In large cohort studies and surveys, only half of patients, or even less in Asia, are treated accordingly. Alterna tive staging or scoring systems have been proposed, such as the Hong Kong classification or the Japan Integrated Staging score. These systems capture extended indications for resection and TACE applied in clini cal practice in Asia. Finally, the tumor-node-metastasis (TNM) stag ing system is not used in HCC since it does not incorporate the main prognostic variables related to liver function and performance status. Due to the complexities of HCC diagnosis and management, it is recommended to refer patients to centers with multidisciplinary liver cancer programs that include a hepatologist, oncologist, hepatobiliary and transplant surgeons, interventional and body imaging radiologist, hepatopathologist, and specialized nurses. ■ ■SURGICAL THERAPIES Resection

Surgical resection is the first-line option for noncirrhotic patients with early-stage HCC (BCLC 0 or A) with solitary tumors

5-year: 60–70% (Fig. 87-3). In cirrhotic patients, ablation competes with resection for BCLC 0 tumors (<2 cm in diameter). Which is better is not defined. Cost-effectiveness approaches report a benefit for local ablation with RF. For single tumors >2 cm (BCLC A), resection remains the mainstay of treatment in patients with Child-Pugh A with normal bilirubin and absence of portal hypertension (no esophageal/gastric varices or platelet count >100,000/μL associated with splenomegaly). Anatomic resections following the functional segments of the liver are recommended to spare uninvolved liver parenchyma and to remove satellite tumors. Applying these criteria, resection is associated with perioperative decompensa tion rate of 5%, perioperative mortality of <1%, and 5-year survival of 60–70%, as opposed to ~35–55% for suboptimal candidates (Table 87-2). Macrovascular invasion, extrahepatic involvement, and liver dys function (Child-Pugh B-C) are major contraindications for resection. Adjuvant Treatments Tumor recurrence represents a major com plication of resection and local ablation (with 5-year rates of 50–70%). Predictors of recurrence are tumor size, tumor number, presence of microsatellites, or microvascular invasion at the specimen analysis. Most recurrences are intrahepatic metastases, but at least one-third are considered de novo tumors, new clones developing in the cirrhotic car cinogenic field. The type of recurrence can only be defined by molecu lar studies. An adjuvant regimen after resection or local ablation with atezolizumab plus bevacizumab for 12 months significantly improved recurrence-free survival in patients at high risk of recurrence and has been incorporated into the guidelines of practice. Liver Transplantation Liver transplantation is the first treatment choice for cirrhotic patients with single tumors ≤5 cm and portal hyper tension (including Child-Pugh B and C) or with small multinodular tumors (three or fewer nodules, each ≤3 cm) (Fig. 87-3). These so-called Milan criteria have been validated over the years and lead to median sur vival times of 10 years. Perioperative mortality rates have been reduced to <3%. Transplantation simultaneously cures the tumor and the

underlying cirrhosis, and it is associated with a low risk of recurrence, around 10–15% at 5 years. No immunosuppressive regimens or antitu mor therapies after transplantation have demonstrated any preventive effect on recurrence. Milan criteria are integrated in the treatment strat egy (BCLC 0 and A) and have also been adopted by the United Network for Organ Sharing (UNOS) pretransplant staging for organ allocation in the United States (stage T2). Aside from size and number, conventional contraindications for organ transplantation procedures (e.g., ABO incompatibility, comorbidities) are applied in this setting. Liver transplantation has a couple of important limitations, such as cost and donor availability, that limit this procedure to <5% of HCC cases worldwide. The scarcity of donors represents a major drawback of liver transplantation. Donor scarcity varies geographically, and deceased liver donation is almost zero in some Asian countries. Due to the shortage of donors, median waiting times in Western programs is ~6–12 months, leading to 20% of candidates dropping off the list due to tumor progression before receiving the procedure. Neoadjuvant treat ments with locoregional therapies are recommended when the waiting time exceeds 6 months. Expansion of Milan criteria by using locoregional therapies to effec tively downstage the tumor (i.e., UNOS-downstaging criteria) have reported good results. Since policies for enhancing organ donation have reached a ceiling during the past several years, alternatives to donation have emerged. Living donor liver transplantation represents a plausible alternative that accounts for ~5% of total transplantations performed globally. Outcomes

