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Review Article

Cholangiocarcinoma in 2026: Pathophysiology, Diagnostic Advances, and Evolving Therapeutic Landscape–A Narrative Review

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ABSTRACT

Cholangiocarcinoma (CCA) is a heterogeneous malignancy of the biliary epithelium, classified into intrahepatic, perihilar, and distal subtypes with distinct molecular signatures, risk factor profiles, and clinical behavior. This narrative review synthesizes current understanding of CCA pathophysiology, established and emerging risk factors, clinical presentation, diagnostic modalities, persistent gaps in diagnosis and treatment, and recent therapeutic advances through mid-2026. Molecular classification has matured substantially, with fibroblast growth factor receptor 2 (FGFR2) fusions and isocitrate dehydrogenase 1 (IDH1) mutations enriched in intrahepatic disease and human epidermal growth factor receptor 2 (HER2) amplification more common in extrahepatic subtypes, each now targetable with U.S. Food and Drug Administration (FDA)-approved agents, including pemigatinib, futibatinib, ivosidenib, and zanidatamab. First-line systemic therapy has shifted meaningfully with the incorporation of immune checkpoint inhibition, established through the TOPAZ-1 and KEYNOTE-966 trials, and investigational first-line FGFR2 inhibition data from the FIGHT-302 trial presented in 2026. Despite these advances, diagnostic delay remains common, driven by the nonspecific presentation of intrahepatic disease and technical limitations in tissue confirmation and serum biomarkers. A distinct and underexplored gap concerns the epidemiology, diagnostic access, and treatment availability for CCA across Arab and African populations, where regional incidence data, molecular testing infrastructure, and equitable access to newly approved therapies remain limited. This review argues that translating molecular and therapeutic precision into equitable outcomes across all affected populations remains the central unmet task facing the field.

Key words: Cholangiocarcinoma, bile duct neoplasms, FGFR2, IDH1, immunotherapy, health equity

INTRODUCTION

Cholangiocarcinoma (CCA) is a heterogeneous group of malignancies arising from the epithelial cells of the biliary tree, anatomically classified into intrahepatic (iCCA), perihilar (pCCA), and distal (dCCA) subtypes based on their site of origin relative to the second-order bile ducts and the confluence of the hepatic ducts. [1] Perihilar CCA, historically termed Klatskin tumor, remains the most common subtype. At the same time, intrahepatic CCA has shown a disproportionate rise in incidence over the past two decades, particularly in high-income countries.

CCA carries a poor prognosis overall, with five-year survival rates remaining below 20% in most series, largely attributable to late-stage presentation and limited systemic therapy options until recently. The global burden is not uniform: Southeast Asia reports the highest incidence rates worldwide, driven predominantly by endemic liver parasitic disease caused by flatworms (trematodes), while sporadic CCA in Western populations is more closely tied to metabolic and hepatobiliary inflammatory conditions. [1,2]

The rationale for this update is threefold. First, the molecular classification of CCA has matured substantially, with actionable alterations (fibroblast growth factor receptor 2 [FGFR2] fusions, isocitrate dehydrogenase 1 [IDH1] mutations, and human epidermal growth factor receptor 2 [HER2] amplification) now routinely informing treatment selection in eligible patients. [3–6] Second, the systemic therapy landscape has shifted meaningfully with the incorporation of immune checkpoint inhibition into first-line regimens. [7,8] Third, significant gaps persist in diagnostic capacity, molecular testing access, and therapeutic availability across low- and middle-income regions, including parts of the Arab world and Africa, where epidemiologic and outcomes data remain sparse relative to the burden of disease.

References for this narrative review were identified through comprehensive searches of PubMed/MEDLINE, Scopus, EMBASE, and Google Scholar, covering the period from January 1, 2020, to June 30, 2026, using combinations of the terms CCA, bile duct neoplasms, pathophysiology, risk factors, diagnosis, biomarkers, FGFR2, IDH1, HER2, immunotherapy, targeted therapy, and health equity, restricted to English-language publications and supplemented by hand-searching of reference lists and cross-checking of clinical trial data against ClinicalTrials.gov. A small number of foundational studies published before 2020, including the ABC-02 trial and early mechanistic work on interleukin-6 (IL-6)/signal transducer and activator of transcription 3 (STAT3) signaling, were retained where they remain the primary source for a concept or regimen still in current clinical use. All references were verified against their source for author accuracy and DOI before inclusion.

PATHOPHYSIOLOGY

Cellular Origin and Molecular Pathogenesis

CCA is thought to arise from malignant transformation of cholangiocytes lining the intrahepatic and extrahepatic bile ducts. However, transformation of epithelial cells within peribiliary glands and biliary stem cells may also contribute to its development, and there is evidence that subsets of CCA and mixed hepatocellular carcinoma/CCA originate from hepatic stem/progenitor cells. [9,10] This heterogeneity is particularly notable for intrahepatic disease: the cell of origin may be a differentiated hepatocyte, dysplastic or immature cholangiocyte, hepatic stem/progenitor cell, or peribiliary gland cell. [11]

This heterogeneity in cellular origin likely explains, in part, the distinct molecular signatures observed across anatomical subtypes. Intrahepatic CCA is enriched for IDH1/IDH2 mutations, occurring in approximately 10% to 20% of cases, and FGFR2 gene fusions or rearrangements, present in roughly 10% to 16% of cases, both of which are now clinically actionable with approved targeted agents. [3–5] Perihilar and distal CCA, by contrast, more frequently harbor KRAS and TP53 mutations and are considerably less likely to carry FGFR2 or IDH1 alterations. HER2 (ERBB2) amplification follows a similar extrahepatic predilection, occurring more commonly in distal CCA, and has emerged as a targetable alteration in a clinically meaningful minority of patients across subtypes. [6]

Chronic Inflammation and the Fibro-Inflammatory Pathway

Chronic inflammation leads to increased exposure of cholangiocytes to inflammatory mediators including IL-6, tumor necrosis factor-α (TNF-α), cyclooxygenase-2 (COX-2), and Wnt, resulting in progressive mutations in tumor suppressor genes, proto-oncogenes, and DNA mismatch-repair genes. [12] IL-6 is elevated in the serum of CCA patients and directly in CCA tumor stroma; mechanistically, IL-6 inhibits cell death by activating STAT3, which in turn upregulates anti-apoptotic survival factors, and a natural inhibitory feedback mechanism for this pathway, suppressor of cytokine signaling 3 (SOCS3), is epigenetically silenced in CCA. [13] Bile acid retention during cholestasis is understood to further promote cholangiocarcinogenesis through activation of inflammatory and growth-signaling pathways, consistent with the broader inflammation- and cholestasis-driven model of CCA pathogenesis. [12]

