Development, Practice Patterns, and Early Clinical Outcomes of a Multidisciplinary Liver Cancer Clinic

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Abstract

Multidisciplinary care has been associated with improved survival in patients with primary liver cancers. We report the practice patterns and real world clinical outcomes for patients presenting to the Johns Hopkins Hospital (JHH) multidisciplinary liver clinic (MDLC). We analyzed hepatocellular carcinoma (HCC, n = 100) and biliary tract cancer (BTC, n = 76) patients evaluated at the JHH MDLC in 2019. We describe the conduct of the clinic, consensus decisions for patient management based on stage categories, and describe treatment approaches and outcomes based on these categories. We describe subclassification of BCLC stage C into 2 parts, and subclassification of cholangiocarcinoma into 4 stages. A treatment consensus was finalized on the day of MDLC for the majority of patients (89% in HCC, 87% in BTC), with high adherence to MDLC recommendations (91% in HCC, 100% in BTC). Among patients presenting for a second opinion regarding management, 28% of HCC and 31% of BTC patients were given new therapeutic recommendations. For HCC patients, at a median follow up of 11.7 months (0.7-19.4 months), median OS was not reached in BCLC A and B patients. In BTC patients, at a median follow up of 14.2 months (0.9-21.1 months) the median OS was not reached in patients with resectable or borderline resectable disease, and was 11.9 months in patients with unresectable or metastatic disease. Coordinated expert multidisciplinary care is feasible for primary liver cancers with high adherence to recommendations and a change in treatment for a sizeable minority of patients.

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Introduction

Liver cancer is the sixth most commonly diagnosed cancer and fourth leading cause of cancer-related deaths worldwide.[1] Hepatocellular carcinoma (HCC) represents more than 80% of primary liver cancers.[2] Overall HCC incidence rates in the United States rose from 1.6 per 100,000 in 1975[3] to 5.86 per 100,000 in 2015.[4] Staging and treatment of HCC through the Barcelona cancer liver clinic (BCLC) approach has guided the conduct of prospective Phase III trials.[5,6] The complexity of HCC disease presentation and treatment options requires interdisciplinary evaluation. Multidisciplinary tumor board discussions have been associated with improved patient outcome.[7,8]

Biliary tract cancers (BTC) include cholangiocarcinoma (CCA) and gallbladder cancer. CCA is the second most common primary liver cancer.[1] The majority of CCAs arise from intrahepatic bile ducts, and extrahepatic CCA is further divided anatomically into perihilar and distal bile duct cancers. Over the past 40 years in the United States, the incidence of intrahepatic CCA has slowly increased to approximately 1.18 per 100,000, while extrahepatic CCA remained constant around 1.0 per 100,000.[9] Surgical resection remains the major established curative therapy; however, resectability remains low at approximately 15%-20% due to the often advanced nature of disease at presentation.[10]

The treatment of primary liver cancers has changed significantly over the past several years, with the development of multiple novel systemic therapies for advanced-stage disease and novel therapeutic approaches for earlier stage disease.[11] In 2019 we launched a new, multidisciplinary liver clinic (MDLC) for the management of primary liver cancers at Johns Hopkins Hospital (JHH), building on our prior experience.[12] The goal of this clinic (MDLC) is to standardize treatment algorithms while simultaneously optimizing individual cancer care in an era of rapid change. Here we describe the JHH MDLC work flow, our treatment paradigms, and clinical outcomes for calendar year 2019.

Patients and Methods

Study Design

A retrospective review was conducted using data from JHH between January 2019 and December 2019. The inclusion criteria for the study were as follows: (1) new patients who were evaluated at the MDLC, (2) HCC diagnosed by radiographic or histologic confirmation or BTC (CCA, gallbladder cancer) by histologic confirmation, and (3) age $\geq$ 18 years. The study protocol was approved by the Johns Hopkins Institutional Review Boards (IRB00231803). Selection of patients is detailed in Figure 1.

MDLC Evaluation and Work-Up

The MDLC team includes physicians from multiple specialties (hepatology, interventional radiology, medical oncology, palliative care, pathology, radiation oncology, radiology, and hepatobiliary surgical oncology). Patient referrals come from the aforementioned JHH specialties, Sidney Kimmel Comprehensive Cancer Center new patient office, and external providers. All referrals are screened by a dedicated full-time MDLC triage nurse, supported by the various departments who participate in the MDLC. Patients who are transplant-eligible are directly referred to the liver transplant clinic. Patients with malignant tumors originating at the ampulla of Vater (ampullary carcinoma) are generally referred to the pancreas multidisciplinary team. The general approach to workup, labs, and imaging for all patients with suspected HCC or BTC presenting to MDLC is presented in Figure 2.

In brief, a pre-review of the patient's history of disease and pertinent work-up is performed and documented by the triage nurse prior to MDLC consultation. The triage nurse obtains outside imaging and pathological slides for JHH internal review, and orders any necessary additional work-up (Figure 2). The MDLC occurs once per week. On the day of MDLC, a history and physical is performed in the morning by a resident physician, physician assistant, or nurse practitioner. Each patient is presented in the afternoon for a multidisciplinary discussion, at which time treatment recommendations are decided and the providers from the various services who will see the patient that day are identified. In the setting of the COVID-19 pandemic, video conferencing and telemedicine were implemented for clinical practice.

Treatment Algorithm

In an effort to prioritize options for patients with HCC and CCA, particularly in an era of evolving systemic and local treatment options, representatives from the various MDLC specialties established staging and treatment pathways. These served as general guidelines for staging and management. For the purpose of this analysis, patients were retrospectively assigned a stage when this was not assigned on the day of MDLC.

