Primary Liver Cancer: Background and Clinical Evidence

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9.1 Introduction

- In the year 2016, it is estimated that there will be 39,230 diagnoses and 27,170 deaths from liver and intrahepatic bile duct cancer in the United States [1].
  - Hepatocellular carcinoma (HCC) accounts for the vast majority of these cases.
- Worldwide, HCC is the second leading cause of cancer deaths, with approximately 782,500 new diagnoses and 745,000 deaths from liver cancer each year [2].
  - The majority of cases occur in developing nations [2], but the incidence of HCC in the United States has been steadily increasing over the past 30 years [3].
  - The incidence of intrahepatic cholangiocarcinoma (ICC) has also increased over the past 20 years [4, 5].

9.2 Epidemiology and Risk Factors

9.2.1 HCC

The risk factors associated with HCC vary by region. Cirrhosis (due to viral, alcoholic, or other etiologies) is associated with the majority of cases (80 %).

- Hepatitis B virus (HBV)
- Hepatitis C virus (HCV)
- Coinfection with HIV in patients with HCV or HBV infection
- Alcoholic cirrhosis
- Additional risk factors include:
  - Nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease
  - Diabetes, in the setting of a metabolic syndrome (which may cause or contribute to NASH)
  - Alpha-1 antitrypsin deficiency, hereditary hemochromatosis, Wilson's disease, autoimmune hepatitis, and exposure to toxins including aflatoxin B_1

9.2.2 ICC

While there are documented risk factors for ICC, many patients will not have a clear associated risk factor identified.

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- Primary sclerosing cholangitis, which may be associated with ulcerative colitis
  - Lifetime risk of developing ICC is 10–15 % [6], with estimated annual risk of 1.5 % [7].
- Liver damage in the setting of hepatitis or cirrhosis
- Fibropolycystic liver disease
- Parasitic infection with *Opisthorchis viverrini* or *Clonorchis sinensis*

9.3 Screening

9.3.1 HCC

- Surveillance recommendations are based on data from patients with HBV cirrhosis. There are no randomized data in patients with HCV cirrhosis or other etiologies of cirrhosis.
- The American Association for the Study of Liver Disease (AASLD) recommends HCC surveillance in patients with cirrhosis, select HBV carriers, and patients with coinfection with HCV/HBV and HIV.
- Surveillance techniques:
  - AASLD recommends hepatic ultrasound every 6 months (sensitivity 63–94 %) [8].
  - NCCN recommends hepatic ultrasound and serum alpha-fetoprotein (AFP) every 6 months.
- In patients with an abnormal finding identified on surveillance imaging, three-phase CT or MRI is recommended.
  - For single nodules < 1 cm, repeat imaging every 3–6 months is recommended, with further workup and treatment for enlarging lesions.
  - For nodules ≥ 1 cm, the presence of two classic enhancement characteristics (arterial enhancement and rapid venous phase washout) confirms the diagnosis of HCC (OPTN Class V). For lesions which do not exhibit classic enhancement features, repeat imaging is recommended.
    - Biopsy is not recommended for diagnosis in OPTN Class V lesions.
    - Biopsy can be considered in tumors which on repeat imaging again fail to demonstrate both classic enhancement patterns.

9.3.2 ICC

- There are no standard screening recommendations for high-risk populations, although some institutions screen patients with primary sclerosing cholangitis with serial imaging and serum CA19-9 levels [7, 9].
- In patients presenting with symptoms concerning for cholangiocarcinoma, including weight loss, jaundice, and right upper quadrant pain, workup should consist of serum chemistries, liver function tests, CA19-9, CEA, and AFP.
- Imaging options include MRI/MRCP, although diagnosis can be challenging in patients with benign biliary strictures in the setting of primary sclerosing cholangitis.
  - ERCP with bile duct brushings may help differentiate between benign and malignant strictures.

9.4 Pathology

9.4.1 HCC

In patients with underlying cirrhosis, HCC is thought to arise from dysplastic nodules which progress from well-differentiated tumor cells with similar appearance to hepatocytes to poorly differentiated infiltrating lesions characterized by pleomorphism, nuclear atypia, and neovascularization. Tumor cells most often appear in a trabecular pattern, although this can be lost in poorly differentiated lesions [10].