Tumor Microenvironment

CCA is characterized by the presence of a desmoplastic stroma consisting of cancer-associated fibroblasts, tumor-associated macrophages, and tumor-infiltrating lymphocytes, considered vital to the cancer's biology and an attractive therapeutic target. [13] In intrahepatic and perihilar CCA specifically, the reactive desmoplastic stroma contains cancer-associated fibroblasts that engage in extensive crosstalk with tumor cells. [13] This stromal-rich, fibrogenic microenvironment has been directly implicated in the historically limited efficacy of immunotherapy as monotherapy in CCA, with inhibition of the IL-6/STAT3 pathway proposed as an adjunct strategy to improve outcomes when combined with other treatments (**Figure 1**). [13]

RISK FACTORS

Established Risk Factors

Primary sclerosing cholangitis (PSC) remains the strongest known risk factor for CCA in the Western world, with CCA developing in an estimated 2% to 8% of PSC patients and representing the leading cause of death in this population; a meta-analysis of cohort studies found the relative risk of CCA in PSC patients to be more than 580-fold that of the general population (though based on only four studies with high heterogeneity), with the majority of PSC-associated CCA developing within the first few years after PSC diagnosis. [14,15] Liver fluke infection with *Opisthorchis viverrini* and *Clonorchis sinensis* represents a major risk factor in South Asian countries, explaining the substantially higher CCA incidence in that region compared with Western countries. [2,14] Other established risk factors include hepatolithiasis, choledochal cysts, and Caroli's disease, alongside viral hepatitis and cirrhosis of any etiology. [2,16]

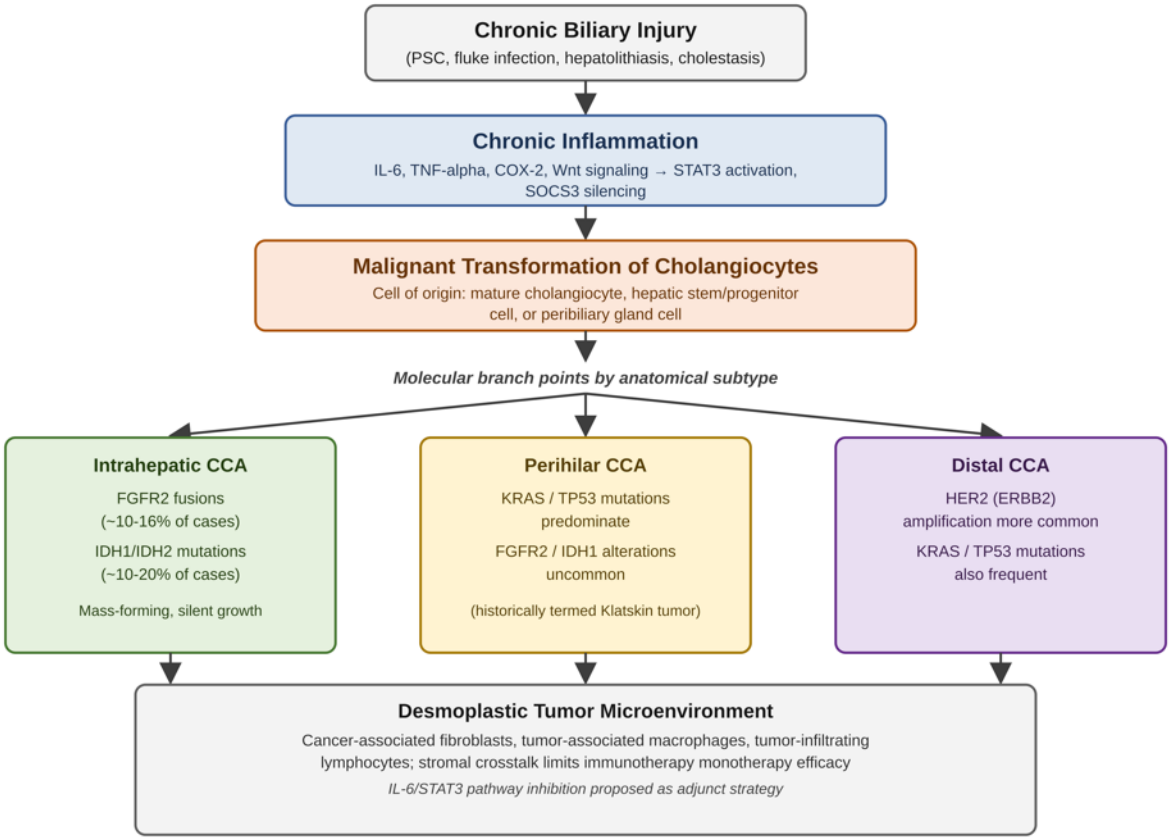

Figure 1: Pathophysiologic pathway from chronic biliary injury to malignant transformation, with molecular branch points by anatomical subtype. Chronic biliary injury (from PSC, liver fluke infection, hepatolithiasis, or cholestasis) drives chronic inflammatory signaling (IL-6, TNF-alpha, COX-2, Wnt), which activates STAT3 and silences SOCS3, promoting malignant transformation of cholangiocytes. Molecular alterations then diverge by anatomical subtype: FGFR2 fusions and IDH1/IDH2 mutations predominate in intrahepatic disease, KRAS/TP53 mutations predominate in perihilar disease, and HER2 amplification is more frequent in distal disease. All subtypes arise within a shared desmoplastic tumor microenvironment that constrains immunotherapy monotherapy efficacy. CCA, cholangiocarcinoma; PSC, primary sclerosing cholangitis; IL-6, interleukin-6; TNF-alpha, tumor necrosis factor-alpha; COX-2, cyclooxygenase-2; STAT3, signal transducer and activator of transcription 3; SOCS3, suppressor of cytokine signaling 3; FGFR2, fibroblast growth factor receptor 2; IDH1/IDH2, isocitrate dehydrogenase 1/2; HER2 (ERBB2), human epidermal growth factor receptor 2.