For HCC, these pathways were broadly based on the BCLC framework (Figure 3).[13] For BCLC A presentations, surgery is preferred. Non-surgical patients with smaller tumors (<2 cm) are offered ablation while larger tumors and/or difficult locations (hepatic dome, caudate lobe, central biliary tree, abutting adjacent organs, proximal to major blood vessels) are considered for radiation. BCLC B patients are predominately managed with locoregional options. Our approach has been to divide advanced stage (BCLC C) presentations into C1 (macrovascular invasion) versus C2 (extrahepatic disease). BCLC C1
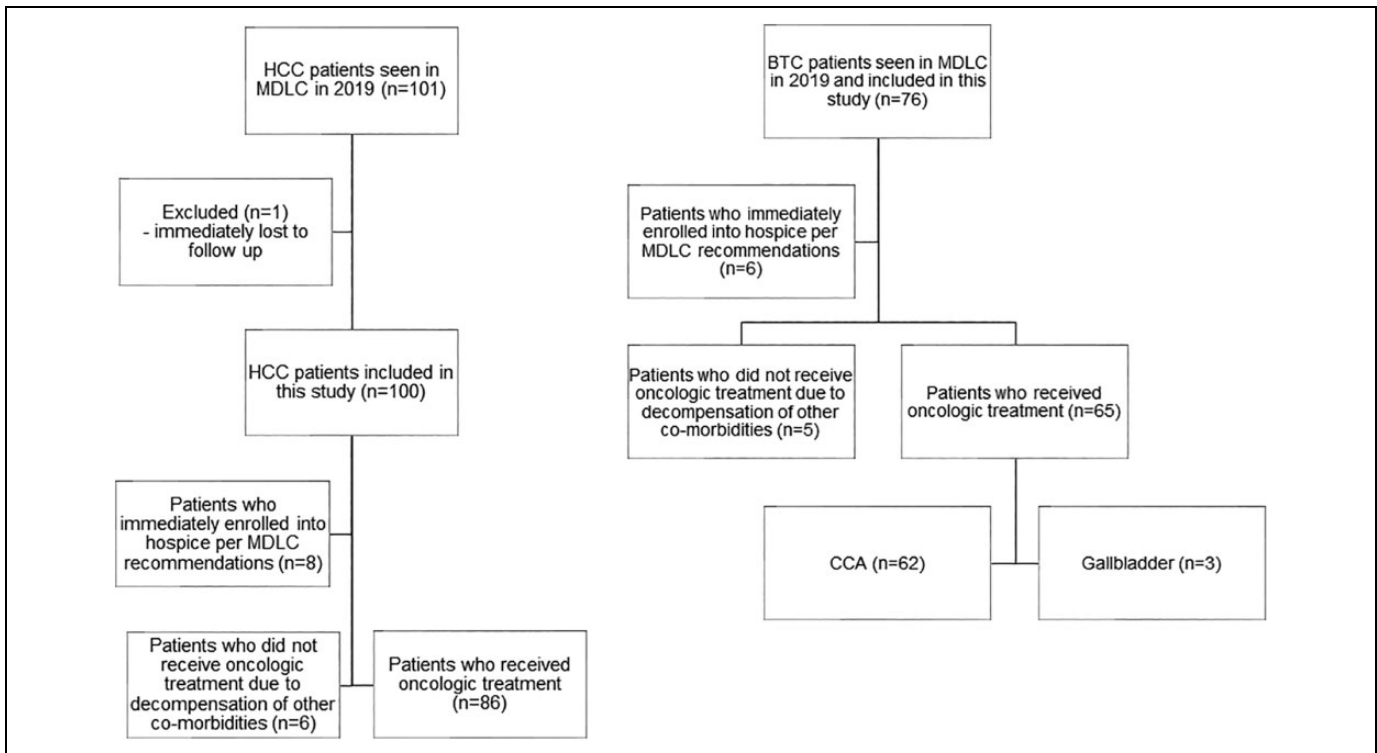
Figure 1. Patient selection flow diagram. Data were abstracted from 101 HCC patients and 76 BTC patients; all were first-time encounters to JHH MDLC (i.e. none were follow up). BTC indicates biliary tract cancer; CCA, cholangiocarcinoma; HCC, hepatocellular carcinoma; MDLC, multidisciplinary liver clinic.

patients are primarily treated with chemoembolization (TACE) plus external beam radiation therapy (EBRT) followed by systemic therapy, or systemic therapy alone, based on the extent of vascular involvement, with locoregional therapies generally offered to those with minimal vascular invasion. BCLC C2 presentations are offered systemic therapy alone.

Given the frequency of genomic aberrations in BTC patients,[14] molecular sequencing of tumors was recommended for all patients. For the management of intrahepatic and peri-hilar CCA, patients were classified based on surgical resectability (Figure 4) into 4 groups: Stage 0, resectable; Stage 1, resectable with high risk features (high risk for micrometastases, such as cN1 disease); Stage 2, borderline resectable (high risk for margin-positive surgical outcome due to vascular involvement, or situations where the future liver remnant is low); Stage 3, unresectable (very locally advanced and/or distant metastases). Stage 0 patients proceed to surgical resection. Margin negative (R0) patients receive adjuvant capecitabine for 6 months. R1 or node positive (pN1) patients receive adjuvant capecitabine and EBRT. Stage 1 and Stage 2 patients receive upfront chemotherapy (gemcitabine, cisplatin, with or without abraxane) for 3 months with repeat imaging assessment for resectability and development of metastatic disease. Patients who remain ineligible for surgery may then be treated with EBRT with or without concurrent chemotherapy. For Stage 3 patients, the primary treatment focus is on systemic therapy, which includes chemotherapy and/or targeted therapy if available.

The above treatment recommendations reflect off-protocol treatments. Patients evaluated in the MDLC are also evaluated for clinical trial enrollment. Trials included neoadjuvant immunotherapy prior to resection (NCT03299946), immunotherapy in combination with TACE for BCLC B (NCT03638141), and novel systemic therapies (NCT03298451, NCT03250273, NCT03833661, NCT03834220).

Treatment and Outcomes

A change in diagnosis or staging was defined as change based on pathological or imaging review by MDLC providers. A change in treatment was defined as a change in recommendation of treatment by MDLC that is different from what the patient was currently receiving or was recommended to receive by an outside provider. For this analysis, new information (e.g. biopsy, imaging) detailed on the day of MDLC that triggered a change in management due to disease progression was not counted as a change in staging or management. Multimodality therapy was defined as a combination of systemic therapy and locoregional therapy. Locoregional therapy was defined as one or a combination of surgical resection, thermal ablation, TACE, Yttrium-90 radioembolization (Y90), and/or EBRT.