- On immunohistochemical stains, HCC often stains positive for hepatocyte paraffin 1 antigen (Hep Par-1), AFP, polyclonal CEA (pCEA), and CD10 and stains negative for CK7, AE1–3, CK19, EMA, and mucin.

  - Hep Par-1 may be used to differentiate HCC from hepatic metastases.
- Variants of HCC include sarcomatous HCC, scirrhous HCC, clear-cell variant HCC, steatohepatic HCC, and fibrolamellar HCC.

9.4.2 ICC

The majority of cholangiocarcinomas are adenocarcinomas.

- The Liver Cancer Study Group of Japan classified ICC based on macroscopic tumor appearance into mass-forming, periductal-infiltrating, and intraductal growth type [11]. Lesions may fall into one or more categories depending on involvement of biliary ducts and hepatic parenchyma.
  - Mass-forming (MF) type: well-defined localized lesions in hepatic parenchyma.
  - Periductal-infiltrating (PI) type: mass extending along biliary ducts which may involve adjacent hepatic parenchyma.
  - Intraductal growth (IG) type: papillary form, involving the lumen of biliary ducts, may present as ductal dilatation or tumor thrombus.
- On immunohistochemical stains, ICC cells will often stain positive for mucin, CEA, CAM5.2, CK 7, and CK 19 and negative for AFP and Hep Par-1.

Mixed hepatocellular cholangiocarcinomas comprise 1–4 % of primary liver neoplasms, with histologic appearances consistent with both HCC and cholangiocarcinoma.

- Unlike patients with HCC, these patients may have minimal elevation in serum AFP.

9.5 Staging

9.5.1 HCC

Assessment of prognosis in HCC is complicated, as patients face significant mortality risks from not only the tumor but also underlying compromised hepatic function. There are several staging systems for HCC, with variable focus on the extent of the tumor, regional or distant metastases, hepatic function, and performance status. The optimal staging system for a given patient also depends on which, if any, therapies they are candidates for.

- The American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) staging system [12] accounts for tumor size, the presence of solitary vs. multiple tumors, vascular invasion, invasion of adjacent organs, regional lymph node involvement, or metastatic disease. The fibrosis score (none or moderate fibrosis vs. severe fibrosis or cirrhosis) has been incorporated into the AJCC/TNM system but is not used to determine overall stage.
  - The AJCC TNM staging system has been validated in patients undergoing orthotopic liver transplantation [13].
- The Barcelona Clinic Liver Cancer (BCLC) staging classification system [14] stratifies patients by performance status, Child-Pugh cirrhosis score, and size and extent of the primary tumor. The BCLC algorithm also recommends treatment options based on a given patient's stage.
  - Very early stage (0) is defined as a single lesion < 2 cm in a patient with an ECOG PS of 0 and Child-Pugh A cirrhosis.
  - Early stage (A) includes patients with a single lesion or three nodules measuring < 3 cm in patients with an ECOG PS of 0 and Child-Pugh A or B cirrhosis.
  - Intermediate stage (B) is comprised of patients with large multinodular tumors, ECOG PS of 0, and Child-Pugh A or B cirrhosis.
  - Advanced stage (C) includes tumors with portal invasion, extrahepatic spread, and/or patients with ECOG PS 1–2 and Child-Pugh A or B cirrhosis.
  - Terminal stage (D) consists of patients with an ECOG PS of 3–4 and Child-Pugh C cirrhosis.

- Okuda system [15]: The Okuda system divides patients into three stages (I, II, III) based on tumor size (ratio of tumor size to liver area), ascites (clinically detectable vs. absent), serum albumin (<3 mg/dl vs. >3 mg/dl), and serum bilirubin (>3 mg/dl or <3 mg/dl).
  - Does not include vascular invasion or lymph node involvement
  - Validated in patients who did not receive treatment
- CLIP score [16, 17]: The CLIP scoring system divides patients into categories (score 0–6) based on Child-Pugh score, the number of tumor nodules and extension through the liver, serum alpha-fetoprotein (AFP) level (<400 or ≥400 ng/ml), and the presence or absence of portal vein thrombosis.
  - For patients with HCC who were treated with TACE, the CLIP system provided the best estimate of overall survival when compared with other classification systems including the Okuda system, the BCLC system, the Japanese Integrated Staging (JIS) system, the Child-Pugh score, and the model of end-stage liver disease (MELD)-modified CLIP system and JIS system [18].