Emerging and Metabolic Risk Factors

Approximately 90% of patients diagnosed with CCA do not have a recognized traditional risk factor, which has intensified interest in metabolic contributors. [2] Type 2 diabetes, obesity, alcohol consumption, and cigarette smoking have each been identified as factors that increase CCA risk, [1] and a dedicated meta-analysis found a positive association between diabetes mellitus and CCA incidence. [16] CCA is also associated with viral hepatitis and metabolic dysfunction-associated steatotic liver disease, particularly in Western populations where fluke- and stone-related etiologies are uncommon. [14]

REGIONAL VARIATION IN ETIOLOGY

The etiologic profile of CCA varies substantially by region, with direct implications for prevention and surveillance strategy. Fluke-driven disease predominates in Southeast Asia, PSC-driven disease predominates in Northern Europe and North America, and a less well-characterized profile, likely shaped by metabolic disease and viral hepatitis, appears to predominate in the Middle East, North Africa, and sub-Saharan Africa (**Table 1**). The Gaps in Diagnosis and Treatment section further addresses the notably limited population-level incidence and risk-factor data from Arab and African cohorts.

CLINICAL PRESENTATION

Perihilar and distal CCA typically present with jaundice, abdominal pain, and pruritus, reflecting biliary obstruction at a level where even relatively small tumors produce clinically apparent cholestasis. [17–19] Intrahepatic CCA, by contrast, typically presents with nonspecific symptoms including abdominal pain, weight loss, and fatigue; because these tumors are discrete from the main bile ducts and rarely cause obstructive jaundice, clinical diagnosis is difficult and many patients initially present with advanced disease. [18] In a retrospective 31-year single-institution review, patients with intrahepatic disease were less likely to experience jaundice or weight loss than patients with extrahepatic disease, a finding confirmed in subsequent studies. [18]

Table 1: Risk factors for cholangiocarcinoma by mechanism, associated anatomical subtype, and regional relevance.

Risk factor	Proposed mechanism	Associated subtype	Regional relevance
Primary sclerosing cholangitis	Chronic cholestasis, biliary dysplasia	Perihilar, extrahepatic	Northern Europe, North America
Liver fluke infection (*O. viverrini*, *C. sinensis*)	Chronic biliary inflammation, direct carcinogenesis	Intrahepatic, perihilar	Southeast Asia (Thailand, Laos, Vietnam)
Hepatolithiasis/recurrent pyogenic cholangitis	Chronic ductal injury, stricture formation	Intrahepatic	East Asia
Choledochal cysts	Bile stasis, mucosal inflammation	Extrahepatic	Global, higher reported incidence in East Asia
Viral hepatitis (HBV/HCV), cirrhosis	Shared hepatocarcinogenic pathways	Intrahepatic	Global, high-prevalence hepatitis regions
MASLD, diabetes, obesity	Metabolic-driven chronic liver injury	Intrahepatic	Western populations, increasingly Gulf region

Established and emerging risk factors for cholangiocarcinoma, organized by proposed carcinogenic mechanism, the anatomical subtype each is most closely associated with, and the world region where each is most clinically relevant. HBV, hepatitis B virus; HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease.

Because intrahepatic tumors are predominantly mass-forming and grow silently within the liver parenchyma, incidental diagnosis in asymptomatic patients is relatively common, accounting for approximately 12% to 30% of diagnoses in some series, with other sources citing a comparable range of 20% to 40%. [18,19] Patients with cirrhosis undergoing regular imaging surveillance for hepatocellular carcinoma may be diagnosed with early intrahepatic CCA lesions through this same incidental pathway, which may be resectable specifically because of earlier detection. [19] A single-institution review found that 54% of intrahepatic tumors were unresectable at presentation despite this pattern of incidental detection. [18]

Across all subtypes, symptoms of CCA are often absent or nonspecific, including jaundice, abdominal pain, decreased appetite, weight loss, and night sweats. Diagnosis usually stems from the identification of masses on imaging performed for other indications or from symptomatic biliary strictures rather than from a specific clinical trigger. [19] In patients with underlying PSC, a new or rising carbohydrate antigen 19-9 (CA 19-9) should prompt heightened suspicion for superimposed CCA rather than an assumption of PSC progression alone. [15]

DIAGNOSIS

Imaging

Contrast-enhanced magnetic resonance imaging (MRI) combined with magnetic resonance cholangiopancreatography (MRCP) is generally preferred for characterizing biliary anatomy, defining the longitudinal extent of ductal involvement, and assessing vascular invasion, particularly for perihilar tumors where precise delineation of ductal confluence and vascular involvement determines resectability. [20,21] Contrast-enhanced computed tomography (CT) works alongside MRI by giving a detailed view of blood vessels and checking for cancer spread to other parts of the body. Endoscopic ultrasound (EUS) adds value for distal CCA, allowing detailed assessment of the periampullary region along with fine-needle aspiration of regional lymph nodes. [22]

Tissue Diagnosis

Various approaches are available to establish cytological or histological diagnosis based on the location of the biliary stricture. The sensitivity of brush cytology for CCA diagnosis is inconsistent across the literature, generally falling below 75% and varying considerably by technique and study population. [23] A meta-analysis of 1123 patients with CCA found diagnostic sensitivity of 56% with brushing alone, 67% with biopsy alone, and 70.7% when combined. At the lower end, other series have reported cytology sensitivity as low as 9% to 24% with substantial inter-pathologist variation, reflecting the tumor's characteristic desmoplastic reaction, in which few malignant cholangiocytes are embedded within extensive fibrous stroma. [24,25] Current clinical practice guidelines recommend that when EUS-FNA is inconclusive, ERCP with brushing and fluorescence in situ hybridization (FISH) testing for polysomy, biopsy, or cholangioscopy-guided biopsy represents the most accurate approach to a final diagnosis of perihilar CCA. [22]

Serum Biomarkers

CA 19-9's diagnostic utility is meaningfully constrained by a specific genetic limitation: approximately 5% to 10% of individuals lack the Lewis antigen (Lea-b-) and therefore cannot synthesize CA 19-9 at all, regardless of tumor burden, producing a false-negative result that is a permanent feature of that patient's biology. [26,27] In patients with PSC specifically, CA 19-9 has shown a sensitivity of around 78.6% at a cutoff of 129 U/mL, although sensitivity and cutoff values vary considerably across studies. [26] An elevated CA 19-9 combined with positive brush cytology improves overall diagnostic performance, achieving a sensitivity of 88% and specificity of 97% in one series. [24] See **Table 2** for comparative performance across modalities.