reported are similar to those with deceased liver donors, and it is recommended as an alternative option in patients on a waiting list exceeding 6 months. The risks and ben efits of this procedure should take into account both donor (death is estimated in 0.3%) and recipient, a concept known as double equipoise. Due to the complexity of this treatment, it must be restricted to centers of excellence in hepatobiliary surgery and transplantation. ■ ■LOCOREGIONAL THERAPIES Local Ablation Thermal ablation with RF or microwave (MWA) is recommended as the primary ablative technique (Fig. 87-4). The Advanced stage HCC (BCLC C, portal invasion and/or extrahepatic spread) or Intermediate stage HCC (BCLC B, multinodular) progressing upon/not candidates for loco-regional therapies. Child-Pugh A, ECOG 0–1 Candidate for immunotherapy? Yes No (Autoimmune disorder, Prior liver transplantation) High risk of gastrointestinal/ esophageal bleeding Yes No First/second line Atezolizumab + bevacizumab* Tremelimumab + durvalumab Sorafenib or Lenvatinib PD Second/third line Regorafenib/cabozantinib/ramucirumab Nivolumab + ipilimumab Pembrolizumab FIGURE 87-4 Treatment strategy for advanced hepatocellular carcinoma with systemic therapies. Drugs in bold have positive results from phase 3 trials with regulatory approval (atezolizumab plus bevacizumab, durvalumab plus tremelimumab, sorafenib, lenvatinib, regorafenib, cabozantinib, and ramucirumab). Drugs in bold italic have received accelerated approval from the Food and Drug Administration on the basis of promising efficacy results in phase 2 trials in second line (pembrolizumab and nivolumab ipilimumab). Key details of the patient populations are provided. BCLC, Barcelona Clinic Liver Cancer (classification); ECOG, Eastern Cooperative Oncology Group; PD, progressive disease. (Modified from JM Llovet et al: Nat Rev Clin Oncol 15:599, 2018.)

energy generated by RF ablation (heating of tissue at 80°–100°C) induces coagulative necrosis of the tumor, producing a safety ring in the peritumoral tissue, which might eliminate small undetected satellites. Treatment consists of one or two sessions performed using a percutaneous approach, although in some instances, ablation with laparoscopy is needed. HCC patients treated by RF ablation have 5-year survival rates of ~60% (Table 87-2). In tumors <2 cm, both RF and MWA ablation achieve complete responses in 90–100% of cases with good long-term outcome and compete with resection in terms of cost-effectiveness as a first-line option. For BCLC A cases, local abla tion techniques are considered in patients with three tumors <3 cm in diameter unsuitable for surgical therapies.

For patients with unresectable HCC >3 cm in diameter who are not candidates for liver transplantation, transarterial radioemboliza tion (TARE) with yttrium-90 and stereotactic body radiation (SBRT) are considered alternative options based on propensity-matched score studies and phase 2 investigations. Chemoembolization TACE is the most widely used primary treatment for unresectable HCC worldwide and the first-line indica tion for patients with intermediate BCLC B stage (Fig. 87-3). Conven tional chemoembolization (c-TACE) consists of local hepatic artery administration of chemotherapy (either doxorubicin 50 mg/m2 or cisplatin) mixed with an emulsion of lipiodol followed by obstruction of the feeding artery with sponge particles. The best randomized phase 3 investigations have provided median survivals for TACE of 20–30 months in properly selected populations (compared to 16 months for pooled control arms). Median objective response rates are 50–70%. In randomized studies, the treatment is either performed at a regular schedule of 0, 2, and 6 months (median number of sessions is three) or on demand according to tumor response. TACE procedures should be stopped upon tumor progression or any other contraindication. Around 50% of patients present with a limited postembolization syndrome of

fever and abdominal pain related to ischemic injury and release of cytokines. Less than 5% of patients have major com plications (liver abscess, ischemic cholecystitis, or liver failure), and CHAPTER 87 Tumors of the Liver and Biliary Tree

in <2% of cases, treatment-related death occurs. Drug-eluting bead chemoembolization (DEB-TACE) differs from c-TACE in the use of more standardized embolic spheres of regular size embedded with chemotherapy. This strategy achieves similar antitumor activity (objec tive responses of ~60%) as c-TACE and is associated with significantly fewer systemic toxic effects and better patient tolerance, but there are no clear differences in clinical outcomes.

