Cholangiocarcinoma

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Introduction

Cholangiocarcinoma is an uncommon cancer that occurs within the intrahepatic and extrahepatic portions of the bile duct system. In North America, the incidence of extrahepatic cholangiocarcinoma is 0.5–2 per 100,000 and 0.95 per 100,000 for intrahepatic cholangiocarcinoma [1]. Up to 50% of patients will be lymph node (LN) positive at presentation, 5% are multifocal tumors, and 10–20% will have peritoneal involvement at presentation (see Table 5.1). Risk factors for cholangiocarcinoma are primary sclerosing cholangitis (PSC) with a lifetime risk 10–40% [2, 3], parasitic infection [1], previous sphincteroplasty [4], congenital anomalies of the biliary tree (choledochal cyst, Caroli's disease, anomalous pancreaticobiliary duct junction) [5], and chronic biliary inflammatory disease (hepatitis B/C, liver cirrhosis [6], recurrent pyogenic cholangitis) (see Table 5.2). The most common presentation is painless jaundice and weight loss in the setting of extrahepatic duct involvement. In Western countries, 80% are extrahepatic (20% distal and 60% hilar) and 20% are intrahepatic (see Tables 5.3 and 5.4).

The recommended staging system is the Union for International Cancer Control and American Joint Committee on Cancer (UICC/AJCC) 8th edition. ICC and ECC are staged differently.

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Table 5.1 Clinical outcome

Presentation	Prognosis 5-year overall survival (OS)
Distal extrahepatic localized, LN negative Hilar extrahepatic localized, LN negative Intrahepatic localized, LN negative	37–54% (fully resected disease) 20–50% (fully resected disease) 20–43% (fully resected disease)
LN positive—resectable	20–25% [7] (median survival 22 months with positive margins, 60 months with negative margins) [8]
Metastatic or unresectable disease	<5%

LN lymph node

Table 5.2 Special cases

Primary sclerosing cholangitis	Congenital cysts
6.8% of patients develop cholangiocarcinoma over 10 years (10–40% lifetime risk) Incidence: 0.6% per year Usually presents within the first 2 years after diagnosis of PSC [10] Screening recommendations: q6 month biliary imaging (CT or MRI/MRCP), Ca 19–9 for 2 years. However, no validated surveillance program in this population [1, 5] There is some emerging evidence to support the use of EUS with biopsy/brushings in this scenario	Incidence of cholangiocarcinoma <1% per year Overall lifetime incidence of 28%, if left untreated [11] Upon identification, ductal imaging is necessary with MRCP; ERCP if needed Recommend cyst excision with hepaticojejunostomy reconstruction Cyst enterostomy is not recommended [12]

PSC primary sclerosing cholangitis, ERCP endoscopic retrograde cholangiopancreatography

Table 5.3 Intrahepatic cholangiocarcinoma

Work-up	Management	Follow-up
History and physical exam Lab work: Ca 19–9, AFP, CEA Imaging: CT chest, multiphasic CT A/P MRI/MRCP Search for primary adenocarcinoma of other site: Endoscopy, chest CT, mammography [13]	Surgical resection is the only potential cure Removal of involved liver segments There is emerging evidence that recommends a routine hilar LN dissection for its prognostic value [14] M1 disease includes involvement of celiac, periaortic, caval LN	CT C/A/P q3–6 months × 2 years However, there is no data to support that aggressive postoperative surveillance as it has not been shown to alter outcome in this disease