Positron Emission Tomography

18F-fluorodeoxyglucose PET-CT has a defined but circumscribed role in CCA diagnosis and staging. Its accuracy for primary tumor detection is dependent on anatomic location, growth pattern, and pathologic characteristics and

Table 2: Diagnostic modality performance summary in cholangiocarcinoma.

Modality	Reported sensitivity/specificity	Key limitation
Brush cytology (ERCP)	Sensitivity ~45%–56%; specificity ~99%–100%	Low sensitivity due to desmoplastic stroma
Brush cytology + FISH	Improved vs. cytology alone	Not universally available outside referral centers
CA 19-9	Sensitivity ~53%–79% (cutoff-dependent)	False-negative in Lewis antigen-negative patients (~5%–10%)
FDG PET-CT (nodal staging)	Pooled sensitivity ~0.52; specificity ~0.92	Frequently misses regional nodal disease
FDG PET-CT (distant metastasis)	High accuracy for unsuspected metastases	Limited local/nodal staging value
FAPI PET-CT	Higher uptake and lesion detection vs. FDG-PET	Requires larger prospective validation

Comparative sensitivity and specificity of the major diagnostic modalities used in cholangiocarcinoma, alongside each modality's principal clinical limitation. ERCP, endoscopic retrograde cholangiopancreatography; FISH, fluorescence in situ hybridization; CA 19-9, carbohydrate antigen 19-9; FDG, fluorodeoxyglucose; PET-CT, positron emission tomography-computed tomography; FAPI, fibroblast activation protein inhibitor.

is limited specifically to detection of extrahepatic, infiltrating, and mucinous CCAs. [28] For regional lymph node staging, a pooled analysis in intrahepatic CCA found sensitivity of only 0.52 (specificity 0.92), and a comparative study of 90 patients found no statistically significant advantage of PET-CT over CT and MRI in detecting multiple tumors, macrovascular invasion, or bile duct invasion. [29] PET-CT's clearest value lies in detecting unsuspected distant metastases and disease recurrence. [28,30] Dual-time-point protocols improve detection modestly: one series of 69 hilar CCA patients found a sensitivity of 69.6% on early-phase imaging versus 76.8% on delayed-phase imaging. [30]

Staging

Current consensus recommends that the 8th edition American Joint Committee on Cancer (AJCC) staging system be used for staging both intrahepatic and perihilar CCA. [22,23] For perihilar tumors, the Bismuth-Corlette classification remains a complementary tool for describing the longitudinal extent of ductal involvement and guiding surgical planning.

MANAGEMENT

Surgical Resection

Surgery follows a subtype-dependent strategy: for intrahepatic tumors, tailored partial hepatectomy combined with extended hilar, suprapancreatic, and celiac axis lymphadenectomy is standard, while perihilar tumors require complete resection of the extrahepatic biliary tree combined with extended hepatectomy inclusive of the caudate lobe and systematic lymphadenectomy, and distal tumors are managed with en bloc pancreaticoduodenectomy. [31,32] For perihilar disease, removing the caudate lobe increases the chances of successful surgery with clear margins and better survival rates without causing major additional complications. The role of routine portal lymphadenectomy in purely intrahepatic disease has not been as well established, given the risk of common bile duct devascularization, in contrast to perihilar disease where lymphadenectomy is standard. [33]

Liver Transplantation

Liver transplantation has an evolving role in the management of unresectable perihilar CCA, particularly in patients with underlying PSC. Early experience produced poor outcomes with high recurrence rates, which changed substantially with the development of structured neoadjuvant protocols, most notably the Mayo Clinic protocol, combining neoadjuvant chemoradiotherapy with strict pretransplant staging criteria including a mass lesion under 3 cm at the biliary stricture and either endoluminal tissue diagnosis or CA 19-9 above 100 U/mL. [21] Transplantation for intrahepatic CCA remains far more controversial and is generally reserved for small, early-stage tumors.

Locoregional Therapies

Hepatic arterial infusion chemotherapy (HAIC) has shown the strongest survival signal among locoregional options: a meta-analysis of 20 studies found HAI produced the highest median overall survival at 22.8 months among arterially directed approaches, though with the highest rate of grade III/IV toxicity, and a subsequent phase 2 trial reported median progression-free survival of 11.8 months and overall survival of 25.0 months. [34] Transarterial chemoembolization (TACE) is superior to supportive care, with a meta-analysis reporting cumulative median overall survival of 12.4 months, and one study found adding TACE to palliative chemotherapy extended median overall survival from 13.1 to 26.2 months. [35,36] Yttrium-90 radioembolization has produced a pooled median survival of approximately 15.5 months, with overall survival comparable to systemic chemotherapy or TACE. In this situation, it is recommended by National Comprehensive Cancer Network (NCCN) guidelines as a palliative option for select patients with unresectable disease. [34]

Systemic Chemotherapy

The combination of gemcitabine and cisplatin has served as the standard first-line chemotherapy backbone for advanced biliary tract cancer for well over a decade, following the ABC-02 trial's demonstration of a median overall survival of 11.7 months versus 8.1 months with gemcitabine alone. [37] This regimen now forms the backbone onto which immunotherapy has been added in first-line treatment. **Figure 2** represents the CCA management algorithm by resectability and molecular subtypes.

RECENT UPDATES IN THERAPY

Table 3 summarizes the current targeted and immunotherapeutic agents approved for CCA, along with their pivotal trials and efficacy data.

