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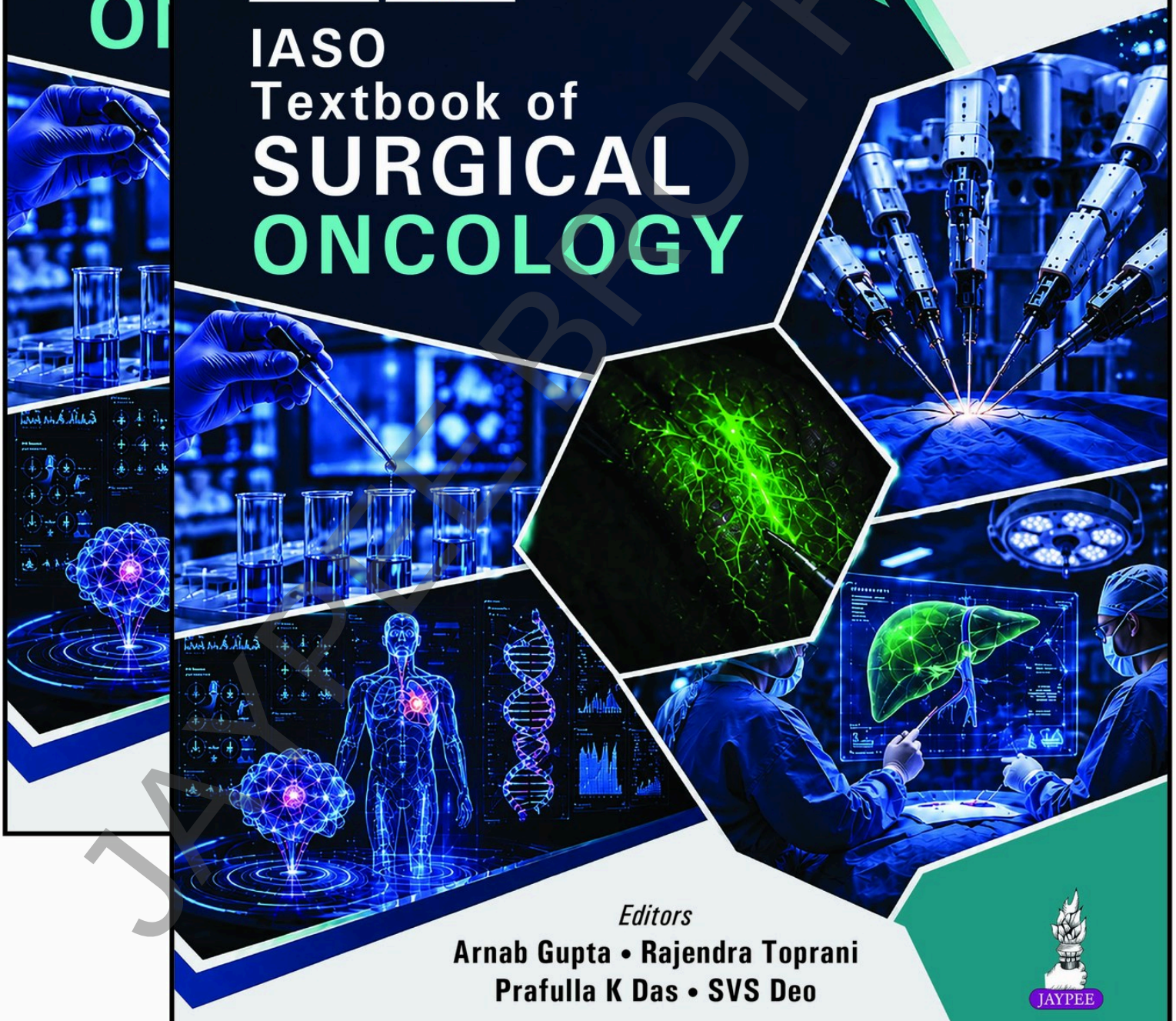