Overall survival (OS) was calculated from the date of MDLC consultation to death from any cause or last live follow-up. In patients who underwent surgical resection, disease free survival (DFS) was calculated from the date of surgical resection to recurrence and/or death.
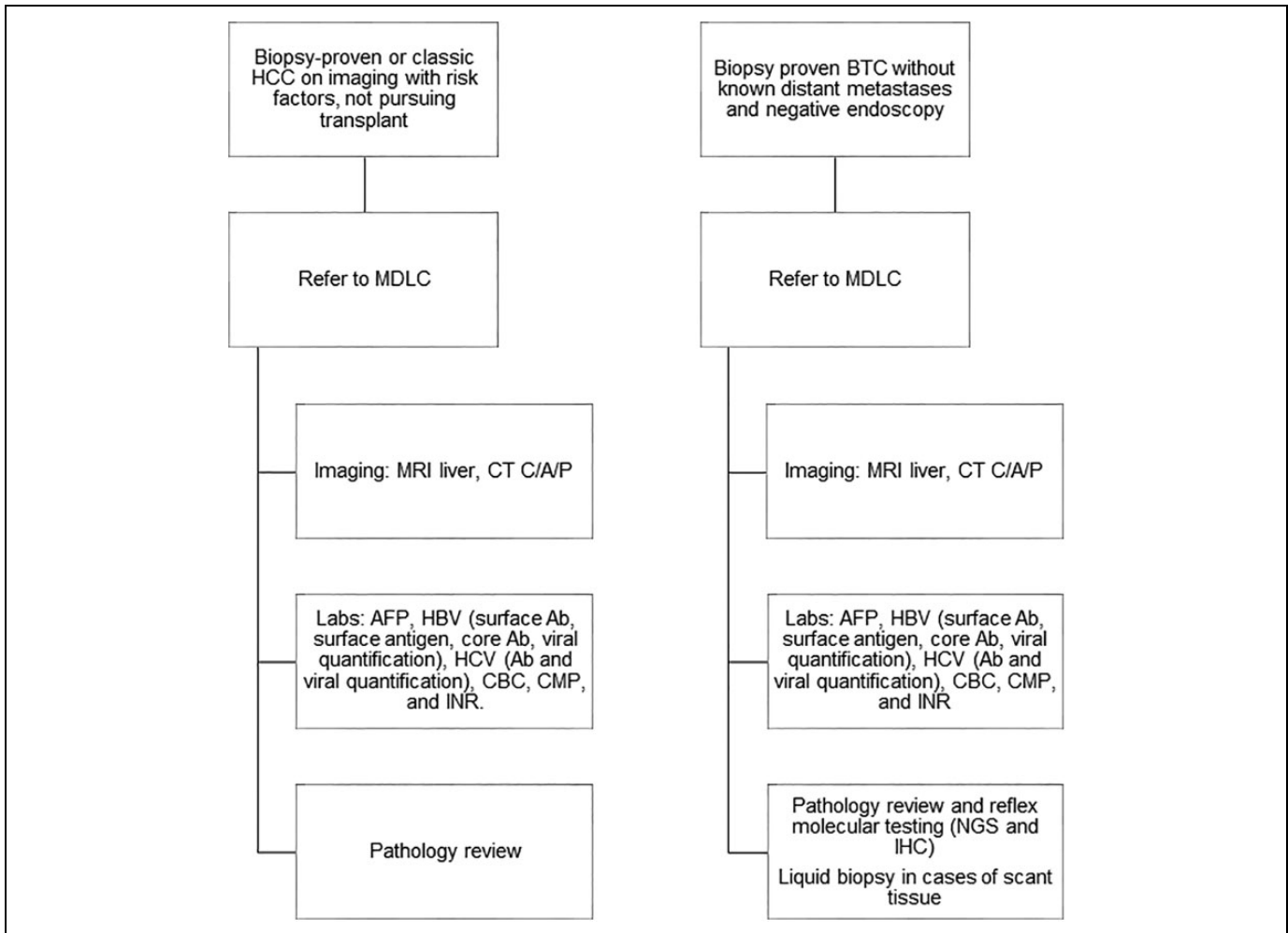
Figure 2. Liver multidisciplinary liver clinic (MDLC) algorithm. MDLC includes physicians from multiple specialties (hepatology, interventional radiology, medical oncology, palliative care, pathology, radiation oncology, radiology, and surgical oncology). All referrals are screened by a dedicated full-time MDLC triage nurse. AFP indicates alpha fetoprotein; BTC, biliary tract cancer; CBC, complete blood count; CEA, carcinoembryonic antigen; CMP, complete metabolic panel; CT C/A/P, computerized tomography scan of chest, abdomen, and pelvis; HBV, hepatitis B virus; Ab, antibody; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IHC, immunohistochemistry; INR, international normalized ratio; MRI, magnetic resonance imaging; NGS, next generation sequencing.

Statistics

Survival was calculated using the Kaplan-Meier method and was compared between the groups using the log-rank test. The day of final follow-up was September 31, 2020.

Results

Patient Characteristics

The annual number of HCC patients consulted in JHH MDLC increased from 52 patients in 2011 to 101 in 2019.[15] Patient demographics, disease characteristics, patterns of consultation, and treatment are summarized in Table 1. Twenty-nine HCC and 29 BTC patients were seeking a second opinion at JHH MDLC. In HCC patients, the majority were male (79%), white race (65%), had good functional status (ECOG 0-1, 77%), had underlying liver disease (86%), and few were early stage BCLC A (15%). In BTC patients, over half the patients were male (57%), white race (80%), had good functional status (ECOG 0-1, 87%), and were without underlying liver disease (82%). Most patients had intrahepatic CCA (68%) and Stage 2 or 3 disease according to the MDLC staging approach (76%). Seventeen patients, 12 (12%) HCC and 5 (7%) BTC, were enrolled onto a clinical trial.