Overall, TACE can only be applied to 50% of patients at intermediate stage, mostly as a result of the presence of liver failure (Child B or asci tes or encephalopathy), technical contraindications to the procedure (i.e., impaired portal vein blood flow), or infiltrative/massive tumor burden (i.e., generally main tumor size >10 cm). Super-selective TACE minimizes the ischemic insult to nontumor tissue. According to guide lines, treatment stage migration allows performing TACE on patients at early stages not suitable for surgical or ablative therapies. TACE plus durvalumab plus bevacizumab significantly increases progression-free survival compared to TACE alone (median progression-free survival, 15.2 vs 8 months) with manageable treatment-related adverse events. Radioembolization and Other Intra-arterial Therapies Trans arterial radioembolization (TARE) using beads coated with yttrium-90 (Y-90)—an isotope that emits short-range β radiation—is the most promising alternative to TACE. Several phase II studies reported objective responses and overall outcome with a safe profile similar to TACE, and thus TARE has been endorsed by clinical practice guide lines. Radioembolization requires prevention of severe lung shunting and intestinal radiation before the procedure. Around 20% of patients experience liver-related toxicity, and <2% experience treatment-related death. Due to the minimally embolic effect of Y-90 microspheres, treatment can be safely used in patients with portal vein thrombosis, a setting where survival results in phase II studies were encouraging. PART 4 Oncology and Hematology ■ ■SYSTEMIC THERAPIES Approximately 50–60% of patients with HCC are currently exposed to systemic therapies during their life span, either because they have been diagnosed at advanced stages or because they have progressed after locoregional therapies. In 2007, a phase III trial demonstrated survival benefits for patients with advanced-stage disease treated with sorafenib, thus becoming the first systemic therapy for HCC. Subsequently atezolizumab plus bevacizumab and durvalumab plus tremelimumab have demonstrated survival superiority compared to sorafenib, whereas lenvatinib showed noninferior effects (Fig. 87-4). In Asia, other combinations (i.e., carmelizumab plus rivoceranib) also were superior versus sorafenib in terms of survival. Three addi tional therapies, regorafenib, cabozantinib, and ramucirumab (only in patients with AFP >400 ng/mL), have been shown to benefit patients progressing on sorafenib. Of note, classical chemotherapy and radio therapy have not resulted in benefits in survival. Similarly, due to the low prevalence of actionable molecular aberrations, precision oncology regimens are not yet available in HCC. First-Line Therapies Atezolizumab (anti–PD-1 checkpoint inhibitor) plus bevacizumab (monoclonal antibody against VEGF-A) demonstrated survival differences compared to sorafenib (median OS, 19.2 vs 13.4 months) and has become the standard of care in first-line treatment (Fig. 87-4, Table 87-2). This combination treatment resulted in improved progression-free survival, patient-reported outcomes reflecting quality of life, and objective response rates (30 vs 12% for sorafenib). The combination had fewer adverse events compared to sorafenib (grade 3-4 adverse events, 36 vs 50%, respectively). The most common side effects associated with the combination are hyperten

sion, proteinuria, and low-grade diarrhea, whereas autoimmune events are infrequent and manageable. Treatment-related adverse event rate leading to discontinuation of any drugs is 15%. Screening for varices with upper gastrointestinal endoscopies has become standard before first-line therapy in advanced HCC to mitigate the risk of bleeding associated with bevacizumab. In cases with varices, the use of one ses sion of banding or carvedilol is recommended. The combination of tremelimumab (a CTLA-4 inhibitor) and dur valumab (a PD-L1 inhibitor) (STRIDE regimen) has demonstrated a

survival advantage versus sorafenib (median OS, 16.4 vs 13.7 months for sorafenib). No differences were identified regarding progressionfree survival, and the response rate was 20.1% with the combination versus 5.1% with sorafenib. This regimen can be administered even in patients with portal hypertension or varices. STRIDE was associ ated with more immune-related adverse events, and 20% of patients required glucocorticoid treatments (Fig. 87-4). Alternatively, sorafenib or lenvatinib is indicated for patients with advanced HCC with contraindications for immunotherapies (i.e., due to autoimmune disease or liver transplantation) (Fig. 87-4, Table 87-2). A phase 3 study comparing sorafenib (a multikinase inhibitor) versus placebo showed increased survival from 7.9 months to 10.7 months (hazard ratio [HR], 0.69; 31% reduction in risk of death). Patients with HCV-related HCC achieve significantly better outcomes with sorafenib, with a median survival of 14 months. Median treatment duration is about 6 months. Treatment is associated with manageable adverse events, such as diarrhea, hand-foot skin reactions, fatigue, and hypertension. These toxicities lead to treatment discontinuation in 15% of patients and dose reduction in up to half. It has been estimated that this therapy cannot be administered to approximately one-third of the targeted patients due to toxicity, advanced age, or liver failure (ascites or encephalopathy). Active vascular disease, either coronary or peripheral, is considered a formal contraindication. Median time to progression on sorafenib is 4–5 months in phase 3 trials. Another alternative to sorafenib is the multikinase inhibitor len vatinib, which was shown to be noninferior in a phase 3 investiga tion (Fig. 87-4). A phase 3 study comparing lenvatinib (an inhibitor of vascular endothelial growth factor receptor [VEGFR], fibroblast growth factor recepctor [FGFR], platelet-derived growth factor recep tor [PDGFR], RET, and c-Kit) with sorafenib showed noninferiority of results in terms of OS (13.6 vs 12.3 months; HR, 0.92). Lenvatinib induces objective responses in 24% of cases. The main side effects are hypertension, proteinuria, asthenia, diarrhea, and weight loss. This treatment is associated with a 55% rate of grade 3-4 drug-related adverse events, resulting in a ~15% withdrawal rate. Second-Line Therapies Three drugs (regorafenib, cabozantinib, and ramucirumab) have shown survival benefits versus placebo in patients progressing to sorafenib, and two additional treatments have been approved by the U.S. Food and Drug Administration (FDA) based on promising phase 2 data (pembrolizumab, and nivolumab plus ipilimumab) (Fig. 87-4). It is estimated that only half of patients progressing on sorafenib can be considered for second-line therapies, and their median survival with no treatment is 7–8 months (obtained from patients allocated to the placebo arm). A phase 3 study comparing regorafenib (a more potent multikinase inhibitor than sorafenib, but targeting similar kinases) versus placebo in patients progressing to sorafenib reported an increase in survival from 7.8 to 10.6 months (HR, 0.62; 38% reduction in risk of death) (Fig. 87-5). Response rate was 10% based on modified Response Evaluation Criteria in Solid Tumors. Median time on treatment was