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CHAPTER 49

Cholangiocarcinoma

Gurudutt P Varty, Shraddha Patkar, Mahesh Goel

INTRODUCTION

Cholangiocarcinoma (CCA) comprises a heterogeneous group of malignant epithelial tumors arising from the biliary tract. Based on their anatomical origin, CCAs are classified into three distinct subtypes: intrahepatic cholangiocarcinoma (iCCA), perihilar cholangiocarcinoma (pCCA), and distal CCA. iCCA originates from the second-order intrahepatic bile ducts or smaller biliary branches within the liver parenchyma and typically presents as a hepatic mass. pCCA arises at the junction of the right and left hepatic ducts, frequently involving both the intrahepatic and extrahepatic biliary tree, and is commonly referred to as a Klatskin tumor.[1] Distal CCA develops distal to the hepatic duct confluence, most often affecting the common bile duct within its intrapancreatic segment. Among these subtypes, pCCA accounts for approximately 67% of all cases, followed by distal CCA (27%) and iCCA (6%).[2] The biological behavior also varies by anatomical subtype: iCCAs most commonly exhibit a mass-forming pattern, pCCAs are predominantly characterized by periductal infiltrative growth, whereas distal tumors frequently demonstrate an intraductal growth pattern. Histologically, the vast majority of CCAs are adenocarcinomas and can be categorized into sclerosing, nodular, and papillary variants, with the papillary subtype generally associated with the most favorable prognosis. Approximately 95% of pCCAs belong to the sclerosing subtype which is associated with extensive longitudinal spread and consequently low rates of curative resection. Overall prognosis remains poor, with reported 5-year overall survival rates of only 6–10% for patients with pCCA.[3] Similarly, iCCA is often diagnosed at an advanced stage, resulting in a 5-year survival of approximately 9%. Surgical resection remains the only potentially curative treatment for patients with localized, technically resectable disease with contemporary series reporting 5-year survival rates approaching 40% following complete resection.[4]

PERIHILAR CHOLANGIOCARCINOMA

Etiology and Risk Factors

The incidence of CCA rises progressively with advancing age with most patients being diagnosed after 65 years of age. The highest incidence is observed during the eighth decade of life, and there is a slight male predominance. Although several predisposing conditions have been identified, the majority of patients develop CCA in the absence of a recognized risk factor.[5] A common pathogenic mechanism linking many of these conditions is chronic inflammation of the biliary epithelium which promotes malignant transformation.

Primary sclerosing cholangitis (PSC): PSC is one of the strongest established risk factors for CCA. The annual incidence of CCA in patients with PSC is approximately 1.5%, with an estimated lifetime risk approaching 10%.[6] Tumors arising in this setting are frequently multifocal at presentation, limiting the possibility of curative surgical resection.[7]

Choledochal cysts: Congenital choledochal cysts are associated with a markedly increased risk of biliary tract malignancy owing to longstanding biliary stasis, chronic inflammation, and recurrent bacterial infection. Early cyst excision substantially reduces this risk; however, malignancy develops in approximately 15–20% of patients with untreated cysts or those managed with internal drainage procedures alone.[7]

Liver fluke infestation: Infection with biliary parasites, particularly *Opisthorchis viverrine* and *Clonorchis sinensis*, is an important etiological factor in endemic regions of Southeast Asia. In these populations, the incidence of CCA may reach 87 cases per 100,000 individuals.[7]

Other risk factors: Additional conditions associated with an increased risk of CCA include chronic ulcerative colitis, chronic liver infections, hepatolithiasis, and exposure

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to environmental carcinogens such as thorium dioxide, asbestos, radon, dioxins, nitrosamines, and tobacco smoke.[5] Hepatitis C infection has also been implicated, with approximately 2% of affected patients eventually developing CCA.[8]

Clinical Features

The clinical presentation of CCA is largely determined by the anatomical location of the tumor. Painless obstructive jaundice is the most frequent presenting symptom occurring in approximately 70–90% of patients. Other common manifestations include pruritus (66%), abdominal pain, unintended weight loss (30–50%), and fever, which is reported in nearly one-fifth of cases.[9] Extrahepatic tumors, including both distal and perihilar CCAs, typically produce biliary obstruction early in their course resulting in earlier onset of jaundice. In contrast, iCCAs often remain clinically silent until they attain a significant size and the development of jaundice usually indicates advanced disease.[10]

Diagnosis and Preoperative Workup

Tumor Markers

Although CA 19-9 and carcinoembryonic antigen (CEA) are limited in their diagnostic utility, they have been recognized as indicators of locally advanced and metastatic disease. Therefore, their assessment at the time of diagnosis is important to evaluate the risk of distant metastases.