MDLC Consensus, Treatment Received and Clinical Outcome

Three HCC patients (3%) and 6 BTC patients (8%) had a significant change in diagnosis or clinical stage resulting from their MDLC encounter. In HCC patients, diagnosis of hepatic adenoma from outside hospital was changed to HCC in 1 patient, a second synchronous CCA was identified in 1 patient, and portal vein invasion upstaged a third patient to BCLC C1
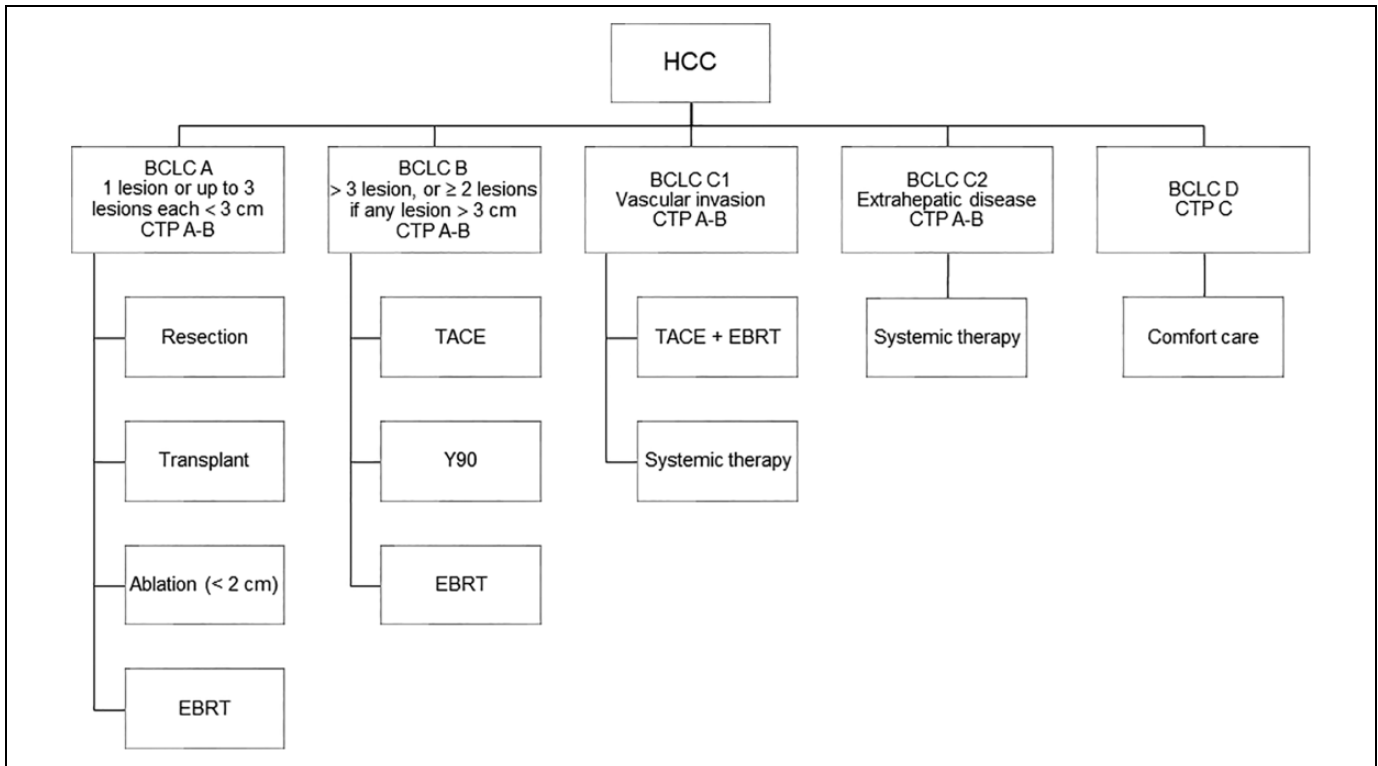
Figure 3. Hepatocellular carcinoma treatment algorithm. These pathways were broadly based on the BCLC framework.[13] We divided BCLC C into C1 (advanced stage due to macrovascular invasion) versus C2 (advanced stage due to extrahepatic disease). BCLC indicates Barcelona cancer liver clinic; CTP, Child-Turcotte Pugh score; EBRT, external beam radiation therapy; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; Y90, Yttrium-90 radioembolization.
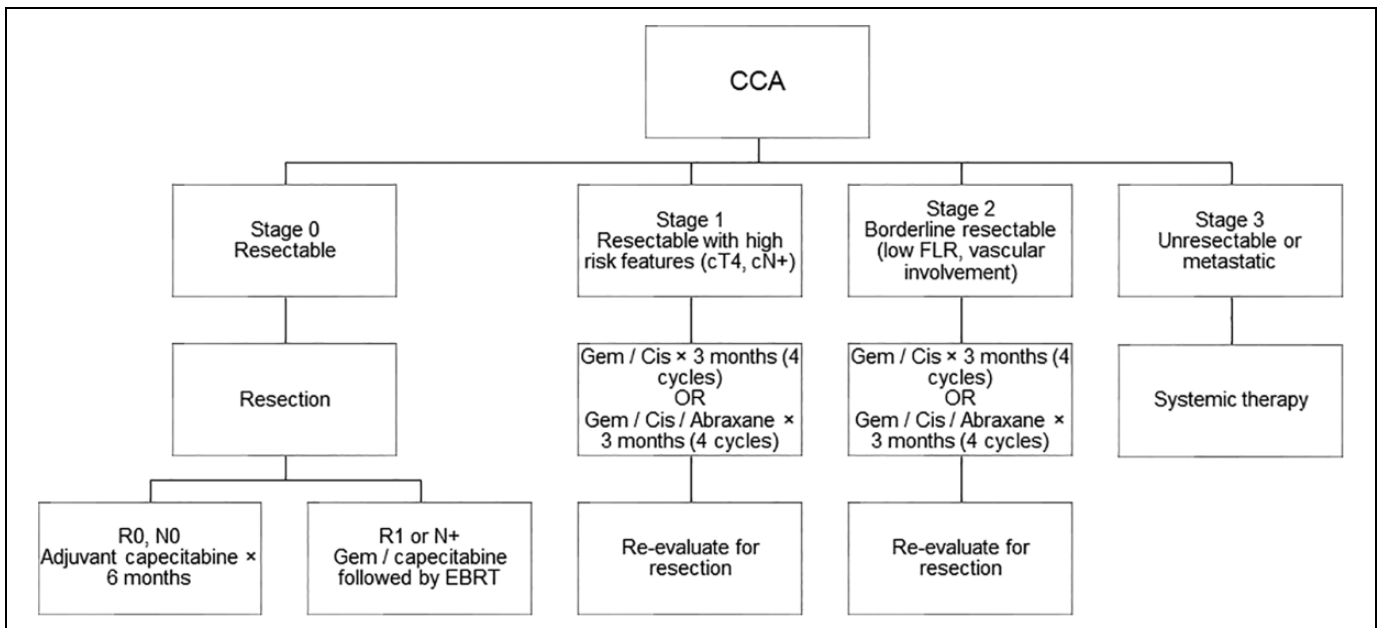
Figure 4. Intrahepatic and perihilar cholangiocarcinoma treatment algorithm. Patients are classified based on surgical resectability. Stage 0 is resectable without high risk features. Stage 1 is resectable with high risk for micrometastases, such as cT4 or cN1 disease. Stage 2 is borderline resectable due to predicted R1 or R2 surgical outcome due to low FLR volume or vascular involvement. Stage 3 is unresectable due to very locally advanced distance or distant metastases. CCA indicates cholangiocarcinoma; Cis, cisplatin; EBRT, external beam radiation therapy; FLR, future liver remnant; Gem, gemcitabine; N1, node positive; R0, margin negative resection; R1, microscopic residual disease after resection; R2, macroscopic residual disease after resection.

Table 1. Patient Demographics, Disease Characteristics, Patterns of Consultation, and Treatment.

