Tumors and Tumor-Like Lesions of the Hepatobiliary Tract
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General and Surgical Pathology

With 880 Figures and 199 Tables
I dedicate this textbook to my wife, Geneviève, who for many years of preparatory work endured much and offered continued interest, help, and compassion while I was creating this work. She accompanied me with great loyalty in this endeavor. I also dedicate this book to my children, Laxmi and Tristan, who have given so much meaning to my life, and to my venerated late teacher in pathology, Professor Hans Cottier.
This textbook is designed to be a comprehensive assessment of current knowledge regarding the surgical and general pathology of hepatobiliary tumors and tumor-like lesions. The scope of the book is broad and provides an up-to-date source for the wide-ranging tumor pathology of the entire hepatobiliary tract. In the planning phase of this work, the question had arisen as to the purpose and need of such a book, in the light of numerous excellent monographs and textbooks that have been published in this field during the last years, but a major justification for a new book relates to the rapid change in the role of pathology in the investigation of hepatobiliary tumors and related lesions. Therefore, an update of the dramatic changes that have taken place in the discovery and application of several lines of knowledge referring to hepatobiliary tumor pathology in a broader sense was regarded a worthwhile task. Notwithstanding the impressive increase in diagnostic precision of modern imaging and other, in particular various molecular, methods, tumor biopsy and its morphological interpretation based on complex techniques is still a central diagnostic instrument that serves refined diagnosis and classification, risk stratification, and therapy planning, also in the light of future personalized treatment strategies. A combined approach by using conventional, fine structural, immunohistochemical and hybridization morphological studies, and molecular techniques generated a new concept of the tight correlation between structure and function in tumor pathology, contributing to advanced modes of diagnosis. Apart from information on a given diagnostic tumor entity, differential diagnosis is discussed in depth as a most critical issue.

The main reason for integrating several important issues of general pathology is based on the rapidly evolving and continued changes that are occurring in the disciplines of tumor biology, genomics, and associated molecular features that characterize tumors. The concept of the present work in fact aims at concentrating detailed aspects of surgical pathology needed for diagnosis and the pathogenic mechanisms behind disease in one source with ample color illustrations and a detailed reference corpus.

In the light of refined imaging techniques and other modern diagnostic approaches that can uncover a host of previously undetectable hepatobiliary lesions, a significant part of the textbook is dedicated to an extensive range of tumor-like lesions, pathologies that may, in a clinical-radiological setting, be confounded with true hepatobiliary neoplasms. Part of the tumor-like lesions, including mass-forming infections and infestations, are common entities
world-wide, while others may appear as unexpected or incidental findings, or rare and “exotic” disorders.

This text has been planned to serve hepatopathologists, hepatologists, and others interested and involved in this field, and it is the author’s hope that the book is a comprehensive account on the surgical and general pathology of hepatobiliary tumors and their tumor-like mimics. The book is also hoped to be a useful source of information for basic scientists active in the field of liver pathophysiology.

To provide a systematic review of the immense field of hepatobiliary tumors and tumor-like lesions, the textbook has been divided into 39 parts, each covering one to several chapters, in order to assist the reader in locating topics of interest. In what follows, brief overviews on the contents of each chapter are presented.

