Proximal Biliary Tumors

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**KEYWORDS**

- Intra-hepatic cholangiocarcinoma
- Peripheral cholangiocarcinoma
- Hilar cholangiocarcinoma
- Klatskin tumor
- Bile duct cancer

**KEY POINTS**

- For cholangiocarcinoma distribution, perihilar location is the most common, followed by distal; intrahepatic is the least common tumor location.
- Contrast-enhanced computed tomography or magnetic resonance imaging with delayed phase is recommended to assess tumor extent and determine resectability.
- Biliary decompression in the absence of cholangitis should only be performed under the direction of the multidisciplinary team that will be treating the patient.
- Complete surgical resection to negative margins is the only hope for long-term survival; highly selected patients with unresectable tumors or underlying liver disease such as primary sclerosing cholangitis may be considered for liver transplant.
- Untreated, unresectable disease portends a median survival of 4 to 5 months; following resection, 5-year survival ranges from 22% to 35%; R0 resection is associated with improved survival.
- Cisplatin-gemcitabine chemotherapy is associated with improved overall and progression-free survival in unresectable disease; a clear benefit in the adjuvant setting has not been established.

**INTRODUCTION: NATURE OF THE PROBLEM**

Cholangiocarcinoma is a tumor arising from the epithelium of the bile ducts and is further classified as intrahepatic, perihilar (also referred to as Klatskin tumor), or distal cholangiocarcinoma based on the tumor location (Fig. 1). Intrahepatic tumors arise from second-order bile ducts or more proximal, without involvement of the hepatic duct confluence; hilar tumors arise at or near the confluence of the right and left hepatic ducts, with further classification based on the extent of involvement (Fig. 2); distal tumors include any extrahepatic location beyond the common hepatic duct, although they essentially are periampullary tumors. Intrahepatic and hilar tumors together are referred to as proximal biliary tumors. Hilar and distal tumors are referred to as...
extrahepatic cholangiocarcinomas. Important demographic aspects of cholangiocarcinomas include the following:

- Cholangiocarcinoma is a rare tumor.
- Approximately 5000 to 6000 new cases of cholangiocarcinoma are diagnosed in the United States every year.
Intrahepatic, perihilar, and distal tumor locations are seen in approximately 10%, 50%, and 40% of cholangiocarcinomas, respectively.\textsuperscript{1}

INTRAHEPATIC CHOLANGIOCARCINOMA

Intrahepatic cholangiocarcinoma (ICC) accounts for 10% to 20% of all primary liver malignancies and is the second most common primary liver tumor after hepatocellular carcinoma (HCC).\textsuperscript{2} There are not any well-established risk factors for developing ICC. However, demographic and clinical factors associated with a higher risk of ICC include

- Male gender;
- Ethnicity—the incidence in Asians is twice that of Caucasians;
- Chronic biliary inflammation from hepatolithiasis, choledochal cysts, and liver fluke infestation; and
- Hepatitis B or C infection.

ICC forms several distinct macroscopic histologic subtypes: mass forming, periductal infiltrating, intraductal, and mixed mass forming-periductal infiltrating. Mass forming is the most common subtype in western series. The association of subtype and biologic behavior of the tumor is inconsistent.\textsuperscript{3,4}

CLINICAL PRESENTATION AND WORKUP

ICC is initially asymptomatic. Patients most often present with nonspecific symptoms including abdominal pain, anorexia, or unexplained weight loss. Jaundice is uncommon. Physical examination findings are also nonspecific. Laboratory results may be normal or there may be elevations in liver transaminases, alkaline phosphatase, or bilirubin. Once a liver mass is identified, tumor markers including carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, and alphafetoprotein should be checked, although these are also nonspecific.

Imaging

In a patient with right upper quadrant complaints, an ultrasound (US) is frequently the first imaging study ordered. On US, ICC may appear as a hypoechoic parenchymal mass or an irregular mass along an intra-hepatic duct. Multiphase cross-sectional imaging with either contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) will provide better anatomic detail of the mass and its relationship to internal hepatic structures. In addition, the presence of enlarged regional lymph nodes, peritoneal carcinomatosis, and distant metastatic disease can be assessed. Delayed-phase imaging is helpful, as these tumors will continue to enhance during the delayed phase. Fig. 3 demonstrates a CT scan of an ICC.