3.5 months. Prevalence of toxicity (hand-foot reaction, fatigue, and hypertension) was higher compared with reported toxicity from sorafenib, but adverse events only led to treatment

discontinuation in 10% of cases. Cabozantinib, a multikinase VEGFR inhibitor with activity against both AXL and cMET, improves survival compared to placebo after progression to sorafenib (10.2 months for cabozantinib vs 8.0 months in the placebo arm; HR, 0.76). Toxicity was manageable, with the most common grade 3–4 events being palmar-plantar erythro dysesthesia, hypertension, increased aspartate aminotransferase level, fatigue, and diarrhea. Ramucirumab, an anti–VEGFR-2 monoclonal antibody, is the only biomarker-guided therapy in HCC based on AFP levels. The randomized, placebo-controlled, phase 3 REACH-2 study studied patients with advanced HCC in second-line treatment with baseline AFP ≥400 ng/dL. This trial demonstrated positive survival results, and a further meta-analysis established a median survival for ramucirumab of 8.1 months compared to 5 months for patients receiv ing placebo. The most common grade 3–4 treatment-related adverse events were hypertension, hyponatremia, and increased aspartate

Mass-forming Periductalinfiltrating Left, right, common hepatic ducts Intraductalgrowing FIGURE 87-5 Anatomical classification of cholangiocarcinoma. Cholangiocarcinoma is classified as intrahepatic (iCCA) and extrahepatic (eCCA). eCCA can be subclassified as perihilar (pCCA) and distal (dCCA). (Reproduced from JM Banales et al: Cholangiocarcinoma 2020: The next horizon in mechanisms and management. Nat Rev Gastroenterol Hepatol 17:557, 2020.) aminotransferase. Patients progressing after second-line therapy might be considered for third-line approaches. Patients with tumors at a BCLC D stage should receive best supportive palliative care, including management of pain, nutrition, and psychological support. CHOLANGIOCARCINOMA Cholangiocarcinoma (CCA) is classified according to its anatomic location as intrahepatic (iCCA; ~20–30%), perihilar (pCCA; ~50–60%), and distal (dCCA: ~20–30%). The latter two are also known as extra hepatic cholangiocarcinomas (eCCA), with the second-order bile ducts acting as the separation point (Fig. 87-5). The three subtypes of CCA differ in their anatomic location, epidemiology and risk factors, cell of origin, pathogenesis, and treatment. iCCA originates from adult cholangiocytes, transdifferentiation of adult hepatocytes, and hepatic progenitor cell–cholangiocyte precursors (Fig. 87-6), as opposed to HCC, which originates only from hepatic progenitor cells or adult hepatocytes. Mixed HCC-iCCA originates from hepatic progenitor cells, whereas eCCA arises from the biliary epithelium and peribiliary glands. Moreover, their mutational profile also differs. FGFR2 fusions and IDH1/2 mutations mostly occur in iCCA, whereas ERBB2/3 ampli fications and SMAD4 aberrations are characteristic of eCCA. iCCA has been recognized as a distinct entity with specific clinical practice guidelines, which should be tailored according to each biological/ anatomical subtype of CCA. ■ ■EPIDEMIOLOGY, RISK FACTORS, AND MOLECULAR TRAITS CCA is the second most common liver cancer following HCC, with a 5-year survival of 10%. iCCA has globally increasing incidence and mortality rates. The incidence of iCCA varies according to exposure to risk factors, ranging from 1–2 cases per 100,000 inhabitants in Europe and North America to the highest incidence in some areas of Southeast Asia, particularly in Thailand (>80 cases/100,000 inhabitants). The male-to-female ratio is 1.2:1. Only 30% of patients with CCA have a known risk factor. The classical risk factors for CCA development include primary sclerosing cholangitis (PSC), biliary duct cysts, hepa tolithiasis, and Caroli’s disease. Parasitic biliary infestation with flukes (most common are Opisthorchis viverrini and Clonorchis sinensis) is a prevalent etiology in Asia that can be prevented with an antihel minth therapy, praziquantel. PSC is a clear risk factor for iCCA and pCCA development, with a lifetime incidence ranging from 5 to 10%. Surveillance in PSC patients is recommended with annual imaging

techniques and CA 19-9 serum determina tion. Common risk factors for HCC, such as HBV and HCV infection and cirrhosis, have been associated with iCCA develop ment. More recently, sweetened beverages were reported to constitute a risk factor in the development of eCCA and gallbladder carcinoma (GBC) in a population cohort study.