	HCC (n = 100)	BTC (n = 76)
Median age at diagnosis, years	66	66
Male gender	79 (79%)	43 (57%)
Race		
White	65 (6%)	61 (80%)
Hispanic	2 (2%)	2 (3%)
Black	25 (25%)	8 (11%)
Asian	6 (6%)	5 (7%)
Mixed	2 2%)	0 (0%)
ECOG		
0	53 (53%)	32 (42%)
1	24 (24%)	34 (45%)
2	15 (15%)	12 (16%)
3	4 (4%)	3 (4%)
4	4 (4%)	2 (3%)
Underlying liver disease[a]		
None	14 (14%)	62 (82%)
Hepatitis B	10 (10%)	4 (5%)
Hepatitis C	46 (46%)	4 (5%)
NASH/NALD	17 (17%)	2 (3%)
Alcohol	21 (21%)	5 (7%)
Primary Sclerosing Cholangitis	0 (0%)	5 (7%)
Other[b]	7 (7%)	1 (1%)
Child-Pugh		
Not cirrhotic	14 (14%)	
A	56 (56%)	
B	19 (19%)	
C	10 (10%)	
Referral from		
Internal medicine (PCP, GI, ID)	47 (47%)	34 (45%)
Self-referral	17 (17%)	16 (21%)
Oncology	20 (20%)	22 (29%)
Surgery	10 (10%)	4 (5%)
Interventional radiology	5 (5%)	0 (0%)
Radiation oncology	1 (1%)	0 (0%)
Previous treatments		
None	65 (65%)	47 (62%)
Surgery[c]	8 (8%)	6 (8%)
Systemic	4 (4%)	23 (30%)
Interventional Radiology[d]	27 (27%)	6 (8%)
RT	4 (4%)	7 (9%)
Diagnosis		
Radiographic	52 (52%)	15 (20%)
Pathologic	48 (48%)	61 (80%)
Recurrent disease	4 (4%)	4 (5%)
HCC Barcelona stage		
A	14 (14%)	
B	32 (32%)	
C1	23 (23%)	
C2	20 (20%)	
D	11 (11%)	
BTC		
Intrahepatic CCA		52 (68%)
Distal CCA		6 (8%)
Perihilar CCA		15 (20%)
Gallbladder		3 (4%)

(continued)

Table 1. (continued)

	HCC (n = 100)	BTC (n = 76)
Resectability (Stage)		
Resectable (0)		11 (15%)
Resectable with high risk features (1)		7 (9%)
Borderline resectable (2)		27 (36%)
Unresectable or metastatic (3)		31 (41%)
Patterns of consultation in MDLC		
Surgery	18 (18%)	24 (32%)
Interventional radiology	49 (49%)	20 (26%)
Medical oncology	62 (62%)	67 (88%)
Radiation oncology	19 (19%)	14 (18%)
Hepatology	53 (53%)	3 (4%)
Palliative Care	6 (6%)	8 (11%)
Change in diagnosis or staging	3 (3%)	6 (8%)
Change from existing treatment	8 (8%)	9 (12%)
Treatment received after MDLC		
Systemic only	18 (18%)	34 (45%)
Locoregional only	36 (26%)	3 (4%)
Radiation	6	1
TACE	25	1
Transplant	2	1
Surgery	2	1
Multimodality	31 (31%)	28 (37%)
Radiation	15	19
TACE	28	5
Systemic	31	27
Surgical resection	9	9
Transplant	0	1
Hospice or no oncologic treatment	14 (14%)	11 (14%)
Treatment consensus established at MDLC	89 (89%)	66 (87%)
Additional testing required prior to any treatment	11 (11%)	10 (13%)
Deviation of treatment from MDLC recommendation	9 (9%)	0 (0%)
Enrolled onto JHH clinical trial[e]	12 (12%)	5 (7%)
BTC tumor molecular sequencing performed		40 (53%)
Actionable mutations identified[f]		23 (58%)
Treatment patterns		
JHH only	71 (71%)	26 (34%)
Partially JHH	12 (12%)	15 (20%)
Local only	17 (17%)	35 (46%)

Abbreviations: BTC, biliary tract cancer; CCA, cholangiocarcinoma; GI, gastroenterologist; HCC, hepatocellular carcinoma; ID, infectious disease; JHH, Johns Hopkins Hospital; MDLC, multidisciplinary liver clinic; PCP, primary care physician; TACE, trans-arterial chemoembolization; Y90, yttrium-90 radioembolization.
[a]19 HCC and 5 BTC patients had >1 liver disease.
[b]Polycystic, cryptogenic, primary biliary cholangitis, and autoimmune hepatitis.
[c]Surgery includes 1 transplant in HCC patients.
[d]TACE, Y90.
[e]HCC clinical trials included: NCT03299946, NCT03638141, NCT03298451. BTC clinical trials included: NCT03250273, NCT03833661, NCT03834220.
[f]Actionable mutation is defined as a finding that will influence immediate or possible subsequent treatment decisions.
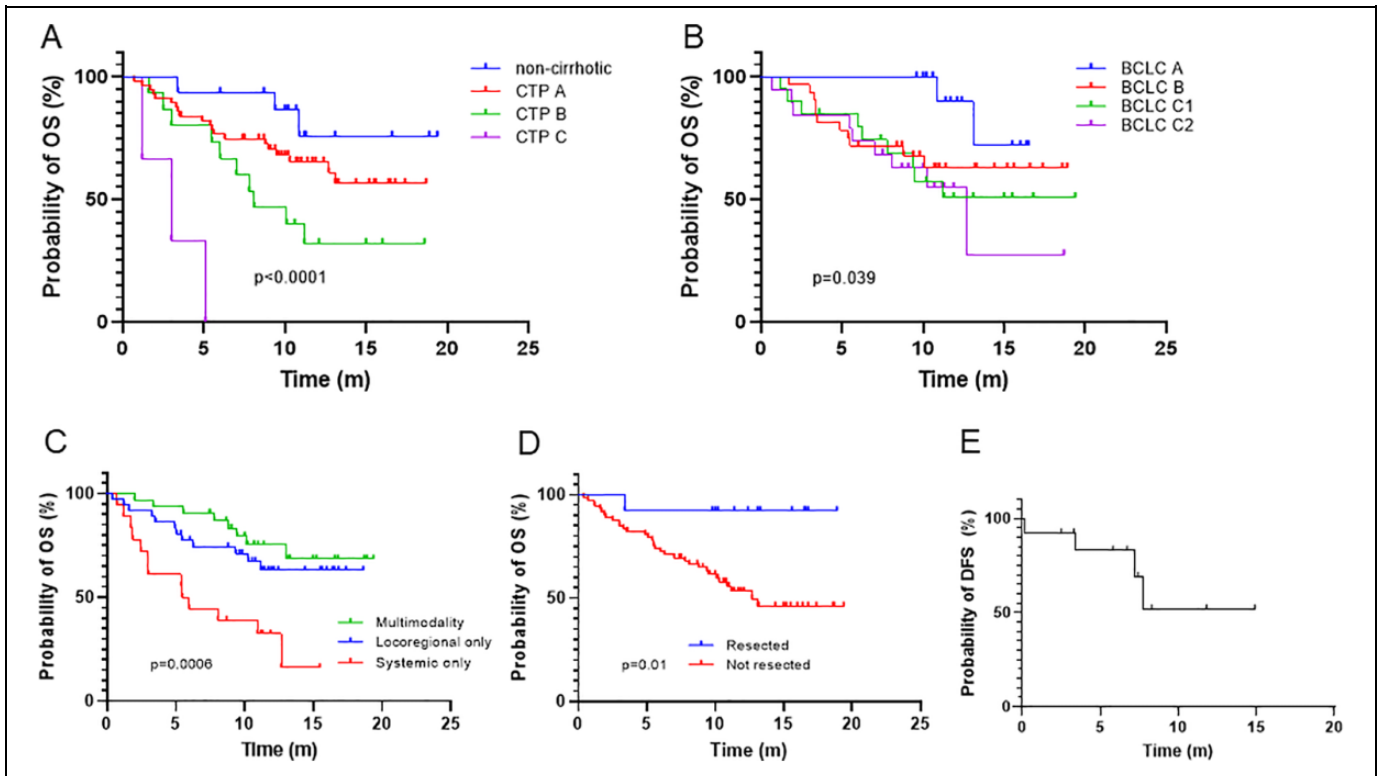
Figure 5. Hepatocellular carcinoma treatment outcomes. Excluding patients who immediately enrolled into hospice (n = 8) per MDLC recommendations, OS based on (A) CTP score (mOS was 8.1 and 3 months in CTP B and C, respectively) and (B) BCLC stage (median OS was 11.2 and 12.7 months in C1 and C2, respectively). Excluding patients who did not receive oncologic treatment (n = 14), OS based on (C) type of treatment received since MDLC (mOS in the systemic only group was 6 months) and (D) surgical resection (mOS was 12.7 months in the absence of resection). (E) DFS in patients who underwent resection (n = 13). Abbreviations: BCLC; Barcelona clinic liver cancer; CTP, Child-Turcotte Pugh score; DFS, disease free survival; MDLC, multidisciplinary liver clinic; mOS, median overall survival.