Key factors to consider in the work up of a suspected ICC are the following:

- ICC does not have sensitive or specific imaging findings, unlike HCC.
- ICC is a diagnosis of exclusion—an intrahepatic mass may be an HCC or metastatic disease from an occult primary.
- Colonoscopy, upper endoscopy, chest CT, and mammography should be considered in evaluating for an occult primary.
- Biopsy is not necessary, but if performed, may show adenocarcinoma suggestive of pancreaticobiliary origin (CK-7+, CK20−, CDX2−) or may show poorly differentiated carcinoma that does not stain for any surface markers.
The 7th edition of the American Joint Committee on Cancer (AJCC) Staging Manual was updated to include a staging system for ICC that is unique from HCC (Table 1). The tumor stage is based on prognostic factors identified by an analysis of data from the Survey, Epidemiology and End Results (SEER) database, including number of tumors, presence of vascular invasion, and direct extrahepatic tumor extension.5

THERAPEUTIC OPTIONS AND SURGICAL TECHNIQUES

Complete surgical resection offers the only hope of long-term survival. Preoperative planning assesses the suitability of the patient for resection, based on tumor factors and comorbidities. Surgery is reserved for the medically fit patient with no evidence of metastatic disease, including no lymph node involvement of the celiac or periaortic lymph nodes.

The goal of surgery is complete tumor removal to negative microscopic margins (R0 resection), and the extent of resection required depends on the tumor location. Up to 70% to 80% of a healthy liver can be resected, and the remaining liver will hypertrophy to the original volume and function. However, the future liver remnant needs to consist of at least 2 contiguous segments that have hepatic arterial and portal venous inflow, hepatic vein outflow, and biliary-enteric drainage. In cases of marginal future liver remnant, preoperative portal vein embolization of the tumor-bearing hemiliver can induce contralateral lobar hypertrophy preoperatively, resulting in a larger future liver remnant and potentially less risk of postoperative hepatic insufficiency.6

Regional lymph node involvement portends a poor prognosis; for this reason, routine regional lymphadenectomy is performed at some centers. However, based on the paucity of evidence to suggest that lymphadenectomy influences survival, many Western centers remove only suspicious lymph nodes.7

Orthotopic liver transplantation (OLT) has been described for ICC, but tumor recurrence is high and survival is not improved compared to resection.8,9 Clinical factors such as multifocal disease, perineural or lymphovascular invasion, or history of primary sclerosing cholangitis (PSC) may help predict which patients will benefit from OLT.9 However, OLT for ICC should only be performed in the context of a clinical trial.

Systemic chemotherapy may be used in an adjuvant setting or as palliative treatment of patients with unresectable or recurrent disease. Historically, 5-fluoro-uracil
was the only agent available, and outcomes were poor.\textsuperscript{10,11} Gemcitabine, as a single
agent, first demonstrated activity against advanced biliary tract cancers with a reason-
able safety profile.\textsuperscript{12,13} Subsequently, gemcitabine-cisplatin systemic chemotherapy
was shown to improve overall survival in patients with unresectable biliary tract can-
cers, compared to single-agent gemcitabine (11.7 months vs 8.1 months).\textsuperscript{14} There
are no randomized studies of adjuvant chemotherapy in ICC; one retrospective study
of 157 patients with cancer arising from the biliary tract, of whom 54 had ICC, found
that neither adjuvant nor neoadjuvant treatment was associated with improved
survival.\textsuperscript{15}

Transcatheter arterial chemoembolization (TACE) with gemcitabine alone or in com-
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Table 1
American Joint Commission on Cancer (AJCC) 7th edition staging classification for ICC

<table>
<thead>
<tr>
<th>Primary tumor (T) staging</th>
<th>Regional lymph node (N) staging</th>
<th>Distant metastasis (M) staging</th>
<th>Stage groupings</th>
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</thead>
<tbody>
<tr>
<td>TX Primary tumor can not be assessed</td>
<td>Nx Regional lymph nodes can not be assessed</td>
<td>MX Distant metastasis can not be assessed</td>
<td>Stage 1 T1 N0 M0</td>
</tr>
<tr>
<td>T1 Solitary tumor, no vascular invasion</td>
<td>N1 No regional lymph node metastasis</td>
<td>M0 No distant metastasis</td>
<td>Stage II T2 N0 M0</td>
</tr>
<tr>
<td>T2a Solitary tumor, vascular invasion present</td>
<td>N2 Regional lymph node metastasis present</td>
<td>M1 Distant metastatic disease present</td>
<td>Stage III T3 N0 M0</td>
</tr>
<tr>
<td>T2b Multiple tumors, with or without vascular invasion</td>
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<td></td>
<td>Stage IVA T4 N0 M0</td>
</tr>
<tr>
<td>T3 Tumor directly invades local extrahepatic structures or perforates visceral peritoneum</td>
<td></td>
<td></td>
<td>Any T N0 M0</td>
</tr>
<tr>
<td>T4 Tumor with periductal invasion</td>
<td></td>
<td></td>
<td>Any T Any N M1</td>
</tr>
</tbody>
</table>