Bile ductules iCCA (10–20%) Segmental ducts Molecular Classification and Actionable Drivers A morphological and molecular classification subclassifies iCCA into the large duct type, which is associated with IDH (15–20%) and FGFR2 (15%) mutations and better prognosis, and the small duct type, which is associated with KRAS (15%) and SMARD4 (<5%) mutations and poor prognosis. Overall, up to 40% of iCCAs have a targetable mutation. Similarly, a molecular classification of eCCA has been proposed, dividing tumors into four cat egories (metabolic, proliferation, mesen chymal, and immune) based on molecular traits. It has been suggested that the prolif eration class with enrichment of ERBB2/3 mutations might respond to monoclonal antibodies against this receptor, while the immune class might respond to checkpoint inhibitors, a fact that needs clinical confirmation. The most common mutations of pCCA/dCCA are P53 (~30%) and KRAS (~25%), whereas ERBB2 amplifications (~20%) are common in gall bladder cancer. pCCA (50–60%) Common bile duct dCCA (20–30%) CHAPTER 87 Tumors of the Liver and Biliary Tree ■ ■INTRAHEPATIC CHOLANGIOCARCINOMA Surveillance, Diagnosis, and Staging Guidelines currently only recommend surveillance for early diagnosis in the following atrisk subpopulations: (1) patients with primary biliary sclerosis (PBS; surveillance is recommended with CA 19-9 and magnetic resonance cholangiopancreatography [MRCP] every 12 months) and (2) patients with cirrhosis or those infected with liver flukes (surveillance is rec ommended with abdominal ultrasound every 6 months). Otherwise, incidental diagnosis occurs due to cross-sectional imaging performed for other reasons. In most cases, iCCA is diagnosed at advanced stages when symptoms such as weight loss, malaise, abdominal discomfort, or jaundice are present. Diagnosis of iCCA requires pathological con firmation. Differential diagnosis should be established with metastatic adenocarcinoma (i.e., colorectal, breast, and lung cancer) and mixed iCCA-HCC tumors. Immunohistochemistry using K7, K19, and K20 is useful to confirm iCCA and to distinguish it from metastatic liver cancer. Hepatocytic markers such as Hep-Par-1, GPC3, and HSP70 may aid in pointing to a mixed HCC-iCCA tumor. Current guidelines recommend the use of abdominal MRI, chest and abdomen CT scan, and PET scan for establishing the disease extension once the pathologi cal diagnosis has been confirmed. Meta-analysis has defined a role for PET scanning in identifying lymph node metastasis in patients with no apparent lymph node invasion with MRI and/or CT scan. Lymph node sampling by endoscopic ultrasound with fine-needle aspiration would be considered before resection in selected unclear cases. Tumor biomarker CA 19-9 at a cutoff level of 100 U/mL has prognostic sig nificance but lacks accuracy (sensitivity and specificity of ~60%) for early diagnosis. ■ ■TREATMENT The European Association for the Study of Liver Disease–International Liver Cancer Association (ILCA) guidelines for management of iCCA proposed an updated treatment algorithm, which has been adapted to the current accepted treatment modalities (Fig. 87-7). iCCA can be classified as early, intermediate, or advanced cases according to size of the nodules and invasion of lymph nodes (N1), metastasis, and ECOG

Hepatic progenitor cell Progenitor-like HCC Progenitor-like iCCA Hepatocyte precursor Cholangiocyte precursor De-differentiation Mixed HCC-iCCA Biliary-like cell Mature hepatocyte Transdifferentiation PART 4 Oncology and Hematology HCC iCCA FIGURE 87-6 Cell of origin of liver cancer. Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA) can develop

from the neoplastic transformation of mature hepatocytes and cholangiocytes, respectively. There is evidence showing that hepatic progenitor cells (HPCs), their intermediate states, or dedifferentiated hepatocytes can originate liver cancers with progenitor-like features, including mixed HCC-CCA (e.g., cholangiolocellular carcinoma [CLC]). Mature hepatocytes can be also reprogrammed into cells that closely resemble biliary epithelial cells and induce the onset of iCCA. (Printed with permission from © Mount Sinai Health System.) performance status and liver dysfunction. Approximately 30–40% of iCCA cases are deemed resectable, and the median reported survival for single tumors is ~40–50 months, whereas survival decreases to ~20 months in intermediate/multinodular resectable tumors. The main predictors of recurrence (~50–60% at 3 years) and survival are identified at the pathological examination, including presence of vascular invasion, lymph node metastases, and poor differentiation degree. In terms of adjuvant therapy, a phase 3 trial (BILCAP trial) including all types of CCA in a prespecified per-protocol analysis reported improved survival (53 vs 36 months; adjusted HR, 0.75). Based on this trial, American Society of Clinical Oncology guidelines recommend adjuvant capecitabine for a period of 6 months. A small proportion of patients with early/intermediate tumors can have contra indications for resection, particularly in cirrhotic patients, and should be first considered for local ablation or even liver transplantation if the diameter of the main tumor is <2 cm. Nonsurgical candidates have a dismal life expectancy. Overall, patients with multinodular unresectable tumors might be considered for locoregional therapies, such as chemoembolization or radioembo lization, but the level of evidence is low and mostly based on cohort studies. A meta-analysis of 14 trials testing locoregional therapies reported median survival times of 15 months. External-beam radiation therapy is not recommended as standard therapy. At more advanced stages in patients with ECOG of 0–1, systemic chemotherapy with the combination of gemcitabine, cisplatin, and durvalumab showed significantly better survival and progression-free survival compared with gemcitabine plus cisplatin alone (12.8 vs 11.5 months) in the setting of the TOPAZ1 phase 3 trial including 685 patients. Objective response was 27%. Similar results were obtained with the combination