Cytology and Pathology

Conventional cytology and transpapillary biopsy have comparable sensitivity (20–40%) and a specificity of 100%.[11] Fluorescence in situ hybridization (FISH) offers improved sensitivity, ranging from 60 to 70%, while maintaining a specificity of approximately 100%.[12] When used together, cytology and FISH can raise sensitivity to around 80%, supporting their use as the standard diagnostic approach.

Radiology

The radiological evaluation of pCCA depends on the availability of imaging modalities and the expertise of the treating institution. The principal imaging techniques include multidetector computed tomography (MDCT), contrast-enhanced magnetic resonance imaging with magnetic resonance cholangiopancreatography (MRI/MRCP) and in selected situations, ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET). Comprehensive staging should also include imaging of the chest and pelvis to identify distant metastatic disease. Although all three modalities are widely used in clinical practice, direct comparative evidence regarding their diagnostic accuracy remains limited. A recent meta-analysis demonstrated that CT-based imaging protocols provide a pooled sensitivity of 89% and specificity of 92% for detecting portal vein involvement while the corresponding values for hepatic artery invasion were 84% and 95%, respectively.[13] Despite its excellent vascular assessment, CT has limited sensitivity for accurately defining the longitudinal extent of tumor spread along the biliary epithelium. In contrast, contrast-enhanced MRI combined with MRCP offers superior delineation of the biliary tree and more precise characterization of intraductal tumor extension.[14] As these modalities provide complementary anatomical information, both MDCT and MRI/MRCP should be incorporated into the preoperative assessment whenever feasible. Routine use of ^{18}F-FDG PET is not recommended for all patients; however, it can be useful when there is concern for occult metastatic disease, with reported sensitivity and specificity of approximately 70–75%.[15]

Assessment of Resectability and Preoperative Staging

Accurate assessment of resectability and precise preoperative staging are critical components in the multidisciplinary management of pCCA. Several staging systems have been developed, each with varying degrees of anatomical detail and clinical applicability. High-resolution, contrast-enhanced cross-sectional imaging remains the cornerstone of this evaluation.

The *modified Bismuth–Corlette classification* **(Table 1)** remains widely utilized due to its simplicity and focus on biliary tract involvement.[16] It stratifies tumors based on their extent of longitudinal spread within the biliary tree, ranging from distal involvement of the common hepatic duct (type I) to bilateral secondary intrahepatic duct extension (type IV). While this system offers practical guidance for planning biliary reconstruction, it is limited as a comprehensive staging tool, as it excludes assessment of vascular involvement and has limited prognostic relevance.

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Similarly, the *eighth edition of the American Joint Committee on Cancer (AJCC) TNM classification* provides a pathologically based staging framework that is applicable postresection. However, due to its lack of preoperative anatomical detail, it has limited utility in the early decision-making process.

To address these deficiencies, the *Memorial Sloan Kettering Cancer Center (MSKCC) classification* was developed to integrate factors predictive of resectability and survival outcomes **(Table 2)**.[17] This system categorizes tumors into T1, T2, and T3 stages, with progressive decline in surgical resectability. Subsequent validation studies have confirmed its utility, showing that T1 tumors exhibit significantly higher resectability rates compared to T3. Nonetheless, despite advancements in cross-sectional imaging, approximately 20% of patients are ultimately deemed unresectable only at the time of operative exploration.

Current standards for evaluating resectability incorporate four key criteria: (1) the longitudinal and radial extent of biliary tree involvement, (2) the presence and severity of lobar hepatic atrophy, (3) vascular involvement of the hepatic artery or portal vein, and (4) evidence of regional or distant metastatic disease. These factors are not only prognostically significant but are also essential in guiding the extent and type of liver resection.

The relationship of the tumor to vascular structures at the hepatic hilum plays a pivotal role in surgical planning. Notably, in left-sided tumors, encasement or invasion of the right hepatic artery, due to its posterior course behind the bile duct may necessitate vascular reconstruction or preclude resection altogether. Hepatic atrophy, often a result of chronic biliary and vascular obstruction, can be recognized radiologically by a combination of reduced lobar volume, ductal crowding, and compensatory hypertrophy of the contralateral liver lobe **(Figs. 1A to C)**. Importantly, all imaging assessments should ideally be performed prior to biliary decompression, as intervention-related changes may obscure anatomical details crucial for preoperative planning.