9.5.2 ICC Staging

- AJCC TNM staging for ICC is based on the number and extent of the primary tumors (including the presence of vascular invasion and invasion into extrahepatic structures) and the presence of nodal or distant metastases.
  - Staging system does not include tumor size. Tumor size was not found to be a significant predictor of OS in a SEER analysis of 598 patients who underwent resection for ICC [19].

9.6 Prognostic Factors

- Hepatic function (Table 9.1)
  - Child-Turcotte-Pugh classification
    - Assigns scores based on serum albumin, serum bilirubin, serum prothrombin time, the presence of ascites, and the presence of encephalopathy (scores 5–15) to stratify patients into three overall categories (Child-Pugh classes A, B, and C) (Table 9.2)
    - Initially developed as a predictor of perioperative mortality in patients with esophageal varices [20, 21]
  - Model of end-stage liver disease (MELD)
    - Based on serum bilirubin, serum INR, and serum creatinine.
    - Developed as a predictor of survival after elective transjugular intrahepatic portosystemic shunt (TIPS) placement [22].
      - Felt to be more accurate than the Child-Pugh score as a predictor of short-term mortality after transjugular intrahepatic portosystemic shunt [23]. Also more accurate as a predictor of 3-month mortality among patients on the Organ Procurement and Transplantation Network (OPTN) wait list [24]
    - In 2002, the MELD score replaced the Child-Turcotte-Pugh score as the system employed by the United Network for Organ Sharing (UNOS) to assign priority for liver transplantation in the United States.
  - Albumin-bilirubin (ALBI) grade [25] employs only albumin and bilirubin levels to divide patients into three grades (A1, A2, and A3) to predict survival in HCC patients.
    - Developed using data from patients with HCC from Japan and validated using international databases and data from two randomized trials of sorafenib for unresectable HCC
    - Divided patients with Child-Pugh A cirrhosis into two prognostically distinct cohorts, with a 6-month difference in overall survival between ALBI grade 1 and ALBI grade 2 patients

Table 9.1 Hepatic function classification systems

	Child-Pugh (CP) score	MELD score	ALBI grade
Prognostic factors included in model	Total bilirubin (mg/dL) INR Albumin (g/dL) Ascites Hepatic encephalopathy	Total bilirubin (mg/dL) INR Creatinine (mg/dL) Hemodialysis twice during prior week Serum sodium (mEq/L)	Total bilirubin (μmol/L) Albumin (g/L)
Additional factors contributing to overall score		Diagnosis of HCC tumor(s) within Milan criteria Time on transplant list	
Score calculation	See Table 9.1 B	MELD = 10 × [0.957 × ln(creatinine)] + [0.378 × ln(bilirubin)] + [1.12 × ln(INR)] +6.43.[a]	Linear predictor (ALBI grade) = ($\log_{10}$ bilirubin × 0.66) + (albumin × −0.085)
Risk categories	CP A: 5–6 points CP B: 7–9 points CP C: 10–15 points	MELD ≤10 MELD 11–18 MELD 19–24 MELD ≥25	ALBI grade 1: ≤−2.60 ALBI grade 2: >−2.60 - ≤−1.39 ALBI grade 3: >−1.39

[a] Hyponatremia can be an important marker of the severity of cirrhosis and portal hypertension. As of January 2016, UNOS now uses the MELD-Na score, which is the MELD score adjusted for serum sodium (MELD Na = MELD score – (serum Na) – [0.025 x MELD × (140 – serum Na)] + 140)

Table 9.2 Child-Turcotte-Pugh classification of cirrhosis

	1 point	2 points	3 points
Total bilirubin (mg/dl)[a]	<3.4	3.4–5.0	>5.0
INR	<1.7	1.7–2.3	>2.3
Albumin (g/dl)	>3.5	2.8–3.5	<2.8
Ascites	None	Mild	Moderate–severe
Hepatic encephalopathy	None	Medically controlled	Refractory

[a] Bilirubin levels are classified differently for patients with primary biliary cirrhosis or primary sclerosing cholangitis

9.7 Molecular Biology

9.7.1 HCC

While HCC often develops in the setting of progression from cirrhosis to dysplastic nodules to invasive carcinoma, the mechanisms underlying this process are not yet fully elucidated.