De-differentiation? CLC Mature cholangiocyte Tumor type HCC iCCA Mixed HCC-iCCA of chemotherapy with pembrolizumab versus chemotherapy alone in a phase 3 trial including 1069 patients. The median OS was 12.7 months in the pembrolizumab group and 10.9 months in the placebo group (HR, 0.83; 95% CI, 0.72–0.95; one-sided p = .0034). Therefore, triplet therapy is now considered the standard for the management of CCA. In the second-line setting, a phase 3 study that randomized patients who had progressed on cisplatin and gemcitabine to mFOLFOX (leucovorin, fluorouracil, and oxaliplatin) versus best supportive care showed improvement in median OS of 5.3 to 6.2 months (adjusted HR, 0.69). In addition, three molecular and immune therapies have been approved in the second-line setting in iCCA patients with IDH1/2 mutations, FGFR2 aberrations, or deficient mismatch repair (dMMR) or microsatellite instability high (MSI-H). A phase 3 trial compared ivosidenib, an IDH-1 inhibitor, versus placebo in the second-line set ting and demonstrated an improved primary end point of progressionfree survival (2.7 vs 1.4 months; HR, 0.37) and improved OS in an adjusted analysis. A single-arm phase 2 study assessing pemigatinib (FGFR2 inhibitor) in iCCA patients with FGFR2 fusions showed a median survival of 21 months with an objective response of 35%, lead ing to FDA accelerated approval. Similar results have been observed in phase 3 trials testing other FGFR2 inhibitors, such as infigratinib and futibatinib. Finally, regulatory agencies granted approval of pembroli zumab for MSI-H or dMMR solid tumors that progressed following prior treatment based on a basket tissue-agnostic trial. This recom mendation excludes patients receiving durvalumab in first line. Mixed HCC-iCCA is a rare

neoplasm accounting for <0.5% of all primary liver cancers. Diagnosis is based on pathology. The 2010 World Health Organization classification defined two subtypes: the classical type and the stem cell feature type. Molecular data have also

Intrahepatic cholangiocarcinoma (iCCA) Advanced, metastatic disease (Periductal invasion, N1, M1) Early and intermediate stages Resectable (30–40%) Intrahepatic Disease only Single iCCA ≤2 cm in cirrhotic patient Extrahepatic Disease Local-ablation (or Liver Transplantation) Surgical resection (curative intent) Adjuvant chemotherapy (capecitabine/6 mo) Median survival: 43 mo Median survival: 15 mo *Treatments used as standard of practice. No enough evidence for standard of care. **Patients with ECOG > 2 or liver dysfunction are only suitable for best supportive care. FIGURE 87-7 Staging and treatment schedule for intrahepatic cholangiocarcinoma (iCCA). (Modified from EASL-ILCA Guidelines. J Hepatol 79:181, 2023.) characterized a third unique entity, cholangiolocellular carcinoma, with distinct molecular traits and better outcome. Due to their low incidence, the demographic features and clinical behavior of these tumors remain ill-defined. Survival and management are similar to iCCA. ■ ■EXTRAHEPATIC CHOLANGIOCARCINOMA Perihilar and Distal Cholangiocarcinoma pCCA tumors arise between the second-order bile ducts up to the insertion of the cystic duct, whereas dCCAs arise from this point to the ampulla of Vater (Fig. 87-5). Thus, dCCA can be difficult to distinguish from early pan creatic cancer. Both entities have a similar diagnostic approach. Acute onset of painless jaundice occurs in 90% of patients with pCCA, and 10% of patients present with cholangitis. Primary biliary cholangitis with a cutoff for CA 19-9 >129 U/mL is suspicious for CCA. Imag ing assessment starts with CT and MRI; they have a good sensitivity and specificity (>85%) for detecting the degree of bile duct involve ment and hepatic and portal vein invasion. MRI cholangiography is optimal for defining the extent of the bile duct lesion. Ruling out IgG4 cholangiopathy by assessing serum IgG4 is mandatory. As a second step, endoscopic retrograde cholangiography with brushing to explore cytology and fluorescence in situ hybridization (FISH)—for exploring polysomy—are recommended. FISH enhances the sensitivity of cytol ogy from 20 to ~40%. Diagnosis is based on pathology. The treatment algorithm for pCCA indicates that in cases of a dominant stricture with positive cytology/biopsy or polysomy, a lymph node biopsy through endo scopic ultrasound should be obtained. pCCA with negative lymph node involvement is best treated by surgery, resection, or transplantation,