TABLE 1: Bismuth-Corlette classification.

Type	*Description*	*Extent of ductal involvement*
Type I	Tumor below the confluence of the right and left hepatic ducts	Involves common hepatic duct only; confluence is intact
Type II	Tumor reaches the confluence but does not extend into right or left hepatic ducts	Involves bifurcation
Type IIIa	Tumor extends into the right hepatic duct	Involves right hepatic duct up to second-order branches
Type IIIb	Tumor extends into the left hepatic duct	Involves left hepatic duct up to second-order branches
Type IV	Tumor involves both right and left hepatic ducts (multifocal or bilateral second-order ducts)	Involves bilateral secondary biliary radicals

Biliary Drainage

To date, no definitive evidence supports the superiority of one biliary drainage technique over the other. Two randomized controlled trials comparing endoscopic biliary drainage (EBD) with percutaneous biliary drainage (PBD) were terminated early, limiting the strength of their conclusions.[18,19] Current international guidelines either advocate for EBD as the initial approach or consider both methods as acceptable, drawing primarily on large-scale retrospective data.[20] Despite this, PBD continues to be the preferred modality in many high-volume centers. Given the

TABLE 2: MSKCC (Blumgart) classification.

Stage	*Biliary involvement*	*Portal vein involvement*	*Lobar atrophy*
T1	Unilateral involvement of secondary biliary radicals (either right or left)	No portal vein involvement	Absent
T2	Unilateral involvement of secondary biliary radicals with ipsilateral portal vein involvement *or* with ipsilateral lobar atrophy	Ipsilateral only	May be present (ipsilateral)
T3	Bilateral involvement of secondary biliary radicals	Contralateral portal vein involvement *or* contralateral lobar atrophy	Present (contralateral)

(MSKCC: Memorial Sloan Kettering Cancer Center)

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Figs. 1A to C: (A) Segment II/III crowding of ducts with left lobar atrophy; (B) Soft tissue anterior to main portal vein; and (C) Soft tissue encasing left hepatic artery and proximal part of right hepatic artery.

lack of conclusive comparative data, the selection between EBD and PBD should be individualized. Key considerations include tumor location and extent, patient-specific factors, institutional experience, and the accessibility of the respective procedures. While EBD is generally favored when anatomically feasible, the consensus emphasizes specific clinical situations where PBD is more appropriate. These include complex anatomical variants that limit the technical feasibility of EBD, prior unsuccessful endoscopic drainage attempts, and surgically altered gastrointestinal anatomy that impedes endoscopic access (e.g., in patients with Roux-en-Y reconstruction). Thus, a tailored approach guided by multidisciplinary evaluation and institutional capabilities remains central to optimizing biliary drainage strategy in patients with pCCA.

Assessment of FLR and Techniques of Liver Hypertrophy

Posthepatectomy liver failure (PHLF) is one of the most serious complications following major liver resection, irrespective of the underlying indication. Its occurrence is primarily determined by the functional capacity, volume, and quality of the liver remnant following hepatectomy. In patients with normal hepatic parenchyma, a future liver remnant (FLR) >30% is generally considered sufficient to support postoperative liver function. In contrast, patients with impaired hepatic reserve, including those with cirrhosis, chemotherapy-associated liver injury, or persistent cholestasis require a larger FLR, as a remnant of this size may still be associated with an increased risk of PHLF.[21] Furthermore, clinical factors such as preoperative cholangitis and low serum albumin have also been linked to an elevated likelihood of PHLF, as shown in various multicenter retrospective analyses.[22] Based on this evidence, a minimum FLR of 30% is recommended for pCCA patients with preserved liver function. In contrast, for patients with comorbidities, malnutrition, cholestatic liver disease, or active cholangitis, a more conservative threshold of at least 40% is advised.

Portal vein embolization (PVE), originally introduced by Makuuchi in 1990, has become a cornerstone in the preoperative management of liver surgery, particularly in patients undergoing major hepatectomies. By diverting portal blood flow, PVE induces hypertrophy of the contralateral liver lobe, typically observed within approximately 3 weeks, and has been shown to reduce the incidence of postoperative liver failure and mortality in cases of pCCA.[23] A key parameter used to evaluate the efficacy of this procedure is the kinetic growth rate (KGR), calculated as the increase in FLR volume per week (%/week) following PVE. Unlike static FLR measurements, KGR provides insight into the functional regenerative capacity of the liver. A KGR of ≥2.66%/week is considered a reliable predictor of adequate liver function and regeneration potential.[24] While alternative hypertrophy-inducing strategies such as associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) and liver venous deprivation (LVD) have been proposed, current evidence does not support their routine application in clinical practice.