Part 1 starts off with a series of chapters that supply comprehensive information on tumors characterized by a hepatocyte-derived lineage and its precursors. Chapter ▶ 1 deals with the role of hepatic stem and progenitor cells in hepatocarcinogenic pathways. Hepatocytes were perceived to represent the major cells of origin for numerous neoplasms of the liver, but stem and progenitor cells have been identified as important sources. The chapter addresses issues of hepatic stem cell niches, types of stem/progenitor cells found in these niches, interactions of stem cells with other cells, changes of their microenvironment, and mechanisms involved in a stem cell-cancer sequence. As cancer initiating cells and cancer-associated stem cells can circulate in blood, the significance of cycling clonogenic cells with longevity and remote spread for tumor progression is discussed. Chapter ▶ 2 provides an in-depth description of ordinary hepatocellular carcinoma (HCC), including classification of gross phenotypes, macroscopic growth patterns, pertinent histologic and diagnostic features, and tumor grading. In Chap. ▶ 3, the numerous immunohistochemical features characterizing ordinary HCC are discussed in detail. Chapter ▶ 4 focuses on invasion and metastatic patterns of ordinary HCC. Patterns of macrovascular and microvascular invasion and the features of intrahepatic and remote metastasis are explained and illustrated. This part also provides information on risk factors for metastasis and on the presentation and frequency of extrahepatic organ metastases. In Chap. ▶ 5, secondary changes that develop in HCCs, and in particular the interesting phenomenon of spontaneous tumor regression, are highlighted. Progression and recurrence of HCC are major elements of the tumor’s biology of disease. Numerous prognostic factors for the natural course of HCC have been delineated, discussed in detail in Chap. ▶ 6. The issues of Chap. ▶ 7 are the various types of HCC precursor lesions that can develop in cirrhotic livers, including small and large cell change, dysplastic foci, and dysplastic nodules. There is a group of ordinary HCCs characterized by small size at the time point of diagnosis, lesions that are more frequently diagnosed due to improved imaging techniques. These intriguing lesions, specifically their morphology, classification, biology, and relationship to early cancer are dealt with in Chap. ▶ 8. The chapters on neoplasms of the hepatocyte lineage are considerably extended to reflect the growing importance of special types of liver cell cancers in the setting of clinical presentation, detectability by modern imaging techniques,
molecular features, and biology of disease (Chaps. 9, 10, 11, 12, and 13). Chapter 9 deals with clear cell HCC, a group of neoplasms that belong to a growing spectrum of epithelial clear cell tumors of the alimentary tract with a distinct biology of disease. A heterogeneous group of HCCs is characterized by the accumulation of neutral fat, including steatotic HCC and its inflammatory variant, steatohepatitic HCC, tumors that also develop in the setting of nonalcoholic and alcoholic fatty liver disease. Part of these tumors are rich in Mallory-Denk bodies (Chap. 10). A rare group of HCCs is characterized by the presence of an abundant desmoplastic stroma, similar to cholangiocarcinoma (sclerosing and scirrhous HCCs; Chap. 11). A further unusual subset of HCCs shows dense infiltrates of mononuclear leukocytes (inflammatory HCCs). One variant of these neoplasms reflects a morphology similar to lymphoepithelial carcinoma, with or without association with EBV virus infection, and another rare variant exhibits a plasmacellular infiltrate and signs of regression (medullary HCC; Chap. 12). Very rare forms of HCCs are characterized by peliotic change, multinucleated giant cells, chromophobe cells, oxyphilic/oncocytic cells, or cells with a Dubin-Johnson-like pigment (Chap. 13). An interesting group of liver cell tumors displays the presence of progenitor cells or stem-like cells. Part of these HCCs with progenitor cell features express cytokeratin 19, a feature conferring a more aggressive course (Chap. 14). A clinically and radiologically intriguing situation is produced by HCCs arising in an ectopic, extrahepatic location (Chap. 15). HCCs also occur in infancy and childhood (pediatric HCC). It is not yet clarified whether these unusual malignancies are the same or different from their adult counterparts (Chap. 16). A neoplasm that in several respects mimics HCC is hepatoid carcinoma, which can develop in numerous organs, but is usually manifest in the liver in the form of metastases (Chap. 17). An intriguing variant of HCC is fibrolamellar HCC, a tumor mainly occurring in younger individuals, showing a biology similar to that of ordinary HCC, and associated with a typical recurrent chimeric transcript (Chap. 18). A rare group of neoplasms composed of immature hepatocyte progenitors (embryonal and fetal hepatocytes) is formed by the various types and subtypes of hepatoblastoma and related neoplasms (Chap. 19). The majority of these cancers develops in children younger than 5 years, but rarely also develop in adults. Unusual variants of hepatoblastoma with aberrant differentiation patterns are treated in Chap. 20, including tumors with a bile duct cell differentiation. The focus of Chap. 21 relates to the biology and prognostic factors of hepatoblastoma, while Chap. 22 treats risk factors and pathogenic pathways of neoplasms of the hepatoblastoma tumor family. An intriguing neoplasm related to hepatoblastoma and associated with an interesting clinical presentation and unique molecular features, nested stromal epithelial tumor, is the theme of Chap. 23. A benign tumor of the hepatocyte lineage is hepatocellular adenoma, which has recently been subdivided into several molecular subtypes associated with distinct morphologic patterns. The discussion of this important hepatic tumor and its variants is found in Chaps. 24 and 25. A rare group of neoplasms containing hepatocyte-like cells is combined hepatocellular-cholangiocarcinoma, malignancies that display a biphenotypic histologic picture. In contrast to HCC, these highly aggressive
neoplasms occur in cirrhotic and noncirrhotic livers with almost the same frequency (Chap. ▶ 26).