stage. In 4 BTC patients, the MDLC team changed the diagnosis from HCC to CCA based on pathological review. One BTC patient was diagnosed with lung sarcoidosis on pathology as opposed to metastatic disease. One BTC patient was upstaged on imaging identification of peritoneal metastases.

Among HCC patients presenting for a second opinion who had previously received a treatment recommendation (n = 29), a change in treatment recommendation was provided at MDLC in 8 cases (28%). These changes were as follows: recommendation for hospice (n = 1), change in systemic agent used (n = 3), change to locoregional treatment (n = 1), and change to multimodality treatment (n = 3). Among the 29 BTC patients presenting for a second opinion, a change in recommendation was provided in 9 patients (31%), as follows: recommendation for hospice (n = 1), change in systemic agent used (n = 4), and change to multimodality treatment (n = 4). Treatment consensus was established in 89% of patients on the day of MDLC, while 11% of patients required additional testing prior to treatment. Deviation from the MDLC plan occurred in 9% of cases, due to patient's clinical deterioration.

Child-Turcotte Pugh (CTP) score and BCLC stage correlated with survival (Figure 5A and B) in patients with HCC.

In the patients who received oncologic treatment, multimodality treatment was associated with improved survival ($P = 0.0003$). Median survival was 6 months in patients who received systemic therapy only (Figure 5C).

In BTC patients, treatment consensus was established in 87% of patients on the day of MDLC, while 13% of patients required additional testing prior to treatment. There were no deviations from MDLC management recommendations. Resectable Stage 0 and Stage 1 patient groups had similar survival outcomes, and better survival outcomes as compared to Stage 2 and 3 patients ($P = 0.05$, Figure 6A). The 1 death within a month of the MDLC presentation, in a patient with Stage 1 disease, occurred due to rapid clinical decline after a cycle of gemcitabine and abraxane. Thirty-four (65%) intrahepatic, 2 (33%) extrahepatic, and 4 (27%) perihilar CCA patients underwent tumor genomic sequencing. An actionable mutation, defined as a finding that will influence immediate or possible subsequent treatment decisions, was identified in 19 (56%) intrahepatic, 1 (50%) extrahepatic, and 3 (75%) perihilar CCA patients. Actionable mutations (in order of most to least common) in our BTC cohort: *IDH 1/2*, *FGFR2* rearrangements, *BRCA1/2*, *BRAFV600E*, *PALB2 Y1183**, and *HER2* amplification.
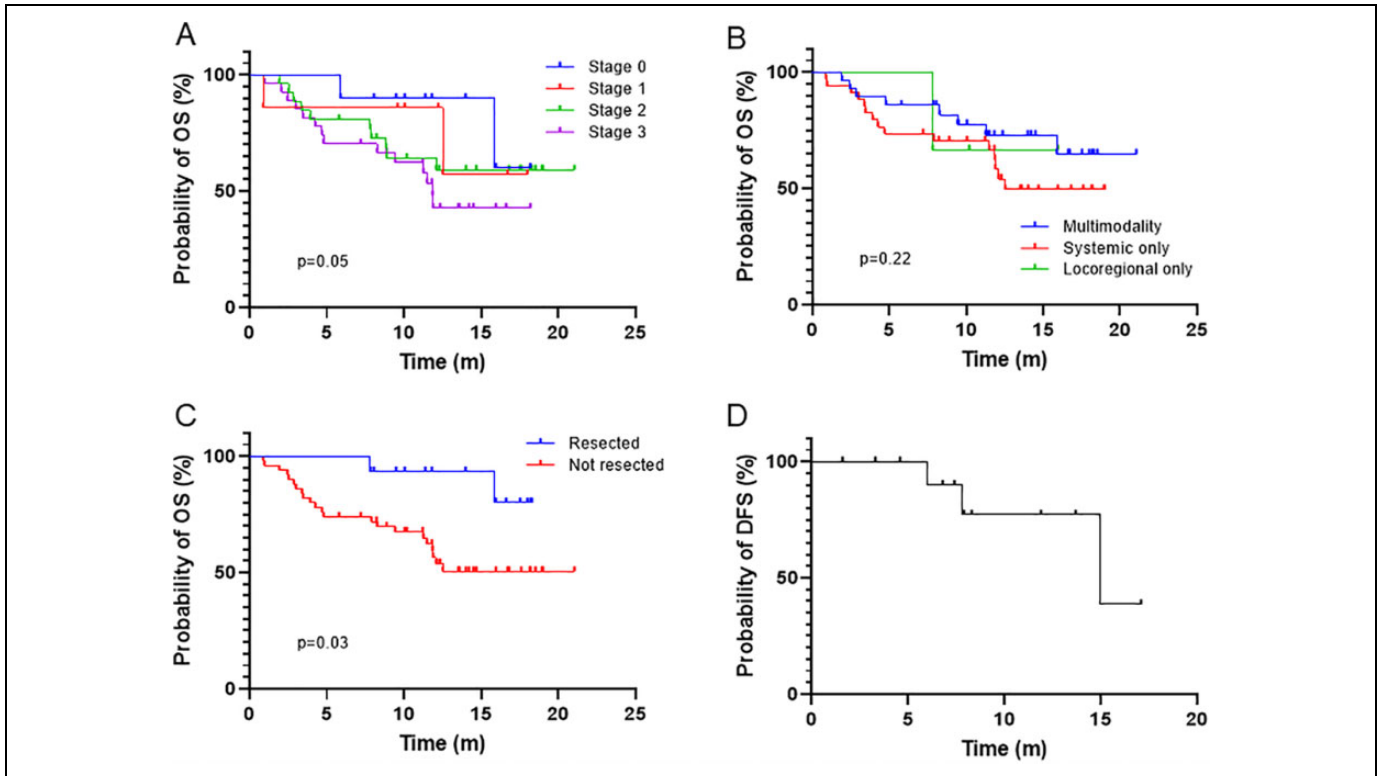
Figure 6. Biliary tract cancer treatment outcome. Excluding patients who immediately enrolled into hospice (n = 6) per MDLC recommendations, OS based on (A) resectability stage (mOS was 11.9 in Stage 3). Excluding patients who did not receive oncologic treatment (n = 11), OS based on (B) type of treatment received since MDLC (mOS in the systemic only group was 12.5 months) and (C) surgical resection (mOS not reached in either group). (D) DFS in patients who underwent resection (n = 15), projected median DFS was 15 months. BTC indicates biliary tract cancer; DFS, disease free survival; MDLC, multidisciplinary liver clinic; mOS, median overall survival.