Surgical Management

Achieving a complete surgical resection with negative microscopic margins (R0) continues to represent the most effective strategy for improving long-term survival in patients diagnosed with pCCA. However, fewer than 40% of patients are deemed candidates for curative resection at the time of diagnosis.[25] Furthermore, intraoperative

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findings reveal that nearly half of those initially thought to be resectable are ultimately found to have unresectable disease during surgical exploration. For those who do undergo an R0 resection, the 5-year overall survival (OS) rate can approach 45%, markedly higher than the dismal 0–23% 5-year OS observed in patients with positive surgical margins (R1 or R2 resections).[26]

The standard surgical approach to pCCA typically consists of either an extended right/left hepatectomy or a left/right hemihepatectomy with caudate lobe resection, combined with extrahepatic bile duct resection, regional lymphadenectomy at the porta hepatis, and bilioenteric reconstruction. Incorporation of caudate lobe resection has been shown to enhance the likelihood of achieving negative surgical margins and improve survival outcomes, without introducing significant additional operative risk.[27] For biliary reconstruction, a Roux-en-Y hepaticojejunostomy remains the preferred technique for restoring biliary continuity. In certain cases, achieving an R0 resection during hepatectomy for pCCA necessitates concomitant vascular resection. This may involve resection of the portal vein, hepatic artery, or both, requiring vascular reconstruction to maintain perfusion to the FLR. Among these, portal vein resection and reconstruction have gained broader acceptance and are increasingly performed in high-volume hepatobiliary centers. In contrast, hepatic artery resection is technically more demanding and associated with higher risk; therefore, it should be reserved for carefully selected patients and undertaken only in specialized centers with expertise in complex hepatobiliary and vascular surgery.

The periductal infiltrative growth characteristic of pCCA often leads to a high incidence of microscopically positive (R1) surgical margins. To assess margin status intraoperatively, frozen section analysis of both proximal and distal bile duct margins is commonly employed. In the event of a positive frozen section, further ductal resection is recommended when technically feasible and not associated with significant additional morbidity. Notably, patients who achieve an R0 resection following additional resection prompted by a positive intraoperative margin may or may not exhibit survival outcomes comparable to those with an initial R0 resection.[28] Persistent R1 margins are associated with significantly poorer prognoses.[29] Extending the bile duct resection, however, can be technically demanding, particularly when the tumor encroaches upon the second-order biliary branches proximally, or when a distal extension necessitates pancreaticoduodenectomy. Finally, the role of liver transplantation in pCCA is a topic of great interest in the surgical community since the inaugural Mayo clinic protocol.[30] The debate centers around appropriate patient selection, devising pretransplant treatment protocols and the role of living donor transplantation.

Adjuvant and Neoadjuvant Strategies

Current evidence supporting neoadjuvant therapy for pCCA is limited and is derived predominantly from retrospective series and a small number of prospective single-center studies involving patients with anatomically defined borderline resectable or locally advanced disease. Nevertheless, a universally accepted definition of locally advanced pCCA has not yet been established. A systematic review evaluating neoadjuvant treatment suggested that preoperative therapy may facilitate tumor downstaging, thereby increasing the likelihood of achieving an R0 resection. However, the available evidence remains insufficient, highlighting the need for well-designed prospective studies to better define the indications and clinical benefit of neoadjuvant treatment in pCCA.[31]

Following curative-intent resection, 6 months of fluoropyrimidine-based adjuvant chemotherapy, using either capecitabine or S-1, is currently recommended for eligible patients. The benefit of perioperative radiotherapy has not been conclusively demonstrated, and its routine use cannot be recommended on the basis of existing evidence. Likewise, although molecularly targeted therapies and immunotherapy have shown promise in biliary tract cancers, their role in the perioperative management of resectable pCCA remains to be clearly established through future clinical trials.