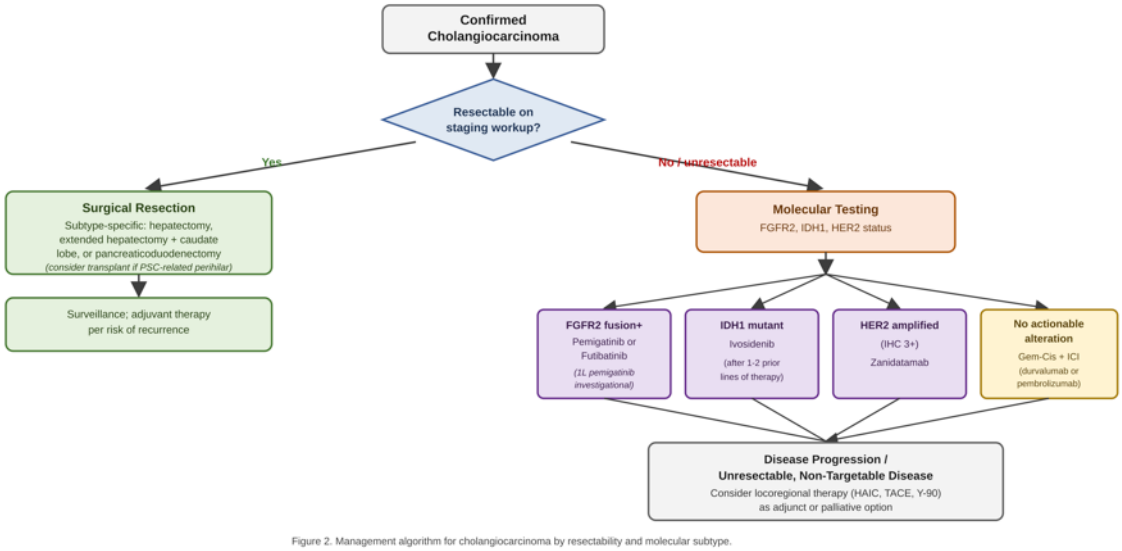

Figure 2. Management algorithm for cholangiocarcinoma by resectability and molecular subtype.

Figure 2: Management algorithm for CCA by resectability and molecular subtype. Following histologic confirmation of CCA, staging determines resectability. Resectable disease proceeds to subtype-specific surgical resection (with transplantation considered for PSC-related perihilar disease meeting strict criteria), followed by surveillance and consideration of adjuvant therapy. Unresectable disease proceeds to molecular testing for FGFR2, IDH1, and HER2 status: patients with an actionable alteration receive the corresponding targeted agent (pemigatinib or futibatinib for FGFR2 fusion, ivosidenib for IDH1 mutation, zanidatamab for HER2 amplification), while those without an actionable alteration receive first-line gemcitabine-cisplatin plus an immune checkpoint inhibitor. Unresectable or progressing patients across all pathways may be considered for locoregional therapy as an adjunct or palliative option. CCA, cholangiocarcinoma; PSC, primary sclerosing cholangitis; FGFR2, fibroblast growth factor receptor 2; IDH1, isocitrate dehydrogenase 1; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; Gem-Cis, gemcitabine and cisplatin; ICI, immune checkpoint inhibitor; 1L, first-line; HAIC, hepatic arterial infusion chemotherapy; TACE, transarterial chemoembolization; Y-90, yttrium-90 radioembolization.

Table 3: FDA-approved targeted and immunotherapeutic agents in cholangiocarcinoma.

Agent	Target	Pivotal trial	FDA approval	Key efficacy
Pemigatinib	FGFR2 fusion/rearrangement	FIGHT-202	April 2020	ORR 36%; DOR 9.1 months
Futibatinib	FGFR2 fusion/rearrangement	FOENIX-CCA2	September 2022	ORR 42%; DOR 9.7 months
Ivosidenib	IDH1 mutation	ClarIDHy	August 2021	PFS HR 0.37 vs. placebo
Zanidatamab	HER2 amplification (IHC 3+)	HERIZON-BTC-01	November 2024	ORR 52%; DOR 14.9 months
Durvalumab + gem-cis	PD-L1 checkpoint (1L)	TOPAZ-1	September 2022	OS benefit vs. gem-cis alone
Pembrolizumab + gem-cis	PD-1 checkpoint (1L)	KEYNOTE-966	October 2023	OS 12.7 vs. 10.9 months

FDA-approved targeted and immune checkpoint inhibitor regimens in cholangiocarcinoma, listing the molecular or immunologic target, the pivotal trial supporting approval, the approval date, and key efficacy outcomes. ORR, overall response rate; DOR, duration of response; PFS, progression-free survival; HR, hazard ratio; OS, overall survival; 1L, first-line; gem-cis, gemcitabine-cisplatin; FDA, U.S. Food and Drug Administration.

FGFR2-Targeted Therapy

Pemigatinib received accelerated U.S. Food and Drug Administration (FDA) approval in April 2020 for adults with previously treated, unresectable locally advanced or metastatic CCA with an FGFR2 fusion or other rearrangement, based on the FIGHT-202 trial, in which the overall response rate was 36% with a median duration of response of 9.1 months. [3]

Another FGFR2-targeted therapy (Futibatinib) was approved based on the FOENIX-CCA2 trial, demonstrating an overall response rate of 42% with a median duration of response of 9.7 months; longer follow-up showed a median progression-free survival of 9 months and an overall survival of 21.7 months. [4]

Results from the phase 3 FIGHT-302 trial showed that first-line pemigatinib significantly improved progression-free survival compared with gemcitabine and cisplatin, with a 42% reduction in the risk of disease progression or death (HR, 0.58 [95% CI, 0.39–0.87]), median progression-free survival of 8.3 months versus 6.8 months, and median duration of response of 14.2 months versus 6.3 months. Overall survival did not differ significantly between arms (24.4 vs. 25.0 months; HR, 1.10 [95% CI, 0.73–1.64]), an outcome the investigators attributed largely to substantial crossover from the chemotherapy arm to pemigatinib or other FGFR inhibitors after progression. This remains experimental rather than an approved first-line indication. [38]

IDH1-Targeted Therapy

Ivosidenib was approved by the FDA in 2021 for adults who have unresectable locally advanced or metastatic IDH1-mutated CCA, especially for those who had disease progression after one to two prior lines of systemic therapy.

Based on the ClarIDHy trial, which reported a significantly improved progression-free survival with a hazard ratio of 0.37. [5]

HER2-Targeted Therapy

Zanidatamab, a bispecific HER2-directed antibody, received FDA accelerated approval in November 2024 for previously treated, unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer, based on the HERIZON-BTC-01 trial, in which 52% of patients had a response, with responses lasting a median of 14.9 months. [6] A confirmatory phase 3 trial, HERIZON-BTC-302, is currently evaluating zanidatamab in combination with standard-of-care chemotherapy in the first-line setting.

Immunotherapy in First-Line Treatment

In TOPAZ-1, durvalumab plus gemcitabine-cisplatin significantly improved overall survival compared with placebo plus gemcitabine-cisplatin, and updated three-year follow-up has continued to support the regimen as a standard of care. [7] In KEYNOTE-966, pembrolizumab plus cisplatin and gemcitabine produced a statistically significant and clinically meaningful improvement in overall survival, with median overall survival of 12.7 months versus 10.9 months and a hazard ratio of 0.83. [8] Both regimens are now used in routine first-line practice pending molecular subtyping results.