- Altered expression of *mTOR*, inactivation of p53, loss of heterozygosity in IGF2 receptor, and disruption of the Ras/MAPK pathway, the Rb pathway, the PI3-kinase/Akt pathway, and the Wnt/beta-catenin pathway have all been demonstrated in HCC [26].
  - Studies have also attempted to classify mutation expression by cirrhosis etiology. A study of exome sequencing of 243 liver tumors identified mutations associated with alcohol use (*CTNNB1*) or HBV (*TP53*) [27].

9.7.2 ICC

- Molecular profiling has demonstrated features distinguishing intrahepatic cholangiocarcinoma from extrahepatic cholangiocarcinoma, including increased rates of *IDH1* and *IDH2* mutations in ICC [28]. Further study is needed to elucidate the specific mutational patterns associated with ICC [29].

9.8 Multidisciplinary Treatment

9.8.1 HCC

Management of HCC depends not only on the size and extent of the hepatic lesion but also on a patient's hepatic function and performance status.

- Early-stage HCC: Early-stage HCC includes patients with smaller tumors with adequate underlying hepatic function, a sufficient volume of uninvolved liver, and no evidence of vascular invasion or extrahepatic disease. Curative treatment options for early-stage HCC include surgical resection, orthotopic liver transplantation, and radio-frequency ablation for small tumors.
  - Surgical resection: preferred in patients with solitary tumors without vascular invasion without underlying cirrhosis and with a sufficient volume of uninvolved hepatic parenchyma
    - In patients with solitary tumors < 5 cm without vascular invasion, 5-year overall survival (OS) rates range from 60 % to 83 % [30]. Survival declines in patients with larger tumors, multiple tumors, and/ or vascular invasion [31].
    - There is a significant risk of recurrence, with predictors of recurrence after resection that include tumor size, number of tumors, margin status, vascular invasion, histologic grade, and underlying cirrhosis [31].
    - The role of adjuvant treatment after resection is not well defined. The randomized phase III STORM trial did not demonstrate an improvement in outcomes with the use of sorafenib after resection or ablation [32].
      - Randomized 1114 patients with HCC who had undergone surgical resection (n=900) or ablation (n=214) with a complete radiographic response to adjuvant sorafenib versus placebo.
      - There was no difference in median recurrence-free survival between the two arms (33.3 months with sorafenib vs. 33.7 months with placebo, HR 0.94, 95 % CI 0.78–1.13, one-sided P=0.26).
    - There is suggestion that antiviral therapy after resection in patients with HBV-related HCC may improve outcomes [33], but further study is needed.
  - Orthotopic liver transplantation (OLT).
    - Preferred treatment option in patients with unresectable HCC with underlying cirrhosis or compromised hepatic function.
    - Criteria for OLT: UNOS defines eligibility for organ transplantation as patients who fit with the Milan criteria on radiographic assessment, with no evidence of vascular invasion or extrahepatic disease.
      - MELD points are assigned based on underlying hepatic and renal function, with additional points included for the presence of HCC and time spent on the OLT waiting list.
      - Milan criteria: one tumor < 5 cm or three tumors all < 3 cm.
        - Based on a trial of 48 patients with HCC in the setting of HCV/ HBV cirrhosis who underwent OLT between 1991 and 1994
          - In patients whose explanted tumors met the above criteria, 4-year OS was 75 %, and 4-year DFS was 83 %, while in patients whose tumors exceeded this criteria, 4-year OS was 50 %, and 4-year DFS was 59 % [34].
      - Beyond Milan criteria
        - UCSF criteria: one tumor < 6.5 cm or maximum of three tumors all < 4.5 cm with cumulative size < 8 cm
          - Based on UCSF review of 467 patients who underwent OLT for HCC between 1984 and 2006 [35].