Part 2 of the textbook relates to benign and malignant neoplasms of the cholangiocyte lineage. Cholangiocarcinomas (CC) are divided into two major groups, extrahepatic and intrahepatic bile duct cancers. Among the former, hilar and perihilar CC form a distinct clinicopathologic entity different from CC originating in the mid-region and distal parts of the large bile duct. Intrahepatic CC is a malignancy that can present in three major gross growth patterns and originates from both small or large intrahepatic bile ducts. CC are malignancies of adult patients, but very rarely also develop in the pediatric age group (Chaps. ▶ 27, ▶ 28, ▶ 29, ▶ 30, ▶ 31, and ▶ 32). A distinct group of bile duct neoplasms is formed by intraductal neoplasms, tumors that resemble their pancreatic counterparts. They display a phase of intraluminal, often papillary noninvasive growth and a later high risk of transition into invasive CC (Chap. ▶ 33). In addition to classical forms of CC, there are tumors developing in the setting of hepatobiliary cystic disease, or exhibit distinct differentiation patterns different from those observed in ordinary CC (Chaps. ▶ 34, ▶ 35, ▶ 36, ▶ 37, and ▶ 38). A rare subset of bile duct tumors is characterized by cysts lined by a mucin-producing epithelium, frequently associated with a subepithelial ovarian-like stroma and expression of sex steroid receptors. These mucinous cystic neoplasms (MCN) can undergo a dysplasia-carcinoma sequence (Chap. ▶ 39). Both the intrahepatic and extrahepatic biliary tree can be the site of several types of benign epithelial neoplasms and hamartomas, including tubular and papillary adenomas, peribiliary gland hamartomas, biliary microhamartoma, and neoplasms and hyperplasias of peribiliary glands (Chaps. ▶ 40 and ▶ 41).

Part 3 covers a heterogeneous group of liver tumors derived from other epithelial lineages. Some hepatobiliary carcinomas are characterized by varying proportions of squamous epithelial cells, including squamous cell carcinoma, adenosquamous carcinoma, and mucoepidermoid carcinoma, or acinar cell and adenoid cystic components (Chaps. ▶ 42 and ▶ 43). Rare carcinomas of the biliary tract are undifferentiated neoplasms, such as nonendocrine small cell and spindle cell carcinomas, and carcinomas with rhabdoid features (Chap. ▶ 44). In a small group of hepatobiliary neoplasms, the cells of origin are not yet fully clarified. These lesions mainly comprise hepatic adrenal rest tumor and progenitor cell neoplasms (Chap. ▶ 45).

Part 4 of the textbook refers to mixed epithelial-mesenchymal tumors of the hepatobiliary tract. Chapter ▶ 46 highlights an intriguing group of hepatobiliary malignancies that are composed of a complex mixture of various neoplastic tissue types. These tumors are classified as carcinosarcomas and carcinomas with sarcomatoid features. Few primary hepatic tumors are characterized by the presence of multinucleated, osteoclast-like giant cells with a macrophage/histiocyte lineage (Chap. ▶ 47). Apart from carcinosarcomas, rare hepatic tumors present a mixed cellular phenotype that is still difficult to classify, including malignant mixed tumors, adenosarcomas, stromal tumors, and adult-type mixed hepatoblastomas (Chap. ▶ 48).

Part 5 focuses on the predominant group of hepatobiliary mesenchymal tumors, i.e., vascular tumors. The most important type of primary hepatic
vascular neoplasm is cavernous hemangioma with its various phenotypes and associations with extrahepatic vascular tumors (Chap. ▶ 49). Less common hepatic vascular tumors include several forms of hemangiomatosis, hemangioblastoma, epithelioid hemangioendothelioma, infantile hepatic hemangioma/hemangioendothelioma, kaposiform hemangioendothelioma, angiosarcoma, Kaposi’s sarcoma, glomus tumors, myopericytoma, and glomangiopericytoma (Chaps. ▶ 50, ▶ 51, ▶ 52, ▶ 53, ▶ 54, ▶ 55, ▶ 56, and ▶ 57). Unusual vascular malformations, which may be part of complex inborn syndromes, can mimic true vascular neoplasms, such as Klippel-Trenaunay syndrome (Chap. ▶ 58). A second group of reactive vascular lesions that can cause tumor-like hepatic manifestations include bacillary angiomatosis and peliosis hepatis (Chap. ▶ 59).