Liquid Biopsy and Emerging Diagnostics

Beyond therapeutics, circulating tumor DNA (ctDNA) and other liquid biopsy approaches remain an active area of investigation for both diagnosis and monitoring, with emerging methodologies including cell-free DNA fragmentomics combined with machine learning proposed as noninvasive early detection methods for biliary tract cancer.

PERSPECTIVES AND INNOVATIONS

Artificial Intelligence (AI) and Machine Learning (ML) in Diagnosis

Radiomics- and AI-based imaging models have emerged as promising tools for the noninvasive detection and differentiation of intrahepatic CCA. [39] Radiomics signatures have been associated with histopathological features influencing prognosis, including microvascular invasion, stromal desmoplasia, and tumor grade, and models incorporating peritumoral radiomic features have shown the ability to predict lymph node metastasis and microvascular invasion with promising accuracy. [39] Molecular prediction from imaging alone remains an early-stage direction rather than a validated tool: a study specifically examining FGFR2 fusion status in intrahepatic CCA using radiomic features found no significant association between FGFR2 fusion and the imaging features tested, tempering enthusiasm for this application. [40]

Novel PET Tracers

A prospective study directly comparing [18F]FAPI-04 PET/CT with [18F]FDG PET/CT in intrahepatic CCA found that FAPI-PET had higher tracer uptake in intrahepatic, lymph node, and distant metastatic lesions and detected more metastatic lesions than FDG-PET, leading to upstaging of TNM classification in a meaningful proportion of patients. [41] A broader systematic review across pancreatic, gastric, and CCA found FAPI-PET superior to FDG-PET, CT, or MRI for staging across T, N, M, and peritoneal carcinomatosis detection. However, the review's authors note this warrants larger prospective studies before it can be considered practice-changing. [42]

Precision Oncology Trial Landscape

The therapeutic advances detailed above have shifted CCA drug development toward a molecularly stratified trial design. Confirmatory and combination trials are now testing whether targeted agents can be moved earlier in the treatment course or combined with immunotherapy and chemotherapy, including the ongoing HERIZON-BTC-302 trial evaluating zanidatamab combined with standard-of-care chemotherapy, with or without checkpoint inhibition, in the first-line setting.

Health Equity as an Innovation Imperative

Genuine innovation in CCA cannot be measured solely by the emergence of new agents in high-income health systems. Innovation for Arab and African populations will require parallel investment in regional epidemiologic research, molecular testing infrastructure, and mechanisms for equitable access to newly approved agents, since a targeted therapy that exists but cannot be diagnosed for or afforded by a given population does not represent a clinical advance for that population.

GAPS IN DIAGNOSIS AND TREATMENT

Diagnostic Gaps

Despite advances in imaging and molecular characterization, CCA continues to be diagnosed predominantly at an advanced stage, a pattern rooted in several compounding factors rather than any single failure point. [18,19] The nonspecific early symptomatology of intrahepatic disease means a substantial proportion of patients have no clinical trigger for imaging until the tumor has already reached an extent incompatible with curative resection. Even when imaging is pursued, tissue confirmation remains technically difficult given brush cytology's limited sensitivity, [23–25] and serum biomarker limitations compound this further given CA 19-9's poor sensitivity in Lewis antigen-negative individuals. [26,27]

Treatment Gaps

Surgical resection, the only potentially curative option, is feasible in only a minority of patients at presentation, and even among those who undergo resection, recurrence rates remain high. [18,32] Systemic therapy has improved with immunotherapy and targeted agents. However, these advances apply to defined molecular subgroups and leave a large proportion of patients, particularly those with perihilar and distal CCA where actionable alterations are less common, dependent on chemotherapy regimens with modest overall survival benefit. [3–6,37] Access to molecular testing itself represents a gap in many settings: without confirmed FGFR2, IDH1, or HER2 status, patients cannot be matched to the therapies most likely to benefit them.

HEALTH EQUITY GAPS IN ARAB AND AFRICAN POPULATIONS

A distinct and underexplored gap concerns the epidemiology, diagnostic access, and treatment availability for CCA across Arab and African populations. Population-level incidence and risk-factor data from this region remain sparse relative to the global literature, which is dominated by cohorts from Southeast Asia, North America, and Europe. This absence of regional data has practical consequences: risk stratification tools and baseline incidence estimates used in regional clinical planning are largely extrapolated from populations with different dominant etiologies rather than the more metabolic- and hepatitis-driven profile that likely predominates in North Africa and the Middle East.

Diagnostic infrastructure also varies considerably across the region. Access to MRCP, EUS with FISH-capable cytopathology, and next-generation sequencing for FGFR2/IDH1/HER2 testing is concentrated in a small number of tertiary referral centers, meaning patients presenting to secondary or peripheral facilities may face substantial delay before reaching a center capable of complete diagnostic workup. This has direct downstream treatment consequences: targeted agents require molecular confirmation before use, and where that confirmation is inaccessible or delayed, patients who might otherwise be eligible for effective targeted therapy default instead to conventional chemotherapy. Therapeutic access compounds this gap further, as newly approved targeted and immunotherapeutic agents carry substantial per-patient cost and are not uniformly reimbursed or available across health systems in the region. Closing this gap will require both expanded regional epidemiologic research and deliberate investment in diagnostic and therapeutic infrastructure.

CONCLUSIONS

CCA remains a biologically heterogeneous and clinically challenging malignancy, but the past several years have brought genuine, verifiable change to how it is understood and treated. The molecular classification of CCA by anatomical subtype has moved from research findings to a framework that directly determines treatment eligibility, and the approval of pemigatinib, futibatinib, ivosidenib, and zanidatamab has given a meaningful subset of patients targeted options that did not exist a decade ago. The first-line movement of both FGFR2 inhibition and immune checkpoint inhibition represents the most substantial shift in systemic therapy for this disease in more than a decade. At the same time, diagnostic delay continues to mean that most patients present beyond the point of curative resection, and this gap has not been closed by any of the therapeutic advances discussed here. The health equity gap affecting Arab and African populations deserves to be treated as a central finding of this review rather than a closing caveat: the absence of regional epidemiologic data, the concentration of molecular testing infrastructure in a small number of tertiary centers, and the cost and reimbursement barriers surrounding newly approved agents mean that the therapeutic advances detailed in this review are not yet equally available to all patients who might benefit from them. Taken together, the evidence reviewed here supports a cautiously optimistic but unfinished picture: CCA is being treated with a precision that was not possible five years ago. However, translating that precision into equitable outcomes across all populations affected by this disease remains the central unmet task facing the field.