  - There was no significant difference in 5-year OS for patients who met Milan criteria versus those patients who exceeded Milan criteria but met UCSF criteria by explant pathology (86 % vs. 81 %, P=0.057).
- "Up-to-seven" criteria: sum of the size of the largest tumor (cm) + the number of tumors ≤ 7 [36]
  - Retrospective review of 1556 HCC patients undergoing liver transplantation suggested that microinvasion and accounting for the size and number of tumors could potentially identify patients outside Milan criteria who were candidates for OLT.
  - Included 1112 patients exceeding Milan criteria, with reduced 5-year OS of 53.6 % compared with 77.7 % in patients meeting Milan criteria.
  - However a subgroup of 238 patients who exceeded Milan criteria but did not have microinvasion and were within "up-to-seven" criteria had 5-year OS of 71.2 %.

- Due to long waiting times, 12–38 % of patients will drop off the transplant list within 1 year due to tumor progression or functional decline [37]. Whether patients should proceed with resection instead is a topic of debate and varies based on the patient's overall performance status and underlying hepatic function.
  - Intention-to-treat analysis of resection versus transplantation found that the survival of patients listed for transplantation declined as the wait list times for transplant increased (84 % from 1989 to 1995 versus 54 % from 1996 to 1997), likely due to increased numbers of patients who dropped off the transplant wait list during the latter era [38].
  - There are limited data on transplantation after surgical resection, with some studies suggesting that there was not a significant increase in toxicity [39]. Of note, "salvage transplantation" or transplant in the setting of recurrence after resection may be associated with increased toxicity.
    - Retrospective comparison of patients receiving primary liver transplantation versus transplantation in the setting of recurrence ("secondary" transplantation) after resection demonstrated that secondary OLT was associated with increased operative mortality, increased recurrence, and decreased disease-free and OS [40].
  - Ablative therapies include radio-frequency ablation (RFA), microwave ablation (MWA), and chemical ablation (percutaneous ethanol injection).
    - Effective therapy in the treatment of smaller tumors (< 4 cm) and as a bridge to transplantation.
    - Potential curative therapy in tumors < 2 cm.
    - Local control declines in tumors which are close to large blood vessels and larger lesions.
    - Randomized trials of resection versus RFA conducted in China between 1999 and 2008 randomized patients showed mixed results. One trial of 230 patients with tumors that fit within the Milan criteria demonstrated an improvement in OS and recurrence-free survival (RFS) with resection compared with RFA (OS, 82.6 % vs. 66.1 %; RFS, 60.9 % vs. 46.1 %) [41]. Two additional trials did not demonstrate an improvement in OS or RFS with resection over RFA [42, 43].

  - A meta-analysis of resection versus RFA did not show an improvement in recurrence but did demonstrate an improvement in survival with resection [44].