Conclusion

Complete surgical resection remains the cornerstone of curative-intent treatment for pCCA. Recent advancements in surgical techniques, such as PVE, major vascular resection and reconstruction, and neoadjuvant chemoradiation followed by liver transplantation, have expanded the pool of patients eligible for potentially curative interventions. While still in the early phases of adoption, minimally invasive approaches and emerging artificial intelligence (AI)-driven tools offer potential to further optimize surgical planning and patient outcomes. Additionally, research into novel biomarkers, including

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liquid biopsies, along with ongoing trials evaluating perioperative systemic therapies, such as chemotherapy, immunotherapy, and targeted treatments hold promise for improving early diagnosis, patient stratification, and long-term survival in pCCA. Continued innovation and multidisciplinary collaboration will be essential to advance the therapeutic landscape of this challenging malignancy.

INTRAHEPATIC CHOLANGIOCARCINOMA

Intrahepatic CCA is traditionally divided into four morphological subtypes:

1. *Mass-forming (MF):* Characterized by a nodular tumor mass within the liver.
2. *Periductal-infiltrating (PI):* Marked by tumor spread along the bile ducts.
3. *MF + PI:* A combination pattern where the tumor both infiltrates along bile ducts and invades adjacent liver tissue forming a mass.
4. *Intraductal-growing:* Previously considered a subtype, this has now been reclassified as *intraductal papillary neoplasm* in the 4th edition of the World Health Organization (WHO) classification.

From a histological perspective, the 5th edition of the WHO classification identifies *two major iCCA subtypes:*

1. Large duct type
2. *Small duct type*, each with distinct pathological characteristics and genetic mutation patterns

Clinical Presentation and Diagnostic Approach

Intrahepatic cholangiocarcinoma often lacks early symptoms and typically does not present with jaundice, unlike perihilar or distal CCAs, due to its origin in the proximal intrahepatic ducts. Patients may report nonspecific symptoms such as abdominal discomfort, bloating, nausea, or weight loss, with many early-stage tumors detected incidentally on imaging. Routine liver function tests are often unremarkable, necessitating a high degree of clinical suspicion. Initial evaluation should include a thorough history and physical examination, focusing on risk factors such as chronic liver disease (e.g., PSC, viral hepatitis, metabolic liver disease, and alcohol use), toxin exposure (e.g., thorotrast and aflatoxin), parasitic infections, and family or personal history of malignancies. Serum tumor markers, particularly CA 19-9, CEA, and AFP, are frequently assessed. While CA 19-9 has approximately 72% sensitivity for iCCA, it lacks specificity and may be falsely negative in individuals who genetically lack its synthesis (~5–10% of Caucasians).[32]

Imaging with contrast-enhanced MDCT or MRI is essential for diagnosis and staging. iCCA typically shows progressive enhancement in both arterial and venous phases, distinguishing it from hepatocellular carcinoma, which shows venous-phase washout. Additional features like capsular retraction and adjacent bile duct dilation can support the diagnosis, although these are not universally present.[33] Chest CT is routinely performed for staging. When imaging is inconclusive, image-guided biopsy may aid diagnosis. If adenocarcinoma is confirmed, endoscopic evaluation [esophagogastroduodenoscopy (EGD) and colonoscopy] is recommended to exclude metastatic disease. For advanced or unresectable cases, molecular profiling is advised to guide targeted systemic therapy.

Surgical Management of iCCA

Surgical resection remains the only potentially curative treatment for patients with iCCA. Beyond the initial diagnostic evaluation, preoperative assessment should address the patient's comorbid conditions, liver function, disease burden, and the technical feasibility of surgery. The primary objective is to achieve an R0 resection, a microscopically negative margin while preserving adequate liver function, guided by the predicted FLR. Generally, an FLR of 20–25% is sufficient in patients with healthy livers. However, this threshold increases to 30% in the setting of hepatic steatosis or chemotherapy-induced injury and to 40–50% in those with underlying cirrhosis or significant liver dysfunction.[34]

Tumor resectability is influenced by multiple factors, including anatomic location, proximity to major vasculature or bile ducts, presence of multifocal disease, lymphadenopathy, and distant metastases.[35] Due to the high incidence of occult metastatic disease—reported in up to one-third of cases, diagnostic laparoscopy is often recommended prior to definitive surgery.[36] Although the yield of laparoscopy remains significant (approximately 20%), there is no consensus on patient selection criteria. Surgical approaches may be either open or minimally invasive, with laparoscopic and robotic resections showing favorable outcomes in selected patients, including reduced blood loss, less postoperative pain, shorter hospital stays, and comparable oncologic results. However, such approaches require appropriate expertise and careful patient selection.