Part 6 refers to tumors and tumor-like lesions of lymph vessels. In the hepatobiliary tract, these are very rare conditions which include cystic and noncystic lymphangioma, capillary lymphangioma, lymphangiomatosis, hepatic lymphangiectasis, and lymphocele (Chap. ▶ 60).

Part 7 is exclusively dedicated to solitary fibrous tumor and tumors with a hemangiopericytoma-like pattern. These lesions now include at least part of the former hemangiopericytomas and are characterized by a distinct somatic fusion of two genes, NAB2 and STAT6 (Chap. ▶ 61).

Part 8 discusses the complex spectrum of nonvascular mesenchymal tumors of the hepatobiliary tract. All these neoplasm are rare lesions and include fibrolamellar and myofibrolamellar neoplasms, leiomyoma and leiomyosarcomas, rhabdomyosarcomas, lipoma, liposarcoma, myelolipoma, hibernoma, tumors with osteosarcomatous and chondrosarcomatous components, gastrointestinal stromal tumors, benign and malignant nerve sheath tumors, granular cell tumors, synovial sarcoma, and undifferentiated high-grade pleomorphic sarcomas (Chaps. ▶ 62, ▶ 63, ▶ 64, ▶ 65, ▶ 66, ▶ 67, ▶ 68, ▶ 69, ▶ 70, and ▶ 71).

Part 9 summarizes tumors with a mesothelial cell lineage. Primary mesotheliomas of the liver are very rare, but characteristic neoplasms mimic mesothelial tumors in other locations. A unique mesothelial tumor occurring also in the liver is adenomatoid tumor (Chap. ▶ 72).

The theme of Part 10 is a heterogeneous group of neoplasms that are derived from, or related to, perivascular epithelioid cells. The liver is the primary site of various perivascular epithelioid cell tumors or PEComas, all with complex cellular compositions. They include PEComa proper, angiomyolipoma with its various subtypes, clear cell myomelanocytic tumors, clear cell and sugar tumors, and lymphangiomymomatosis (Chap. ▶ 73).

Part 11 presents hepatobiliary tumors of neuroendocrine lineages. Chapter ▶ 74 provides pertinent information regarding extraadrenal paraganglioma, neoplasms that also in the liver range in biology from a benign to frankly malignant behavior. In Chap. ▶ 75, the various types and subtypes of hepatobiliary neuroendocrine tumors are treated, emphasis being placed on novel classifications and grading systems.

In Part 12, a rare group of small tumors that also originate in the liver are discussed. The lesions comprise various small cell blue tumors, such as primitive neuroectodermal tumors (PNET), desmoplastic small round cell tumor, NUT midline carcinoma, and hepatic neuroblastoma (Chap. ▶ 76).
Part 13 refers to the interesting group of primary and secondary melanotic tumors of the hepatobiliary tract. Emphasis is placed on primary and metastatic melanoma, in particular also metastatic ocular melanoma, melanotic progonoma, and manifestations of melanoma of soft parts (Chap. ▶ 77).

Part 14 focuses on hepatic tumors with a rhabdoid cell lineage. Liver and bile duct tumors with rhabdoid cell components are, at least in part, associated with absence of the chromatin remodeling factor SRF5/INI1 and include malignant rhabdoid tumor proper, carcinomas with rhabdoid features, and a subset of small cell hepatoblastoma (Chap. ▶ 78).

In Part 15, primary and metastatic germ cell tumors are treated. Most germ cell tumors occurring in the gonads can occur as primary lesions in the liver, but teratomas, yolk sac tumor, and choriocarcinoma prevail, also in the pediatric age group. The liver is a well-known site of metastatic germ cell tumors and can be the site of growing teratoma syndrome (Chap. ▶ 79).

Part 16 summarizes the pathology of hepatic manifestations of myeloid neoplasms. With the exception of granulocytic sarcomas, these neoplasms cause diffuse infiltration of the liver substance. The conditions discussed comprise polycythemia vera, several types of myeloproliferative syndrome, chronic eosinophilic leukemia and idiopathic hypereosinophilia, mast cell neoplasms, acute leukemias, myeloid neoplasms with a monocytoid lineage, and blastic plasmacytoid dendritic cell neoplasms (Chaps. ▶ 80, ▶ 81, ▶ 82, ▶ 83, ▶ 84, ▶ 85, ▶ 86, and ▶ 87).