Surgical Outcomes

In HCC patients with newly diagnosed disease, 11 underwent resection and 2 underwent transplant (Table 2). Nine of these patients had BCLC B or C disease. The majority of patients received neoadjuvant treatment (84.6%) in the form of TACE/Y90 and/or systemic therapy, most as part of ongoing clinical trials. Seven patients enrolled onto NCT03299946 (CaboNivo): 2 BCLC A, 3 BCLC B, and 2 BCLC C1 patients. One BCLC B patient who presented with multifocal unresectable disease enrolled on NCT3638141, where he received DEB-TACE followed by 1 dose of tremelimumab and 3 doses of durvalumab, and re-staging performed at 12 weeks from start of therapy revealed resectable disease. Two BCLC B patients were down-staged to Milan transplant criteria after TACE and underwent liver transplant. Ten of 11 hepatectomies were margin negative, and 1 had a positive margin due to vascular involvement. There was 1 deceased patient due to perioperative hemorrhage. HCC patients who received oncologic treatment but did not undergo surgical resection had a median survival of 12.7 months; both the median OS and DFS in resected patients were not reached (Figure 5D and E).

In BTC patients with newly diagnosed disease, 13 underwent resection and 2 underwent transplant. The 1 Stage 3 patient who underwent resection had 1 isolated pancreatic metastasis that was treated with stereotactic RT. In patients where adjuvant treatment was deferred, 2 underwent liver transplant and 2 were due to other co-comorbidities. Surgical resection was associated with a longer OS ($P = 0.03$), median OS as not reached in either group.

Discussion

We present real world outcomes for primary liver cancers from the JHH MDLC in 2019. Multidisciplinary methods of care delivery have been associated with improved survival in patients with liver cancer.[7,8] In our cohort, 3% of HCC and 8% of BTC patients had a change in diagnosis or clinical stage; in patients who presented to the JHH MDLC for a second opinion, 28% of HCC and 31% of BTC patients were recommended a change from existing treatment plans. Our report demonstrates that a treatment consensus was finalized on the day of MDLC for the majority of patients (89% in HCC, 87% in BTC), with high adherence to MDLC recommendations (91% in HCC, 100% in BTC).

Practical staging categorization can help guide rational combinations and sequencing of systemic and local-regional treatments. Our approach to HCC is centered around the BCLC staging system, with the subdivision of the C stage into C1 and C2. Other groups have also proposed subcategorization for

Table 2. Surgical Resection or Transplant in Newly Diagnosed Patients With Hepatocellular Carcinoma or Biliary Tract Cancer.[a]

	HCC (n = 13)	BTC (n = 15)
Surgical resection		
Resection prior to MDLC	1 (8%)	2 (13%)
Resection after MDLC	12 (92%)	13 (87%)
Child-Pugh		
Not-cirrhotic	5 (38%)	
A	8 (62%)	
ECOG		
0	11 (85%)	7 (47%)
1	2 (15%)	7 (47%)
2	0 (0%)	1 (7%)
BCLC		
A	4 (31%)	
B	7 (54%)	
C1	2 (15%)	
BTC		
Intrahepatic CCA		9 (60%)
Distal CCA		1 (7%)
Perihilar CCA		4 (27%)
Gallbladder		1 (7%)
Resectability stage		
Resectable (0)		8 (53%)
Resectable with high risk features (1)		3 (20%)
Borderline resectable (2)		3 (20%)
Unresectable or metastatic (3)		1 (7%)
Neoadjuvant treatment		
None	2 (15%)	8 (53%)
Radiation	0 (0%)	2 (13%)
TACE, Y90	6 (46%)	0 (0%)
Systemic	9 (69%)	7 (47%)
Resection		
Transplant	2 (15%)	2 (13%)
R0	10 (77%)	8 (53%)
R1	1 (8%)	2 (13%)
Unknown[b]	0	3 (20%)
Adjuvant treatment		
Surveillance	13 (100%)	4 (27%)
Systemic	0 (0%)	11 (73%)
Radiation	0 (0%)	3 (20%)
Disease outcome		
Alive	12 (92%)	13 (87%)
NED	9	10
SD	1	2
PD	2	2
Deceased[b]	1 (8%)[c]	2 (13%)[d]
DOD	0	1