- Advanced HCC: For patients with unresectable HCC who are not candidates for transplant, treatment options include ablation (described above), arterially directed therapies, radiotherapy, and systemic therapy.
  - There are no randomized data directly comparing these techniques.
  - Selecting an optimal treatment for a given patient depends on multiple factors including:
    - Hepatic function
    - Performance status
    - Tumor characteristics
      - Size and number of tumors
      - Tumor location
      - Vascular invasion
  - Arterially directed therapies include bland embolization, transarterial chemoembolization (TACE), and transarterial radioembolization (TARE).
    - Arterially directed therapies exploit the blood supply of HCC, which is primarily supplied by the hepatic artery as compared to normal hepatic parenchyma which is primarily supplied by the portal vein.
    - Arterially directed therapies, including TACE, have been shown to improve palliation and survival when compared with supportive care [45–47], but there are no randomized trials of arterially directed therapies versus ablative techniques or radiotherapy.
    - Arterially directed therapies are also often not possible in patients with tumor vein thrombosis due to the risk of treatment-related ischemic injury and hepatic failure.
      - Although TARE or selective internal radiotherapy (SIRT) is thought to function via microvascular rather than primarily macrovascular occlusion, outcomes still decline in patients with thrombosis or compromised hepatic function [48].
    - Combination of arterially directed therapies with systemic and other locoregional therapies is an ongoing topic of research.
      - The SPACE (Sorafenib or Placebo plus TACE with doxorubicin-eluting beads for Intermediate Stage HCC) trial [49] showed that the combination of TACE with sorafenib was technically feasible but did not demonstrate an improvement in time to progression with the addition of sorafenib to TACE in patients with intermediate-stage HCC without macrovascular invasion or extrahepatic disease. Phase III trials are ongoing.
      - Multiple series have explored the use of arterially directed therapies in conjunction with RT. RT is discussed in further detail below.
  - Radiotherapy
    - Radiotherapy was historically relegated to the palliative setting; however, the development of modern RT techniques, including intensity-modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT), has enabled safe and effective delivery of ablative doses of radiotherapy to tumors while sparing uninvolved hepatic parenchyma.
    - RT has been safely used to treatment numerous patients with HCC, ranging from patients with small tumors who are not operative candidates to patients with large tumors or tumor venous thrombosis. Much of the original data of RT included patients who previously failed arterially directed therapies [50].
      - A series of dose-escalation protocols of hyperfractionated conformal RT with concurrent arterial chemotherapy at the University of Michigan demonstrated the feasibility of liver-directed

RT and provided a framework for assessing the optimal RT dose while minimizing the risk of hepatotoxicity.
    - The series included 128 patients (47 with liver metastases, 35 patients with HCC, and 46 patients with cholangiocarcinoma). Median OS was 15.2 months in patients with HCC and 13.3 months in patients with cholangiocarcinoma.
    - Tumor dose ≥ 75 Gy was predictive of improved overall survival on multivariate analysis (23.9 months vs. 14.9 months, p<0.01) [51].
- Multiple phase I and II prospective single-arm trials and retrospective series have shown impressive local control and survival outcomes, particularly with SBRT and hypofractionated RT, with 1-year OS rates of 48–100 % and 1-year local control rates of 64–100 % [52].
    - Prospective phase I and II trials of 102 HCC patients treated at Princess Margaret Hospital with SBRT reported an overall response rate of 54 %, 1-year local control rate of 87 %, and 1-year OS rate of 55 % [53].
    - Prospective phase II trial of 92 patients with HCC or ICC treated at Massachusetts General Hospital and MD Anderson Cancer Center with hypofractionated proton therapy reported a 2-year local control rate of 94.8 % and 2-year OS rate of 63.2 % for patients with HCC [54].
        - There were low rates of toxicity, with four patients (4.8 %) experiencing grade ≥3 toxicity and only three patients (3.6 %) experiencing a decline in Child-Pugh score from CP A to CP B cirrhosis.
    - The University of Tsukuba reported the largest series of liver-directed proton therapy, consisting of 318 patients with HCC and primarily CP A cirrhosis (73.6 % of patients had CP A cirrhosis, 24.2 % had CP B cirrhosis, and 2.2 % had CP C cirrhosis) [55].
        - For the overall cohort, 1-year OS was 89.5 %, 3-year OS was 64.7 %, and 5-year OS was 44.6 %.
        - Survival was improved in patients with CP A cirrhosis compared with patients with CP B cirrhosis, with 5-year OS of 55.9 % in CP A cirrhosis and 44.5 % in CP B cirrhosis.
        - There were five cases of grade ≥ 3 toxicities.
        - 63 patients in the cohort received more than one course of proton therapy, with 5-year OS of 50.5 %.
    - In patients with smaller tumors (≤ 5 cm) who were not candidates for ablative therapies or resection, outcomes with RT have been particularly impressive, with two series reporting 1-year local control rates of 95–100 % and 1-year OS of 99–100 % [56, 57].
    - Prospective phase II multi-institutional trial demonstrated the safety of 3D-CRT following incomplete TACE, with an overall response rate of 64.5 % [58].
    - RT in conjunction with TACE has also been safely employed in patients with large tumors (> 10 cm), with one series of 72 patients reporting an overall response rate of 76.1 % and a median survival of 12.2 months, without any cases of grade ≥3 toxicity [59].
- Patients with tumor vein thrombosis have particularly poor outcomes, with median survival of 2–4 months. These patients are often not candidates for arterially directed therapies due to the risk of ischemic injury and hepatic failure. Many patients with TVT have been successfully treated with RT with