CLINICAL OUTCOMES

- In experienced centers, surgical resection of ICC can be performed with less than
  3% mortality.\textsuperscript{4,17–21}
- Complication rates range from 6% to 38%.\textsuperscript{1,3,17,18,21–24}
Morbidity and mortality are influenced by the extent of liver resection and the need for vascular or biliary reconstruction. 5-year overall survival after resection ranges from 20% to 40%. Median survival after resection is 19 to 53 months. Overall survival in unresectable disease is less than 1 year.

HILAR CHOLANGIOCARCINOMA

Hilar cholangiocarcinoma most commonly develops in the absence of risk factors but may be associated with inflammatory conditions of bile ducts, including PSC, ulcerative colitis, or parasitic infestation. These tumors tend to be locally invasive and slow growing, with spread to locoregional lymph nodes, liver, or peritoneum; systemic metastasis occurs late in the disease process. Hilar tumors may be characterized by macroscopic subtype, although the location and extent of involvement are more commonly used to classify tumors for staging and treatment purposes (see Fig. 2).

CLINICAL PRESENTATION AND WORKUP

- Early signs and symptoms are most commonly nonspecific.
- One-third of patients will have weight loss, abdominal pain, jaundice, or pruritus.
- Physical examination may show hepatomegaly or skin excoriations from pruritus.
- Most common laboratory abnormalities are elevated bilirubin and alkaline phosphatase levels; aspartate aminotransferase/alanine aminotransferase may also be elevated.
- CEA and CA 19-9 are often ordered but are nonspecific; IgG4 can help distinguish malignancy from IgG4-associated inflammatory disease.
- Cholangitis is a very rare presentation in the absence of instrumentation of biliary tree.
- An alternative diagnosis is seen in 10% to 15% of patients with focal strictures of proximal biliary tree, including gallbladder cancer, Mirizzi syndrome, benign stricture, benign fibrosing disease, hepatic pseudotumors, and iatrogenic injury.

Imaging

Ultrasound is often the first imaging study performed for nonspecific abdominal symptoms or jaundice. US will show unilateral or bilateral intrahepatic biliary ductal dilatation with decompressed extrahepatic ducts. US may show a mass, invasion of liver parenchyma, or portal vein involvement with loss of vascular flow. Cross-sectional imaging is necessary for precise staging. Contrast-enhanced CT will show the level of biliary obstruction, the presence of atrophy, and may show a mass, or vascular involvement. Delayed-phase imaging is recommended for cholangiocarcinoma, as enhancement will persist (contrast retention) in the delayed phase. Although CT may allow determination of resectability, it is not always helpful in demonstrating the proximal extent of ductal involvement, which is a key feature for determining resectability.

Historically, direct imaging of the bile ducts with percutaneous transhepatic cholangiography (PTC) or endoscopic retrograde cholangiography (ERCP) was used to determine the extent of biliary involvement and to perform preoperative decompression. However, ERCP is often unable to traverse strictures and risks contamination of otherwise sterile bile in the obstructed ducts. In both procedures, decompression of the hemiliver that would ultimately be removed during surgery reverses the natural
atrophy that occurs in a chronically obstructed hemiliver, as well as the compensatory hypertrophy of the future liver remnant. This works against the usual preoperative strategy of maximizing the future liver remnant. Thus, ERCP and PTC are no longer routinely used in the preoperative imaging of hilar cholangiocarcinoma.

MRI with magnetic resonance cholangiopancreatography (MRCP) is a more sensitive noninvasive modality for the preoperative assessment of a hilar cholangiocarcinoma. MRI/MRCP is able to image obstructed or isolated ducts; better determine the level of ductal involvement; and assess vascular invasion, nodal involvement, and distant metastases (Fig. 4A).

**Tissue Diagnosis**

The need for preoperative tissue diagnosis in a patient with a potentially resectable proximal biliary stricture is somewhat controversial. Although a negative or nondiagnostic biopsy does not exclude a cancer, and therefore surgical resection may still be performed, tissue confirmation is sometimes necessary for treatment plans that include preoperative chemotherapy or radiation therapy and may be helpful in preoperative patient counseling.