Part 17 refers to the complex pathology of hepatobiliary Hodgkin’s disease. This disorder causes, on the one hand, tumorous hepatic lesions that can clinically be confounded with liver cancer, but on the other hand also reveals associations with paraneoplastic changes, including vanishing bile duct syndrome (Chap. ▶ 88).

Part 18 covers the large field of hepatobiliary non-Hodgkin’s lymphomas, other lymphoproliferative disorders, and neoplasms of dendritic and histiocytic cell systems. Major groups comprise B-cell and T-cell neoplasms that occur in numerous extrahepatic sites, but pseudolymphomas, neoplasms of the Langerhans cell and histiocytic systems, dendritic cell neoplasms, and reactive histiocytic syndromes (such as Rosai-Dorfman syndrome) are also discussed (Chaps. ▶ 89, ▶ 90, ▶ 91, ▶ 92, ▶ 93, ▶ 94, ▶ 95, ▶ 96, ▶ 97, ▶ 98, ▶ 99, ▶ 100, ▶ 101, ▶ 102, and ▶ 103).

Part 19 treats mesenchymal hamartoma of the liver and related neoplasms. Mesenchymal hamartoma and undifferentiated embryonal sarcoma of the liver are typical pediatric hepatic neoplasms, but they have rare counterparts in adult patients (Chaps. ▶ 104 and ▶ 105).

Part 20 is a large complex of chapters that relates to the very important issue of metastatic liver disease. The chapters discuss in detail aspects of gross and microscopic pathology of liver metastases in general, a specific chapter on colorectal cancer metastases, other common and rare metastatic cancers, secondary changes that frequently develop in hepatic metastases, secondary spread of metastatic disease into locoregional lymph nodes, associated liver lesions, growth and regrowth of metastases, and pathogenic features of liver metastasis (Chaps. ▶ 106, ▶ 107, ▶ 108, ▶ 109, ▶ 110, ▶ 111, ▶ 112, ▶ 113, ▶ 114, and ▶ 115).
In Part 21, a small theme of liver tumor pathology is addressed, tumors and tumor-like lesions of hepatic ligaments. Falciform and round hepatic ligaments are the site of rare primary benign and malignant neoplasms, metastases, and various types of cysts (Chap. ▶ 116).

Part 22 contains chapters on reactive nodular hyperplastic hepatocyte lesions of the liver. Focal nodular hyperplasia (FNH) of the liver is an important mass-forming regenerative condition that often develops secondary to localized vascular and circulatory abnormalities of the liver. After hemangiomas, FNH is the second most common benign hepatic tumorous lesion (Chap. ▶ 117). A second important regenerative condition of the liver is nodular regenerative hyperplasia, which is associated with a broad array of causative factors (Chap. ▶ 118).

In Part 23, pseudotumors of the hepatobiliary tract are discussed. Pseudotumors and inflammatory pseudotumors form a heterogeneous group of lesions that share spindle cell proliferations and inflammatory infiltrates of variable density. Inflammatory myofibroblastic tumors is a lesion that contains a subset with neoplastic features and aberrant ALK expression (Chap. ▶ 119).

Part 24 relates to nonneoplastic tumor-like lesions of the liver. The liver is the site of tumor-like ectopias and heterotopias, mass-forming malformations, solitary necrotic nodule, various types of dust-induced nodular lesions, tumor-like lesions caused by gallstones and foreign bodies, pseudotumors consisting of reactive proliferations of hematopoietic cells and macrophages, pyogenic liver abscesses mimicking cancer, numerous hepatic bacterial, fungal, and protozoal infections causing tumor-like hepatic masses (tuberculosis, syphilis, brucellosis, and amebiasis representing prominent examples), tumor-like parasitic lesions (mainly echinococcosis), and liver infarcts (Chaps. ▶ 120, ▶ 121, ▶ 122, ▶ 123, ▶ 124, ▶ 125, ▶ 126, ▶ 127, ▶ 128, ▶ 129, ▶ 130, ▶ 131, ▶ 132, ▶ 133, ▶ 134, ▶ 135, ▶ 136, and ▶ 137).

Part 25 refers to reactive cystic lesions of the liver that may mimic cystic neoplasms. They include simple nonparasitic cysts, ciliated foregut cyst, pancreatitic pseudocysts, and cerebrospinal fluid pseudocysts (Chap. ▶ 138).