response rates range from 50 to 79 % and overall survival of 3.8–22 months [52, 53].
  - Prospective phase I and II trials of 102 patients treated with SBRT at Princess Margaret Hospital included 56 patients with TVT, who had a 1-year OS of 44 % [53]. TVT was a strong adverse prognostic factor on multivariate analysis (AHR 2.47, 95 % CI 1.25–4.88, P=0.01).

- Systemic therapy: Sorafenib is the first-line therapy for patients with advanced and metastatic HCC, with randomized data demonstrating a small but significant improvement in overall survival.
  - The Sorafenib HCC Assessment Randomized Protocol (SHARP) Trial [60]
    - Randomized 602 patients with advanced HCC and Child-Pugh A cirrhosis to sorafenib versus placebo. 28 % of patients had HCV-related cirrhosis, 26 % had EtOH-related cirrhosis, and 12 % had HBV-related cirrhosis.
    - Trial was stopped after the second planned interim analysis demonstrated improvement in OS with sorafenib (10.7 months vs. 7.9 months, HR 0.59, 95 % CI 0.55 to 0.87, P<0.001).
    - There were no complete responses. The partial response rate was 2 % in the sorafenib arm vs. 1 % in the placebo arm (P=0.05).
    - Unplanned subgroup analyses [61] by cirrhosis etiology showed increased OS with sorafenib in both HCV-related and HBV-related cirrhosis; however there was no improvement in time to progression in patients with HBV-related cirrhosis. Analysis was limited by small numbers and lack of stratification by viral status.
  - Asia-Pacific Trial [62]
    - Randomized 226 patients with advanced HCC and Child-Pugh A cirrhosis to sorafenib versus placebo. 73 % had HBV-related cirrhosis, and 8.4 % had HCV-related cirrhosis.
    - Median OS was 6.5 months in patients treated with sorafenib vs. 4.2 months in the placebo arm (HR 0.68, 95 % CI 0.5 to 0.93, P=0.014).
    - As in the SHARP Trial, there were no complete responses. The partial response rate was 3.3 % in the sorafenib arm versus 1.3 % in the placebo arm.
    - Potential reasons for decreased OS in the Asia-Pacific Trial as compared with the SHARP Trial include the increased number of patients with more advanced disease in the Asia-Pacific Trial (as demonstrated by the higher numbers of patients with extrahepatic disease, increased number of intrahepatic tumors, and poorer performance status in patients in the Asia-Pacific Trial as compared with the SHARP Trial) [62].
    - While there was a difference in cirrhosis etiology between the two studies, neither study was stratified by HCV or HBV status, making comparisons challenging.

9.8.2 ICC

- Early stage/resectable: Surgical resection is considered the only curative treatment option for patients with early-stage ICC, including those patients with solitary tumors without vascular invasion, involved lymph nodes, or distant metastases.
  - Outcomes are poor even in patients able to undergo resection, with a median 5-year OS of 25–35 % [63–65]. Margin status and involved lymph nodes are significantly associated with survival [66, 67] with R0 resections associated with 5-year OS as high as 63 % [68].
  - Adjuvant therapy: While there is a significant recurrence risk in ICC, particularly in the setting of R1 resection or involved lymph nodes [66, 67], there are no randomized data