- ERCP with brushings may be used to establish a tissue diagnosis—30% sensitivity; risks include cholangitis (see Fig. 4B).
- PTC can be performed with blind brushings.
- SpyGlass Direct Visualization System is a new endoscopic technology allowing visualization of the bile duct and thus more focused, directed biopsy; sensitivity is higher than blind brushings.
- Endoscopic ultrasound (EUS) directs US beams from the lumen of the stomach or duodenum; EUS-directed needle biopsy requires passage through peritoneum, with concerns for tumor seeding; this modality is not often used for hilar tumors.
- Invasive procedures for diagnostics should only be performed under the direction of the multidisciplinary team that will be providing treatment of the patient.

Fig. 4. Imaging studies used to assess extent of tumor in hilar cholangiocarcinoma. (A) MRCP image showing dilated intrahepatic bile ducts that abruptly terminate just proximal to the confluence of the right and left hepatic ducts (arrow). (B) ERCP image of a hilar cholangiocarcinoma, showing dilated intrahepatic ducts and an absence of contrast material throughout the malignant stricture.
Preoperative staging of hilar cholangiocarcinoma requires

- Precise knowledge of the proximal extent of tumor on the left and right side;
- Assessment of presence or absence and extent of vascular invasion; and
- Evaluation for distant metastases—abdomen and chest.

The current AJCC staging classification is inadequate for surgical planning, as it does not incorporate resectability criteria for the tumor. The Blumgart staging system takes resectability factors into consideration and has been shown to correlate with survival. Both systems are presented in Table 2. A recent international collaborative proposed a new staging system that takes into account the degree of bile duct involvement, tumor size, macroscopic histologic subtype, degree of portal vein and hepatic artery involvement, future liver remnant volume, underlying liver disease, as well as the presence of lymph node or distant metastasis. The correlation between this staging system and prognosis remains to be determined.

**THERAPEUTIC OPTIONS AND SURGICAL TECHNIQUES**

**Surgical Resection**

As with ICC, complete surgical resection is the only potentially curative treatment available for hilar cholangiocarcinoma and is possible in 30% to 40% of patients. Resection of the involved extrahepatic bile ducts, en bloc liver resection of the hemiliver with most extensive tumor involvement, and lymphadenectomy are the standard operations. The extent of liver resection depends on the tumor location, as demonstrated in Fig. 5. Caudate lobe resection is recommended based on evidence for increased rates of R0 resection compared to cases where caudate resection is omitted. Biliary-enteric continuity is reestablished via Roux-en-Y hepaticojejunostomy.

Potential surgical candidates need careful assessment of their fitness for surgery. Given the complexity of these cases, correction of malnutrition and coagulopathy

<table>
<thead>
<tr>
<th>Table 2</th>
<th>AJCC and Memorial-Sloan Kettering T-Stage criteria for hilar cholangiocarcinoma</th>
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<tbody>
<tr>
<td><strong>AJCC</strong></td>
<td><strong>MSKCC</strong></td>
</tr>
<tr>
<td>T1 Confined to the bile duct</td>
<td>Tumor involves biliary confluence +/– extension to secondary bile duct unilaterally</td>
</tr>
<tr>
<td>T2 Invades beyond the wall of the bile duct to adjacent adipose (a) or hepatic parenchyma (b)</td>
<td>Same criteria as T1 AND ipsilateral PV involvement and/or ipsilateral hepatic lobar atrophy</td>
</tr>
<tr>
<td>T3 Invades unilateral PV or HA branches</td>
<td></td>
</tr>
<tr>
<td>T4 Invades main PV or bilateral PV branches or CHA or secondary bile ducts bilaterally, OR unilateral secondary bile duct involvement with contralateral PV or HA involvement</td>
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</table>

**Abbreviations:** CHA, common hepatic artery; HA, hepatic artery; PV, portal vein.

should be undertaken. The multidisciplinary team may consider preoperative stenting of the future liver remnant if the patient is severely jaundiced or if there is evidence of infection, but this is not routine practice. Ideally, time should be given for jaundice to resolve before resection if stenting is used. The future liver remnant should be calculated to be at least 30% to 35% of liver volume in a patient with no underlying liver disease; in cases of borderline remnant volume, portal vein embolization of the hemiliver to be removed can be used to induce hypertrophy of the future liver remnant.