Part 26 provides information related to hepatic mass lesions caused by noninfectious granulomas. The main disorder is sarcoidosis that can also cause a complex form of sclerosing bile duct disease with bile duct loss. Blau syndrome and complex inflammatory disorders in part involving deregulated inflammasome function are also discussed (Chap. ▶ 139). A small chapter refers to chronic granulomatous disease (Chap. ▶ 140).

Part 27 presents the hepatic pathology of interesting fibrosclerotic disorders. The conditions include idiopathic retroperitoneal fibrosis and its variants, and the complex spectrum of IgG4-associated systemic sclerosing disease (Chap. ▶ 141).

In Part 28, numerous reactive bile duct alterations that can mimic biliary neoplasms are discussed. Intrahepatic and extrahepatic bile ducts can be involved with inflammatory stenosing polyps, granulomatous cholangitis, follicular cholangitis, oriental cholangitis, xanthogranulomatous cholangitis, bile duct cholesterolosis, sclerosing eosinophilic cholangitis, mechanical and anatomical bile duct alterations, bile duct stenosis caused by congenital
anomalies and acquired disorders of the splanchnic arterial tree and the portal vein, and postcholecystectomy changes (Chaps. ▶ 142, ▶ 143, ▶ 144, ▶ 145, and ▶ 146).

Part 29 addresses the important issue of gallbladder cancer and other tumors and tumor-like lesions of this organ. Ordinary gallbladder carcinoma usually develops in a gallbladder that has undergone secondary changes related to longstanding cholelithiasis and associated inflammations. This neoplasm, an adenocarcinoma, can be associated with epithelial precursor lesions and presents in the form of distinct growth patterns (Chap. ▶ 147). Biology of disease, prognosticators, staging, risk factors, and pathogenic pathways of gallbladder carcinoma are treated in more detail in Chaps. ▶ 148 and ▶ 149. Apart from the common ordinary adenocarcinoma of the gallbladder, several rare variants with other differentiation patterns are recognized, including mucinous, signet ring cell, and squamous cell carcinomas (Chaps. ▶ 150 and ▶ 151). The gallbladder is also the site of rare cystic and mixed neoplasms, such as cystadenoma and cystadenocarcinoma (Chap. ▶ 152). As outlined in Chap. ▶ 153, the gallbladder can give rise to a spectrum of adenomatous, borderline, and dysplastic lesions. Of differential diagnostic importance is the observation of various types of hyperplastic and metaplastic lesions in the gallbladder mucosa (Chap. ▶ 154). Similar to the bile duct system and liver, the gallbladder is a well-known origin of diverse types of neuroendocrine tumors, mesenchymal neoplasms, malignant melanoma, and a wide spectrum of other, however very rare, neoplasms (Chaps. ▶ 155, ▶ 156, and ▶ 157). A broad array of reactive, inflammatory, and noninflammatory alterations of the gallbladder can result in mass lesions that mimic neoplasms, and in particular gallbladder cancer (Chaps. ▶ 158, ▶ 159, ▶ 160, and ▶ 161). A rare group of malignant and benign tumors takes its origin in the cystic duct (Chap. ▶ 162).

Part 30 refers to a heterogeneous group of tumorous and tumor-like peritoneal lesions that may involve the liver surface. They include several primary carcinomas and other malignancies, pseudomyxoma peritonei, gliomatosis peritonei, and various forms of metaplasia, granulomas, endometriosis, and decidualis (Chap. ▶ 163).

Part 31 is the first part of the textbook referring to aspects of general pathology of hepatobiliary tumors, specifically etiology and pathogenesis of hepatocellular carcinoma (HCC). A first chapter discusses in depth inflammatory and toxic causes, in particular the role of hepatitis virus infections, fatty liver and steatohepatitis, and nutritional and other toxins in hepatocarcinogenic pathways (Chap. ▶ 164). The following chapter (Chap. ▶ 165) discusses HCC that arises in the setting of inborn errors of metabolism, in particular various forms of chronic hepatic iron overload. Chapter ▶ 166 focuses on chromosomal alterations, oncogenes, tumor suppressors, and associated signaling networks that are involved in tumorigenesis, while Chap. ▶ 167 puts emphasis on the roles of transcription factors, regulators of growth and apoptosis, and telomere homeostasis. Finally, Chap. ▶ 168 is an overview on the etiologic and pathogenic significance of epigenetic mechanisms in hepatocarcinogenesis (the epigenome).