Unresectable (60–70%) Local-regional therapy* Chemoemboliation (TACE) Radioembolization (TARE) 1st line**: Gemcitabine+ cisplatin+ (durvalumab or pembrolizumab) CHAPTER 87 2nd line FOLFOX FGFR2 inhibitor (pemigatinib) IDH inhibitor (ivosidenib) Checkpoint inhibitor for MSI-H/dMMR Tumors of the Liver and Biliary Tree Median survival: 1st line : ~13 mo 2nd line : 6–12 mo the sole curative options. Staging laparoscopy is recommended to exclude metastatic disease prior to surgery, which occurs in 15% of cases. Resection entails hepatic and bile duct removal and Roux-enY hepaticojejunostomy with regional lymphadenectomy. Bilobular involvement is considered a surgical contraindication. Perioperative mortality rate is up to 10%, mostly as a result of liver failure. In a few referral centers, unresectable single pCCAs <3 cm without dissemi nation can be considered for liver transplantation with neoadjuvant chemoradiation. This procedure is associated with 5-year survival rates of ~70%. If lymph node involvement is present, systemic chemotherapy can be considered along with biliary tract stenting. Surgical resection (Whipple procedure) is the primary option for management of dCCA, a procedure that achieves a median survival of 24 months and 5-year survival rates of ~25%. Main contraindications for resection are pres ence of distant lymph node involvement, metastases, or major vascular invasion. At the

pathological examination, perineural invasion, lymph node metastasis, R0 resection (absence of residual tumor at pathologi cal examination), and tumor differentiation are predictors of survival. Adjuvant therapy with capecitabine for 6 months is accepted based on the BILCAP study, which has been previously discussed. For advanced cases, consensus statements endorse first-line (gemcitabine and cis platin plus durvalumab or pembrolizumab) and second-line therapies (FOLFOX) similar to those for iCCA. No molecular targeted therapies are available for these entities. ■ ■GALLBLADDER CANCER Gallbladder cancer is the most common cancer of the biliary tract worldwide. The estimated number of cases of gallbladder cancer in the United States in 2016 was 11,400, more than CCA. The female-to-male

ratio is 3:1. Cholelithiasis is the major risk factor, but <1% of patients with cholelithiasis develop this cancer. Gallbladder polyps at risk of transformation are those ≥10 mm in diameter. Early cases are discov ered incidentally at routine cholecystectomy. Clinical symptoms, such as jaundice, pain, and weight loss, are associated with advanced stages. Staging of gallbladder cancer involves local disease (tumor confined to the gallbladder) and advanced disease (tumor outside gallbladder with lymph node or distant metastases). The most accurate technique to define staging and vascular and biliary tract invasion is the magnetic resonance cholangiopancreatography. CT and PET scan can also be useful for preoperative staging.

The mainstay of treatment is surgical resection, either simple or radical cholecystectomy (partial hepatectomy and regional lymph node dissection) for local disease. Only ~20% of patients are candidates for surgery with curative intent, and 5-year survival rates range from 60 to 90% depending on prognostic factors such as lymph node or tumor invasion beyond muscular layer. Adjuvant therapy with capecitabine is recommended in R0 cases. Gallbladder cancers at advanced stage are considered unresectable. For patients with ECOG of 0–1, chemother apy with gemcitabine, cisplatin, and durvalumab is the standard of care based on the TOPAZ 1 phase 3 trial that included 171 patients with gallbladder cancer (25%). Overall, median survival is 10–12 months in advanced cases. Second-line therapy includes FOLFOX chemotherapy. Percutaneous transhepatic drainage is indicated in case of biliary obstruction. Radiotherapy is not effective. PART 4 Oncology and Hematology ■ ■OTHER MALIGNANT LIVER TUMORS Fibrolamellar Hepatocellular Carcinoma Fibrolamellar hepa tocellular carcinoma (FLC) is a rare form of primary liver cancer that typically affects children and young adults (10–30 years of age) with out background liver disease. FLC accounts for 0.85% of all primary hepatic malignancies in the United States, and its incidence rate is 0.02 cases per 100,000 inhabitants. FLC is considered a unique entity with a specific fusion oncogene PRKACA-DNAJB1 present in 80–100% of cases. Few additional mutations have been described in <10% of cases. FLC has a better prognosis than HCC, probably due to the absence of cirrhosis and the earlier age of presentation. Surgical resection is the mainstay of treatment, and indications are less restrictive than for HCC. A retrospective series of 575 FLC cases reported a median survival of 70 months after resection. At advanced stages, the expected outcome is <20 months. There is no standard systemic therapy, and clinical trials are focused on targeting the fusion protein with kinase inhibitors or immunomodulatory agents. Hepatoblastoma Hepatoblastoma (HB) is the most frequent pri mary liver tumor in children. The incidence of the disease is 1.5 cases per 1,000,000, and onset of the disease occurs before the age of 3 years. Background liver disease is rare in these patients. WNT signaling plays a major role, with CTNNB1 mutations (70%) as the most frequently reported molecular event. Overexpression of IGF2 and genes in the 14q32 DLK1/DIO3 locus is also very prevalent. At diagnosis, ~30% of patients are