AUTHORS' CONTRIBUTION

All authors have significantly contributed to the work, whether by conducting literature searches, drafting, revising, or critically reviewing the article. They have given their final approval of the version to be published, have agreed with the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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REFERENCES

1. Squires MH, Cloyd JM, Dillhoff M, Schmidt C, Pawlik TM. Cholangiocarcinoma. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2024.
2. Shaib Y, El-Serag HB. The epidemiology of cholangiocarcinoma. Semin Liver Dis. 2004;24(2):115–125. https://doi.org/10.1055/s-2004-828889
3. Abou-Alfa GK, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: A multicentre, open-label, phase 2 study. Lancet Oncol. 2020;21(5):671–684. https://doi.org/10.1016/S1470-2045(20)30109-1
4. Goyal L, Meric-Bernstam F, Hollebecque A, Valle JW, Morizane C, Karasic TB, et al; FOENIX-CCA2 Study Investigators. Futibatinib for FGFR2-rearranged intrahepatic cholangiocarcinoma. N Engl J Med. 2023;388(3):228–239. https://doi.org/10.1056/NEJMoa2206834
5. Abou-Alfa GK, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): A multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2020;21(6):796–807. https://doi.org/10.1016/S1470-2045(20)30157-1
6. Harding JJ, Fan J, Oh DY, Choi HJ, Kim JW, Chang HM, et al; HERIZON-BTC-01 study group. Zanidatamab for HER2-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): A multicentre, single-arm, phase 2b study. Lancet Oncol. 2023;24(7):772–782. https://doi.org/10.1016/S1470-2045(23)00242-5
7. Oh DY, He AR, Qin S, Chen LT, Okusaka T, Kim JW, et al. Durvalumab plus chemotherapy in advanced biliary tract cancer: 3-year overall survival update from the phase

III TOPAZ-1 study. J Hepatol. 2025;83(5):1092–1101. https://doi.org/10.1016/j.jhep.2025.05.003
8. Kelley RK, Ueno M, Yoo C, Finn RS, Furuse J, Ren Z, et al. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2023;401(10391):1853–1865. https://doi.org/10.1016/S0140-6736(23)00727-4
9. Guest RV, Goeppert B, Nault JC, Sia D. Morphomolecular pathology and genomic insights into the cells of origin of cholangiocarcinoma and combined hepatocellular-cholangiocarcinoma. Am J Pathol. 2025;195(3):345–361. https://doi.org/10.1016/j.ajpath.2024.08.014
10. Nakagawa H, Hayata Y, Yamada T, Kawamura S, Suzuki N, Koike K. Peribiliary glands as the cellular origin of biliary tract cancer. Int J Mol Sci. 2018;19(6):1745. https://doi.org/10.3390/ijms19061745
11. Goral V. Cholangiocarcinoma: New insights. Asian Pac J Cancer Prev. 2017;18(6):1469–1473. https://doi.org/10.22034/APJCP.2017.18.6.1469
12. Labib PL, Goodchild G, Pereira SP. Molecular pathogenesis of cholangiocarcinoma. BMC Cancer. 2019;19:185. https://doi.org/10.1186/s12885-019-5391-0
13. Fabris L, Perugorria MJ, Mertens J, Björkström NK, Cramer T, Lleo A, et al. The tumour microenvironment and immune milieu of cholangiocarcinoma. Liver Int. 2019;39(suppl 1):63–78. https://doi.org/10.1111/liv.14098
14. Catanzaro E, Gringeri E, Burra P, Gambato M. Primary sclerosing cholangitis-associated cholangiocarcinoma: From pathogenesis to diagnostic and surveillance strategies. Cancers (Basel). 2023;15(20):4947. https://doi.org/10.3390/cancers15204947
15. Weismüller TJ, Trivedi PJ, Bergquist A, Imam M, Lenzen H, Ponsioen CY, et al. Patient age, sex, and inflammatory bowel disease phenotype associate with course of primary sclerosing cholangitis. Gastroenterology. 2017;152(8):1975–1984. https://doi.org/10.1053/j.gastro.2017.02.038
16. Li J, Han T, Xu L, Luan X. Diabetes mellitus and the risk of cholangiocarcinoma: An updated meta-analysis. Prz Gastroenterol. 2015;10(2):108–117. https://doi.org/10.5114/pg.2015.49004
17. Zhang W, Yan LN. Perihilar cholangiocarcinoma: Current therapy. World J Gastrointest Pathophysiol. 2014;5(3):344–354. https://doi.org/10.4291/wjgp.v5.i3.344
18. Blechacz B, Komuta M, Roskams T, Gores GJ. Clinical diagnosis and staging of cholangiocarcinoma. Nat Rev Gastroenterol Hepatol. 2011;8(9):512–522. https://doi.org/10.1038/nrgastro.2011.131
19. Rushbrook SM, Kendall TJ, Zen Y, Albazaz R, Manoharan P, Pereira SP, et al. British Society of Gastroenterology guidelines for the diagnosis and management of cholangiocarcinoma. Gut. 2023;73(1):16–46. https://doi.org/10.1136/gutjnl-2023-330029
20. Ruys AT, van Beem BE, Engelbrecht MR, Bipat S, Stoker J, Van Gulik TM. Radiological staging in patients with hilar cholangiocarcinoma: A systematic review and meta-analysis. Br J Radiol. 2012;85(1017):1255–1262. https://doi.org/10.1259/bjr/88405305
21. Ellis RJ, Soares KC, Jarnagin WR. Preoperative management of perihilar cholangiocarcinoma. Cancers (Basel). 2022;14(9):2119. https://doi.org/10.3390/cancers14092119
22. Alvaro D, Hassan C, Cardinale V, Carpino G, Fabris L, Gringeri E, et al; Cholangiocarcinoma Working Group. Italian clinical practice guidelines on cholangiocarcinoma - Part I: Classification, diagnosis and staging. Dig Liver Dis. 2020;52(11):1282–1293. https://doi.org/10.1016/j.dld.2020.06.045
23. Banales JM, Rodrigues PM, Affò S, Andersen JB, Aspichueta P, Boulter L, et al. Cholangiocarcinoma 2026: Status quo, unmet needs and priorities. Nat Rev Gastroenterol Hepatol. 2026;23(1):65–96. https://doi.org/10.1038/s41575-025-01153-w
24. Navaneethan U, Njei B, Lourdusamy V, Konjeti R, Vargo JJ, Parsi MA. Comparative effectiveness of biliary brush cytology and intraductal biopsy for detection of malignant biliary strictures: A systematic review and meta-analysis. Gastrointest Endosc. 2015;81(1):168–176. https://doi.org/10.1016/j.gie.2014.09.017
25. Aljiffry M, Walsh MJ, Molinari M. Advances in diagnosis, treatment and palliation of cholangiocarcinoma: 1990-2009. World J Gastroenterol. 2009;15(34):4240–4262. https://doi.org/10.3748/wjg.15.4240
26. Lee T, Teng TZJ, Shelat VG. Carbohydrate antigen 19-9 - tumor marker: Past, present, and future. World J Gastrointest Surg. 2020;12(12):468–490. https://doi.org/10.4240/wjgs.v12.i12.468
27. Liu C, Deng S, Jin K, Gong Y, Cheng H, Fan Z, et al. Lewis antigen-negative pancreatic cancer: An aggressive subgroup. Int J Oncol. 2020;56(4):900–908. https://doi.org/10.3892/ijo.2020.4989
28. Moon CM, Bang S, Chung JB. The role of (18) F-fluorodeoxyglucose positron emission tomography in the diagnosis, staging, and follow-up of cholangiocarcinoma. Surg Oncol. 2011;20(1):e10–e17. https://doi.org/10.1016/j.suronc.2009.08.003
29. Nishioka E, Tsurusaki M, Kozuki R, Im SW, Kono A, Kitajima K, et al. Comparison of conventional imaging and 18F-fluorodeoxyglucose positron emission tomography/computed tomography in the diagnostic accuracy of staging in patients with intrahepatic cholangiocarcinoma. Diagnostics (Basel). 2022;12(11):2889. https://doi.org/10.3390/diagnostics12112889
30. Pang L, Bo X, Wang J, Wang C, Wang Y, Liu G, et al. Role of dual-time point 18F-FDG PET/CT imaging in the primary diagnosis and staging of hilar cholangiocarcinoma. Abdom Radiol (NY). 2021;46(9):4138–4147. https://doi.org/10.1007/s00261-021-03071-2
31. Uesaka K. Left hepatectomy or left trisectionectomy with resection of the caudate lobe and extrahepatic bile duct for hilar cholangiocarcinoma (with video). J Hepatobiliary Pancreat Sci. 2012;19(2):195–202. https://doi.org/10.1007/s00534-011-0474-6
32. Lauterio A, De Carlis R, Centonze L, Buscemi V, Incarbone N, Vella I, et al. Current surgical management of peri-hilar and intra-hepatic cholangiocarcinoma. Cancers (Basel). 2021;13(15):3657. https://doi.org/10.3390/cancers13153657
33. National Cancer Institute. Bile duct cancer (cholangiocarcinoma) treatment (PDQ®)-health