Part 32 contains an important chapter on the general pathology of structural and functional nuclear changes in hepatobiliary cancer. In Chap. ▶ 169,
relevant diagnostic and theoretical aspects of nuclear and nucleolar abnormalities, anaplasia, and chromatin alterations are addressed. Numerous types of structural abnormalities of cancer cell nuclei are directly associated with functional disorders of nuclear homeostasis, DNA replication, cell division, and organization of chromatin superstructures during interphase. Abnormal heterochromatin generation, a deranged production of euchromatin strings, malposition of interphase chromosomes, and anomalies of intranuclear chromosome movements are hallmarks of nuclear function failure in cancer cells (Chap. ▶ 170).

Part 33 addresses mitochondrial structure and function in normal and malignant neoplastic cells. Apart from their central role in energy production, mitochondria play a significant role within carcinogenic pathways involving abnormal stress responses and deregulation of cell death pathways. This role has led to the “mitochondrial malignancy theory.” Mitochondria hold a central position in apoptosis induction, but they also modulate cell shape and engage in complex interactions with other organelles. Cancer cells exhibit various types of structural abnormalities of mitochondria and may show changes in mitochondrial number, mitochondrial fission, and elimination of this organelle. Part of these alterations are associated with losses and mutations of mitochondrial DNA (Chap. ▶ 171).

The contents of Part 34 pertain to tumor growth and its regulation. Uncontrolled, progressive growth is a key feature of cancers. Net mass increase of tumors not only depends on cell proliferation, but also on cell loss caused by various forms of apoptosis and necrosis and the contribution of nonneoplastic tissues and cells accompanying neoplasms, in particular stroma, blood vessels, and leukocytes. Cell proliferation in liver cell cancer reflects features of normal liver regeneration which is therefore discussed in some detail. The aberrant proliferation of liver cancer cells is related to deranged functions of factors orchestrating cell division, checkpoint regulators, proteins involved in DNA synthesis, proteins of the mitotic apparatus, and the numerous components of the cytoskeleton. Similar to the regenerating liver, growth of liver neoplasm is regulated by numerous growth factors and their receptors, including factors produced by platelets and antagonists of proliferation. Furthermore, hepatobiliary cancers reveal abnormal expression patterns of proteins that control entry into and passage through the cell division cycle, including cyclins and cyclin-dependent kinases. Finally, regulation of tumor growth strongly depends on various epigenetic mechanisms, specifically on complex expression patterns of microRNAs and other RNA classes (Chaps. ▶ 172, ▶ 173, ▶ 174, and ▶ 175).

Part 35 informs the reader about important aspects of the necrobiology of hepatobiliary cancer. An intricate process to control tumor cell mass is apoptosis, a complex form of tightly controlled cell death. Growth caused by proliferation is also counteracted by necrosis which, in contrast to traditional views, is a controlled process rather than a passive phenomenon. In liver cancer, apoptosis can be assessed by immunohistochemical and molecular methods. In addition to classical apoptosis, necrobio logic processes active in cancer also include various forms of cell death related to, but not identical with, apoptosis. These pathways may play a significant role for future novel
therapies (Chaps. ▶ 176 and ▶ 177). A special chapter is dedicated to the pathophysiology of classical (passive) necrosis in comparison with regulated necrosis (necroptosis). The latter involves a complex signaling platform, the necrosome, a molecular machine that senses ATP depletion and transmits this signal into kinase execution switches (Chap. ▶ 178). An important role in cancer cell biology is played by autophagy, a process involved in the maintenance of cell and tissue homeostasis, control of the protein composition of cells, aging, senescence, and neoplastic transformation. Autophagy is the instrument to eliminate altered proteins, damaged or superfluous organelles, and pathogens, and is a complex system connected with inflammasome function, inflammation, immunogenic cell death, and cell senescence. Special forms of autophagy in cancer cells include mitophagy and nucleophagy (Chap. ▶ 179).