Abbreviations: BTC, biliary tract cancer; CCA, cholangiocarcinoma; DOD, dead of disease; HCC, hepatocellular carcinoma; MDLC, multidisciplinary liver clinic; NED, no evidence of disease; PD, progression of disease; SD, stable disease; TACE, trans-arterial chemoembolization; Y90, yttrium-90 radioembolization.
[a]Patients with a history of resection presenting with recurrent disease were excluded (n = 4 HCC, n = 4 BTC). The 2 HCC transplant patients were both BCLC B who were down-staged to meet Milan criteria after TACE. No HCC patient received adjuvant treatment (all were on surveillance until progression of disease). The 2 BTC transplant patients were an intrahepatic CCA and a perihilar CCA; neither received adjuvant treatment. Another 2 BTC patients did not receive adjuvant treatment due to medical co-morbidities.
[b]Surgery was performed at an outside institution, records were not available.
[c]One patient died of peri-operative complications.
[d]One patient died of post-operative complications, 1 died of disease.

specific BCLC stage groups.[16,17] In the C1 disease state there is no gross evidence for cancer beyond the liver, and thus local-regional therapies may play an important role in disease control, with or without systemic therapy, with clinical trial evidence supporting this approach.[18] Combinations of multiple local therapies, including radiation therapy, with systemic therapy allows for treatment of clinically apparent disease and subclinical micrometastatic disease, a treatment paradigm applied to many solid tumors but, to date, not extensively studied in HCC.

BTC represents a heterogeneous group of tumors where resectability is often not adequately portrayed in the current tumor-node-metastasis (TNM) staging. We have adopted a practical staging approach similar to 1 that is now widely applied to pancreatic adenocarcinoma, where the emphasis is on operability and considerations of risk of local-regional and distant disease recurrence. Upfront resectability, Stage 0, is determined by presence of a minimum of 2 contiguous liver segments uninvolved by tumor with adequate perfusion, venous, and biliary drainage.[19] Stage 1 captures technically resectable primary tumors but with high risk imaging features, including cN1 disease. For such patients, upfront/neoadjuvant chemotherapy is given to address both the primary disease as well as the high risk for micrometastatic cancer. After initial chemotherapy and re-staging, patients without evidence for disease progression are offered surgery. Borderline resectable, Stage 2, patients do not meet criteria for upfront resectability due to low future liver remnant or high risk of margin-positive surgery.[20] In such patients, there is a concern for microscopic (R1) or macroscopic (R2) residual disease following upfront surgery. Similar to Stage 1 management, the focus is on neoadjuvant chemotherapy to address possible micrometastatic disease as well as to allow for downstaging of the primary tumor. This stage is similar to the situation of borderline resectable pancreas cancer.[21] One retrospective series demonstrated that neoadjuvant chemotherapy converted 53% (n = 39) of initially unresectable intrahepatic CCA to resectable status, of which 31% (n = 12) achieved R0 outcomes[22] In our cohort, 3 Stage 1 patients (43%) underwent resection and all achieved R0 surgeries; 3 Stage 2 patients (13%) underwent resection, with 2 proceeding to transplant and 1 hepatectomy with unknown margin status. At a median follow-up of 15 months in resected patients (n = 15), median OS was not reached. Consensus for adjuvant capecitabine in resected BTC comes from the Phase III randomized trial that demonstrated improved OS of 51 months in the capecitabine arm.[23] The data supporting use of adjuvant RT in CCA is mainly retrospective or limited by small numbers. We extrapolate from SWOG 0809, which demonstrated feasibility of adjuvant chemotherapy followed by concurrent chemoradiotherapy in extrahepatic CCA in the setting of pN+ or R1, and achieved a median OS of 35 months.[24] We define Stage 3 as metastatic disease or very locally advanced disease that is highly unlikely to be downstaged to resectable status. Stage 3 patients are offered upfront gemcitabine and cisplatin based on the Advanced Biliary Cancers (ABC)-02 trial.[25] In our cohort, median OS was not reached

in Stage 2 (median follow-up 17.5 months, n = 27) and 11.9 months in Stage 3, similar to 11.7 months in ABC-02.[25]

Approximately 40% of BTC patients harbor actionable mutations.[26] The frequency of molecularly actionable alterations is higher in patients with intrahepatic CCA, where alterations in *IDH1* and *FGFR2* rearrangements are the most common.[26,27] Recent Phase II trials of FGFR inhibitors demonstrate an objective response rate of 35.5% using pemigatinib[28] and 37.1% using futibatinib.[29,30] Of the 40 CCA patients who underwent tumor sequencing, 23 (58%) had an actionable mutation that guided subsequent treatment decision making. Targeted therapies that were used include: ivosidenib (*IDH1* inhibitor), enasidenib (*IDH2* inhibitor), pemigatinib and futibatinib (*FGFR* inhibitors), olaparib (for patients with *BRCA1/2* and *PALB2 Y1183** mutations), dabrafenib and trametinib (for patients with the *BRAFV600E* mutation), and trastuzumab (antibody against *HER2*).

A subset of patients presenting to our MDLC were also provided the opportunity to participate in unique clinical trials, including a trial of neoadjuvant immunotherapy prior to resection (NCT03299946), immunotherapy in combination with TACE for BCLC B (NCT03638141), and trials of novel systemic therapies (NCT03298451, NCT03250273, NCT03833661, NCT03834220). In our cohort, 12 (12%) HCC and 5 (7%) BTC patients enrolled onto a clinical trial. These clinical trials will each be reported individually in the future when data collection has been completed. The ability to participate in clinical trials involving multimodality therapy is an important advantage of our MDLC.

In summary, we describe our MDLC work flow, treatment paradigms, and real-world outcomes for HCC and BTC patients. Future data that should be captured in MDLC include patient reported outcomes as patient engagement and empowerment have been shown to improve psychosocial and economic health outcomes,[31,32] and cost analysis as health care-related financial distress is associated with worse quality of life, lower treatment adherence, and increased mortality.[33-35] Strengths of this study include the use of a rigorously annotated clinical liver cancer cohort with longitudinal follow up and clinical outcomes data. Limitations of this analysis include its retrospective nature, limited numbers of patients within certain disease subsets (e.g. gallbladder cancer), and short follow-up analysis of oncologic outcomes. The present report will serve as a benchmark, enabling future analyses of how real world outcomes change over time.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Statement

Ethics approval to review this data was obtained from the Johns Hopkins Institutional Review Boards: IRB00231803. Retrospective collection of patient data did not require patient consent.

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