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Achieving an R0 margin is a key determinant of long-term survival, as positive margins, multifocal tumors, vascular invasion, and nodal metastases are associated with poorer outcomes.[37] Several studies suggest that wider negative margins (≥1 cm) are associated with improved recurrence-free and overall survival. A meta-analysis involving over 3,000 patients demonstrated that margin widths exceeding 5–10 mm are associated with significantly better survival outcomes.[38] While parenchymal-sparing resections are well-established for hepatocellular carcinoma and colorectal liver metastases, their role in iCCA remains controversial.[39] Currently, the focus remains on achieving complete tumor clearance, irrespective of the extent of resection. In carefully selected patients, combined major vascular resection may be required to obtain a margin-negative (R0) resection. When performed in experienced centers, this approach can achieve acceptable perioperative outcomes without adversely affecting long-term oncological results.

Regional lymph node status is a major determinant of prognosis in iCCA and is an important consideration when planning postoperative adjuvant treatment. Therefore, regional lymphadenectomy should be performed routinely as part of curative hepatic resection. Guidelines, including those from the National Comprehensive Cancer Network (NCCN), suggest retrieving a minimum of six lymph nodes, typically including those in the hepatoduodenal ligament (station 12) and along the common hepatic artery (station 8). The extent of lymphadenectomy may be tailored according to the primary tumor location and its expected pattern of lymphatic spread, with additional nodal dissection of the lesser curvature or retropancreatic region performed when indicated. Although regional lymphadenectomy improves the accuracy of pathological staging and provides important prognostic information, current evidence has not demonstrated a definitive survival advantage.[40] A meta-analysis including 17 studies demonstrated that lymph node dissection was not associated with a significant improvement in either disease-free survival or overall survival when compared with omission of lymphadenectomy.[41] Nevertheless, accurate identification of nodal metastases remains clinically important, as patients with node-positive disease have a substantially greater risk of recurrence and are more likely to derive benefit from adjuvant systemic chemotherapy, consistent with the findings of the BILCAP trial.[42]

Neoadjuvant and Adjuvant Strategies in iCCA

Currently, neoadjuvant chemotherapy is not standard for resectable iCCA. However, a phase II multi-institutional trial evaluating the GAP regimen (gemcitabine, cisplatin, nab-paclitaxel) in high-risk patients demonstrated its safety and feasibility without compromising surgical outcomes. While not yet routine, neoadjuvant therapy may be considered in select high-risk cases, preferably within clinical trials. The role of adjuvant chemotherapy in iCCA remains an area of active investigation, particularly given the high risk of recurrence even after curative-intent resection.[43] The BILCAP trial, a phase III randomized controlled trial, demonstrated a survival benefit with capecitabine in the adjuvant setting across all biliary tract cancers, and posthoc analyses suggest its relevance in iCCA.[44] As a result, capecitabine is currently recommended by major guidelines, including NCCN and European Society for Medical Oncology (ESMO), as the standard adjuvant therapy following resection. While other agents such as gemcitabine-based regimens have been explored, their benefit in the adjuvant setting remains less clearly defined. Ongoing trials and molecular profiling may further refine patient selection and tailor adjuvant strategies in the future.

Conclusion

Intrahepatic cholangiocarcinoma is a rare and often late-presenting malignancy with a high risk of recurrence despite curative-intent resection. Negative surgical margins and regional lymphadenectomy offer the best chance for long-term survival, but most patients remain at substantial risk for disease relapse. Adjuvant capecitabine is currently the recommended first-line therapy for patients with adequate performance status, especially those with high-risk features such as positive margins or nodal involvement. Molecular profiling of resected tumors is encouraged to guide personalized treatment approaches, particularly in the recurrent or metastatic setting where targeted therapies or immunotherapy combinations (e.g., durvalumab with gemcitabine and cisplatin) may be considered. Multiple ongoing trials—including ATTICA-1, GAIN, and OPTIC—are exploring the role of perioperative and molecular-based strategies. As the landscape of precision oncology evolves, multidisciplinary collaboration and continued engagement with clinical trials will be essential to improving outcomes in this challenging disease.

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