Part 36 covers several important aspects of cancer invasion and metastasis. Invasion and metastatic spread of cancer cells involve a highly complex sequence of events that comprise tumor cell individualization, tumor cell polarization, migration, and the acquisition of a secretory phenotype, with release of histolytic enzymes. It is not yet fully known how these features are acquired by cancer cells in a seemingly concerted fashion. For being able to locomote, cancer cells, similar to leukocytes, must be able to undergo shape change and polarization, a process that requires numerous cytoskeletal components and specific polarity proteins. The invasive process strongly depends on the generation of invadosomes, including podosomes and invadopodia, matrix-degrading adhesive, and actin-dependent dynamic cellular structures or “organelles” that can also extend through endothelial linings and mediate extravasation of tumor cells. An important role for the invasion of carcinomas is the distinct tumor stroma. Stroma is composed of cancer-associated fibroblasts/CAFs, myofibroblasts, mesenchymal stem cells, stellate cells, blood vessel cells, extracellular matrix, and several classes of infiltrating leukocytes. The interaction of stromal cells with cancer cells affects invasive functions and modulates epithelial-mesenchymal transition (Chaps. ▶ 180, ▶ 181, ▶ 182, and ▶ 183). Metastatic spread of cancer cells, preceded by invasion, is a process that depends on the construction of premetastatic niches, the expression of distinct prometastatic genes and metastasis suppressors, on numerous microRNAs, and on the exchange of cellular information through exosomes and other vehicles that transfer signal cargo and extracellular nucleic acids (Chap. ▶ 184).

Part 37 is reserved for a distinct tumor tissue that affects numerous biologic functions of neoplasms, i.e., tumor stroma. Stroma forms a specific microenvironment that critically regulates the development and behavior of malignant neoplasms. Stromal cells interact with tumor cells directly, in part through cell fusion, and via molecular signals, resulting in a complex signal platform that expands in parallel with tumor growth. Stroma regulates tumor growth, differentiation, invasion, and metastatic spread. The various types of leukocytes present in stroma, in particular tumor-associated macrophages, myeloid-derived suppressor cells, lymphocytes, and neutrophils, create a unique inflammatory microenvironment which, through chemokines and other signal substances, significantly affects tumor biology (Chap. ▶ 185).
Part 38 shows how tumor angiogenesis functions and how it is an essential process in many aspects of liver tumor invasion and progression. Angiogenesis, the formation of new tumor blood vessels, is a critical mechanism for the development and progression of hepatobiliary tumors, which are often highly vascular lesions. In contrast to normal tissues, tumor blood vessels often form highly atypical branching patterns, with irregular diameters and abrupt changes from large to small diameters. The cells mediating tumor angiogenesis are endothelial cells and auxiliary cells that modulate the biology of endothelial cells, in particular perivascular cells, stromal cells, and tumor-associated macrophages and other leukocytes. As in normal tissue, initiation and progression of angiogenesis in tumors involve the action of numerous angiogenic factors, but neoplasms also produce several antiangiogenic factors. Tumor angiogenesis is modulated by epigenetic mechanisms, mainly microRNAs expressed by tumor cells and stromal cells (Chap. ▶ 186). This chapter is supplemented by a chapter that addresses basic questions of vasculogenesis, angiogenesis, and lymphangiogenesis (Chap. ▶ 187).

The last part of the present book, Part 39, provides a summary of current systems of tumor staging. As with other cancers, staging of hepatobiliary cancers is critical for prognostication and optimal treatment planning. Staging is a complex task that depends on multiple factors. In recent years, several staging systems have been developed and markedly improved the methods to arrive at optimal risk stratification procedures. Apart from hepatocellular carcinoma, highly reproducible staging systems have been developed for extrahepatic and intrahepatic cholangiocarcinoma and for hepatoblastoma (Chap. ▶ 188).

Arthur Zimmermann
Bern, Switzerland
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About the Author

Professor Arthur Zimmermann is an internationally known specialist in hepatobiliary tumor pathology. Following his training as MD and pathologist at the University of Berne, Switzerland, he worked in basic research for several years, focusing on tumor cell growth regulation, tumor cell locomotion, and cell cycle mutants of cancer cells. In surgical pathology, he analyzed more than 20,000 liver specimens, described new tumor entities, and was an author or coauthor of more than 500 publications in his field of interest. As chapter author, he participated in several well-known books on liver and biliary tract disease, including the 2010 edition of the *WHO Classification of Tumors of the Digestive System*, and was one of the editors of the book, *Pediatric Liver Tumors* (Pediatric Oncology Series, Springer). Professor Zimmermann developed the pathology review center for the multinational SIOPEL pediatric liver cancer treatment studies and was involved in the formulation of the new classification of pediatric liver tumors.