professional version. Bethesda, MD: National Cancer Institute; 2024. Available from: https://www.cancer.gov/types/liver/hp/bile-duct-treatment-pdq. Accessed May 2026.
34. Boehm LM, Jayakrishnan TT, Miura JT, Zacharias AJ, Johnston FM, Turaga KK, et al. Comparative effectiveness of hepatic artery based therapies for unresectable intrahepatic cholangiocarcinoma. J Surg Oncol. 2015;111(2):213–220. https://doi.org/10.1002/jso.23781
35. Mosconi C, Gramenzi A, Ascanio S, Cappelli A, Renzulli M, Pettinato C, et al. Yttrium-90 radioembolization for unresectable/recurrent intrahepatic cholangiocarcinoma: A survival, efficacy and safety study. Br J Cancer. 2016;115(3):297–302. https://doi.org/10.1038/bjc.2016.191
36. Gairing SJ, Thol F, Müller L, Hahn F, Thomaidis T, Czauderna C, et al. The addition of transarterial chemoembolization to palliative chemotherapy extends survival in intrahepatic cholangiocarcinoma. J Clin Med. 2021;10(12):2732. https://doi.org/10.3390/jcm10122732
37. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362(14):1273–1281. https://doi.org/10.1056/NEJMoa0908721
38. Bekaii-Saab TS, Melisi D, Wilmink H, Garufi C, Tran N, Tortora G, et al. Pemigatinib for unresectable or metastatic cholangiocarcinoma with fibroblast growth factor receptor-2 rearrangement: Results from the phase III FIGHT-302 trial. J Clin Oncol. 2026;44(23):2187–2197. https://doi.org/10.1200/JCO-26-00788
39. Alidina Z, Banani I, Abiha UE, Sultan U. Radiomics for detection and differentiation of intrahepatic cholangiocarcinoma: A systematic review and meta-analysis. Cancers (Basel). 2026;18(6):937. https://doi.org/10.3390/cancers1806093
40. Jolissaint JS, Wang T, Soares KC, Chou JF, Gönen M, Pak LM, et al. Machine learning radiomics can predict early liver recurrence after resection of intrahepatic cholangiocarcinoma. HPB (Oxford). 2022;24(8):1341–1350. https://doi.org/10.1016/j.hpb.2022.02.004
41. Liang J, Jiang S, Song J, Chen D, Weng S, Li S, et al. Role of [18F]FAPI-04 in staging and therapeutic management of intrahepatic cholangiocarcinoma: Prospective comparison with [18F]FDG PET/CT. EJNMMI Res. 2024;14:82. https://doi.org/10.1186/s13550-024-01145-y
42. Veldhuijzen van Zanten SEM, Pieterman KJ, Wijnhoven BPL, Pruis IJ, Groot Koerkamp B, van Driel LMJW, et al. FAPI PET versus FDG PET, CT or MRI for staging pancreatic-, gastric- and cholangiocarcinoma: Systematic review and head-to-head comparisons of diagnostic performances. Diagnostics (Basel). 2022;12(8):1958. https://doi.org/10.3390/diagnostics12081958