The following factors should be considered when selecting a patient for surgical resection of ICC:

- **Patient factors**
  - No significant comorbidities—cardiopulmonary, cirrhosis
  - Optimized nutritional, coagulation status
  - Reasonable age and functional status
  - Bilirubin level less than or equal to 10 mg/dL

![Cartoon depiction of (A) resection of the left hemiliver for a type IIIb tumor, with biliary-enteric anastomosis to the right hepatic duct, and (B) extended left hepatectomy for a type IIIa tumor that involves the right anterior sectoral duct, requiring resection of segments I-IV, V and VIII and a biliary-enteric anastomosis to the right posterior sectoral duct draining segments VI and VII.](image-url)
- Tumor factors
  - No encasement or occlusion of main portal vein or hepatic artery (bilateral arterial involvement or arterial involvement proximal to the bifurcation)
  - No involvement of bilateral secondary (sectoral) ducts or unilateral ductal involvement with contralateral vascular involvement or compromise
  - No atrophy of one hemiliver with contralateral secondary ductal or portal venous involvement
  - No metastatic disease beyond regional (hepatoduodenal ligament) lymph nodes

**Transplantation**

Complete resection of the liver and biliary tree with OLT has been used in the treatment of highly selected patients with unresectable hilar cholangiocarcinoma or patients with an underlying liver condition such as PSC that precludes surgical resection. Centers offering this treatment use preoperative chemotherapy and radiation therapy and a staging laparotomy. For patients who do not progress while waiting for transplantation, post-transplant overall 5-year survival is as high as 70%, and 20% to 44% of patients will have tumor recurrence.

**Adjuvant Therapy**

Studies evaluating systemic chemotherapy in the adjuvant setting are lacking; local recurrence is the more common pattern of failure, which indicates a possible role for adjuvant radiotherapy. However, an analysis of SEER data from 1973 to 2005 found no survival difference at 5 years between patients treated with and without adjuvant radiotherapy. Given the paucity of data to support adjuvant treatment, chemotherapy and/or radiation should only be given in the context of a clinical trial.

**Palliative Treatment**

Patients who are not appropriate for surgical resection or transplantation may be treated with systemic chemotherapy with or without radiation, with phase III evidence to support the use of gemcitabine and cisplatin over single-agent gemcitabine (overall survival 11.7 vs 8.1 months). Transcatheter arterial chemoembolization is another option, with single-agent gemcitabine or gemcitabine-containing regimens. Biliary obstruction is the most common symptom considered for palliative treatment. Indications for intervention include cholangitis, intractable pruritus, and the need to normalize bilirubin to deliver chemotherapy. Percutaneous drainage is more effective than endoscopic approaches due to technical and mechanical limitations of the latter; initial percutaneous drainage can be followed by self-expanding metallic stent placement. Although 2 or 3 stents may be necessary to drain all ducts, partial decompression can offer symptom relief. As many as 50% of patients explored for potentially resectable hilar cholangiocarcinoma will be unresectable, usually due to metastatic disease discovered at laparotomy; these patients may benefit from an intrahepatic biliary-enteric bypass, the most common of which is a segment III hepaticojejunostomy at the umbilical fissure.

**CLINICAL OUTCOMES**

- Patients with unresectable tumors have a median survival of 4 to 5 months.
- Treatment with gemcitabine-cisplatin can prolong median overall survival to approximately 12 months.
Surgical resection is associated with a mortality of 2% to 10% and 25% to 44% rate of morbidity.\textsuperscript{30,33,35,41–44} Five-year overall survival following resection is 20% to 35%.\textsuperscript{35,41–44} Median overall survival is approximately 40 months.\textsuperscript{33,35,41,43} Factors associated with improved survival include
- Complete (R0) resection\textsuperscript{35,44};
- Concomitant liver resection versus bile duct resection only\textsuperscript{35};
- Well-differentiated histology\textsuperscript{35}; and
- No lymph node metastases\textsuperscript{42,44}
Patients undergoing resection for hilar cholangiocarcinoma have a higher likelihood of a complete (R0) resection when en bloc liver resection is performed with the bile duct resection.\textsuperscript{42}
Five-year overall survival following transplant is approximately 65% to 70%.\textsuperscript{36}

**SUMMARY**

Proximal biliary tumors are relatively uncommon; hilar tumors are more common than ICC. Both are associated with a poor prognosis, and complete surgical resection offers the only hope of long-term survival. Contrast-enhanced imaging with delayed phase is the most effective modality for preoperative staging and treatment planning. For perihilar tumors, precise identification of the proximal and distal extent of tumor involvement bilaterally is necessary for determining eligibility for resection. Transplant is an option for highly selected patients as part of established protocols including preoperative chemoradiation, chemotherapy, and operative staging. Overall survival after resection is low, although patients with R0 resections have improved prognosis. Gemcitabine-cisplatin is offered to medically fit patients with preserved organ function and unresectable tumors.

**REFERENCES**