amenable to surgery. Resection followed by chemo therapy with doxorubicin/cisplatin is the mainstay treatment strategy. Among the remaining 70% of patients, neoadjuvant chemotherapy achieved response in >90% of cases and enabled resection with good clinical outcomes. A study including 1605 patients randomized in eight clinical trials reported better outcome for patients with stage I–II of the PRETEXT (Pretreatment Extent of Tumor) classification (out of four stages), age <3 years, AFP >1000 ng/mL, and absence of metastases. As opposed to HCC, low AFP <100 ng/mL indicates poor prognosis. Overall, 5-year survival is 70% (ranging from 50 to 90% depending on PRETEXT stage). BENIGN LIVER TUMORS The most common benign liver tumors are hemangiomas, focal nodu lar hyperplasia (FNH), and hepatocellular adenomas (HCA). Most benign tumors are identified incidentally by abdominal ultrasound

or other imaging techniques. Hemangiomas are present in ~5% of the general population and are diagnosed by ultrasound except in cirrhotic patients or oncology patients, in whom contrast-enhanced imaging (contrast-enhanced ultrasound, CT, or MRI) is required. Conserva tive management is appropriate, and follow-up is not recommended. Exceptionally, growing lesions causing symptoms by compression can be considered for resection. FNH is a benign tumor present in <2% of the population and occurring mostly in females aged 40–50 years. FNH is a polyclonal hepatocellular proliferation due to an arterial mal formation. MRI has the highest diagnostic accuracy with a specificity of 100%, when typical imaging features are present (homogeneous enhancement in the arterial phase with a central scar). Atypical FNH requires biopsy for diagnosis. Treatment is not recommended because these tumors do not degenerate or cause complications. In exceptional cases of expanding symptomatic lesions, surgery is the treatment of choice. Hepatic adenomas are clonal benign proliferations resulting from single-gene driver mutations. HCAs have a low prevalence of 0.001% of the population and are frequently diagnosed in women aged 35–40 years. The female-to-male ratio is 10:1, and the main risk factors are oral contraceptives in females and use of anabolic androgenic steroids in male body builders. HCAs have the potential for hemorrhage and HCC development, particularly when >5 cm. Nowadays, there is a clear understanding of the molecular classification of HCA in subtypes defined by CTNNB1 mutations (10–20%), HNF1A inactivation, and activation of inflammatory pathways (50–60%) or Hedgehog signaling pathway. Diagnosis is based on MRI, which is able to correlate with molecular subtypes in 80% of cases (inflammatory and HNF-1A type). For defining HCA with CTNNB1 mutations, biopsy is required. Upon diagnosis, discontinuation of oral contraceptives and weight loss are recommended. Resection is indicated in all cases >5 cm, in men, or with CTNNB1 mutation. For HCA <5 cm, 1-year follow-up is recom mended. In case of active HCA bleeding, embolization followed by resection is the treatment of choice. The presence of multiple HCAs is common, and guidelines endorse treating them based on the size of the main nodule. ■ ■FURTHER READING EASL-EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 69:182, 2018. EASL-ILCA Clinical Practice Guidelines on the management of intra hepatic cholangiocarcinoma. J Hepatol 79:181, 2023. Finn RS et al: Atezolizumab plus bevacizumab in unresectable hepato cellular carcinoma. N Engl J Med 382:1894, 2020. Haber PK et al: Evidence-based management of hepatocellular carci noma: Systematic review and meta-analysis of randomized controlled trials (2002-2020). Gastroenterology 161:879, 2021. Ilyas SI: Cholangiocarcinoma: novel biological insights and therapeu tic strategies. Nat Rev Clin Oncol 20:470, 2023. Llovet JM et al: Hepatocellular carcinoma. Nat Rev Dis Primers 21;7:6, 2021. Llovet JM et al: Locoregional therapies in the era of molecular and immune treatments for hepatocellular carcinoma Nat Rev Gastroen terol Hepatol 18:293, 2021. Llovet JM et al: Immunotherapies for hepatocellular carcinoma. Nat Rev Clin Oncol 19:151, 2022. Llovet JM et al: Molecular pathogenesis and systemic therapies for

hepatocellular carcinoma. Nat Cancer 3:386, 2022. Oh DY et al: Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. NEJM Evid 1:2022. Singal AG et al: AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology 78:1922, 2023. Villanueva A: Hepatocellular carcinoma. N Engl J Med 380:1450, 2019.

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