Hepatobiliary cancers, comprising those of the liver and biliary tract, are highly lethal conditions with increasing incidence worldwide. In fact, hepatocellular carcinoma (HCC), the most common primary liver malignancy, is now the fastest growing cause of cancer-related death. Surgical resection and liver transplantation remain the only curative therapies, though recurrence rates are high even after an R0 resection. Unfortunately, most patients present with inoperable, advanced disease at diagnosis. For these reasons, better screening strategies and more effective therapies are urgently needed.

While precision medicine with targeted therapies has been successful for several tumor types, its potential for hepatobiliary cancer has yet to be recognized. Over the past decade, several large omic-based studies have been completed in an attempt to identify actionable genetic drivers and molecular subtypes of hepatobiliary cancers. Although intratumor heterogeneity remains a challenge for large lesions, these studies should now pave the way for precision-guided, patient-selected trials over the next few years. For example, dysregulation of several signaling pathways including MET, ERK, PI3K, WNT, HDAC, and SHH seem to be common themes in hepatobiliary cancers along with activation of several miRNAs. In addition, good response rates have been observed with immunotherapy in a subset of hepatobiliary cancers, and studies aimed at characterizing the tumor microenvironment should allow for more appropriate patient selection for therapy.

Underlying liver disease is a major risk factor for hepatobiliary cancers and an obstacle for treatment. While alcohol excess and viral hepatitis infection have historically been the most common causes of liver disease, fatty liver disease is becoming increasingly prevalent as a result of obesity, diabetes, and the metabolic syndrome. Over the past few years, the mechanisms involved in the progression of various etiologies of liver disease have been elucidated and new treatment strategies are starting to emerge. Chemoprevention after successful treatment of the underlying liver disease also has great potential for improving the dismal prognosis of hepatobiliary cancers.

In this book, we explore several of these topics including the effect of intratumor heterogeneity on HCC chemoresistance, the analysis of omics data to predict new prognostic biomarkers and therapeutic targets for HCC and gallbladder cancer, the role of cancer stem cells in the treatment of HCC, and the emergence of SHH inhibitors for the treatment of gallbladder cancer. While much work is still needed to be done, precision medicine may finally offer some hope for the prevention and treatment of these highly lethal cancers.

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