defining the optimal adjuvant treatment regimen.
  - Retrospective series often include patients with both intra- and extrahepatic cholangiocarcinoma, further complicating assessment.
  - A meta-analysis including both gallbladder and biliary tract cancer supported the role of adjuvant therapy (chemotherapy, radiotherapy, or chemoradiotherapy) after resection, particularly in patients with involved lymph nodes or positive margins [69]. Retrospective series also support the role of adjuvant therapy in this population [63, 70].
  - The NCCN guidelines recommend adjuvant therapy, including chemotherapy and/or chemoradiotherapy, for patients with positive margins, involved lymph nodes, and/or gross residual disease after resection [71].
- Locally advanced/metastatic disease: The majority of patients (up to 70 %) have unresectable disease at diagnosis due to vascular invasion, the presence of multiple tumors, and/or nodal or distant metastases [72]. There are limited data, as patients with intrahepatic cholangiocarcinoma are often grouped into studies of patients with extrahepatic cholangiocarcinoma and/or hepatocellular carcinoma.
  - The NCCN guidelines [71] recommend chemotherapy with gemcitabine and cisplatin for patients with unresectable and metastatic intrahepatic cholangiocarcinoma based on the ABC-02 [73] trial.
    - Randomized 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer to cisplatin plus gemcitabine versus gemcitabine monotherapy. 59 % of patients had biliary tract cancer, including both intra- and extrahepatic cholangiocarcinoma.
    - After a median follow-up of 8.2 months, median OS was 11.4 months in patients treated with cisplatin plus gemcitabine versus 8.1 months in patients treated with gemcitabine monotherapy (HR 0.64, 95 % CI 0.52–0.80, $P<0.0001$). There was no significant increase in toxicity with the use of cisplatin in addition to gemcitabine.
  - Meta-analysis of ABC-02 and a Japanese randomized controlled trial (BT-22) continued to demonstrate an improvement in OS with the use of gemcitabine plus cisplatin versus gemcitabine monotherapy [74].
- Radiotherapy has also been employed in patients with unresectable disease [54, 75, 76], with single-arm phase II and retrospective series demonstrating impressive local control and survival rates with increasing doses of RT [77].
  - A retrospective series from Fudan University of 84 patients with unresectable ICC reported improved survival in patients treated with radiotherapy [78].
    - 49 patients did not receive RT, and 35 patients received radiotherapy to the area of gross disease to a total dose of 30–60 Gy in 1.8–2 Gy daily fractions. There was no significant difference in clinicopathologic characteristics (age, stage, tumor size, multifocality) between the two groups.
    - 1-year OS was 38.5 % in the radiation group versus 16.4 % in the non-radiation group. Median OS was 9.5 months in the radiation group versus 5.1 months in the non-radiation group (P=0.003).
  - Prospective phase II trial from Massachusetts General Hospital and MD Anderson Cancer Center of hypofractionated proton therapy for HCC and ICC reported a 2-year local control rate of 94.1 % and 2-year OS rate of 46.5 % for patients with ICC [54].
  - A retrospective series from MD Anderson Cancer Center of 79 patients with ICC reported an overall 3-year survival rate of 44 %, with an impressive

3-year OS rate of 73 % and 3-year local control rate of 78 % in patients treated with increasing doses of RT (BED >80.5Gy) [76].

9.9 Future Directions

- Further study is needed to determine the optimal combination of treatment modalities in both hepatocellular carcinoma and intrahepatic cholangiocarcinoma, particularly in those patients with unresectable disease. We strongly recommend protocol enrollment whenever possible. There are numerous ongoing protocols, including the following exploring the role of radiotherapy in conjunction with systemic therapies in HCC and ICC.
  - RTOG 1112 [79], a phase III trial of sorafenib with or without SBRT in patients with unresectable BCLC stage B (intermediate) or C (advanced) HCC who were refractory to TACE or are not candidates for RFA or TACE, will provide prospective data on the role of SBRT in patients with advanced HCC.
    - A study in Singapore of patients with BCLC stage B or C HCC without TVT is randomizing patients to sorafenib versus SIRT with SIR-Spheres (Sirtex Medical, Lake Forest, IL) [80].
  - NRG GI001 [81], a phase III trial of gemcitabine and cisplatin with or without liver-directed radiotherapy for unresectable intrahepatic cholangiocarcinoma, is currently accruing patients.

Conclusions

- The incidence of hepatocellular carcinoma and cholangiocarcinoma continues to rise, and treatment remains challenging, particularly in the advanced setting.
- Cooperation across specialties, including hepatobiliary and transplant surgery, medical oncology, radiation oncology, and interventional radiology, is key to maximizing patient outcomes.

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