LN lymph nodes, *CT C/A/P* computed tomography of chest, abdomen, and pelvis

Table 5.4 Extrahepatic cholangiocarcinoma

Site	Work-up	Management	Follow-up
Distal bile duct (below the cystic duct)	History and physical exam Labs: Ca 19–9 Imaging: CT chest, multiphasic CT A/P MRI/MRCP Consider biliary decompression if: Jaundice present with ERCP/ PTC Consider EUS for biopsy of lesion and lymph nodes (biopsy should be avoided in surgically resectable patients) [13] Specificity of brush cytology is almost 100%, but sensitivity only 18–40% [16] Consider serum IgG4 to rule out IgG4 related sclerosing cholangitis	Surgical resection is the only potential cure Pancreaticoduodenectomy including en bloc resection of extrahepatic bile duct and gallbladder Regional nodes include: Hilar (CBD, common hepatic, portal, cystic) Posterior and anterior pancreaticoduodenal Nodes along SMV Nodes along right lateral wall of SMA	CT C/A/P q3–6 months for 2 years There is no data to support that aggressive surveillance alters outcome in this disease
Hilar (above the cystic duct)		En bloc resection of extrahepatic bile duct and gallbladder, including right and left hepatectomy, or extended right/left hepatectomy [7] Caudate lobe should be removed [13] Regional nodes include: Hilar (CBD, hepatic, portal, cystic) Pericholedochal nodes in hepatoduodenal ligament	

ERCP endoscopic retrograde cholangiopancreatography, *PTC* percutaneous transhepatic cholangiography, *EUS* endoscopic ultrasound, *CBD* common bile duct, *SMV* superior mesenteric vein, *SMA* superior mesenteric artery

Definitions/Terminology

- *Extrahepatic Cholangiocarcinoma* (Bismuth/Corlett Classification system) [9].
  - Type 1: Distal to hepatic duct bifurcation *(distal).*
  - Type 2: Involving the bifurcation *(hilar).*
  - Type 3a/3b: Occlusion of common and either right (a) or left hepatic duct (b).
  - Type 4: Multicentric or involve bifurcation and both right and left hepatic ducts.

Special Notes

- Ca 19–9 can be elevated in up to 85% of patients with cholangiocarcinoma, but is not specific; elevation can also occur in the setting of obstructive jaundice without malignancy. If it remains elevated after biliary decompression, it could indicate the presence of malignancy. Elevated pre- and postoperative Ca 19–9 predict poor survival [15].
- For perihilar tumors, decisions regarding which side of the liver to resect depend on right- or left-sided dominance, volume of future liver remnant, and the extent of vascular and ductal involvement.
- Some centers report that 30–50% of tumors will be deemed unresectable at the time of surgery, despite accurate preoperative imaging (see Table 5.5) [11].
- Quality Indicators: Pathologic Analysis—R0 margin, regional lymphadenectomy includes three or more LN.

Special Notes

- In Ontario, all patients with known or suspected cholangiocarcinoma should be referred for management at a high-volume hepatopancreaticobiliary surgical oncology center.
- *Radiologic assessment* should include the following: level of involvement of the biliary tree, extent of vascular involvement, identification of hepatic lobar atrophy, and identification of metastatic disease [17].
- *Role of Frozen Section*: Although frozen section is frequently employed intraoperatively, it has differing uses depending on the type of cholangiocarcinoma.

Table 5.5 Unresectable/metastatic disease

Criteria of unresectability	Management
Metastatic disease: Liver, lung, peritoneum, distant lymph nodes (N2 disease: celiac, SMA nodes) Patient factors: Comorbidities rendering patient unable to tolerate potentially curative surgery Anatomical factors: (adapted from Jarnagin et al. [20], JHPB surgery guidelines [23]) Encasement of bilateral hepatic arteries or proper hepatic artery Extension into secondary biliary radicals bilaterally with no chance for an R0 resection Extension into biliary radicals unilaterally, with contralateral hepatic artery encasement/occlusion or contralateral atrophy of one hepatic lobe Relative contraindication: Atrophy of one hepatic lobe with contralateral portal vein encasement/occlusion—dependent upon the extent of portal vein involvement, this can be resected and reconstructed	Consider transplant candidacy (Mayo protocol) if unresectable for local tumor invasion Consider nonoperative approach to palliation if able (e.g., Stent/PTC placement) [21] and biopsy Consider radiation/chemotherapy options

SMA superior mesenteric artery, *PTC* percutaneous transhepatic cholangiography/catheter

In extrahepatic cholangiocarcinoma, it has a definite mandatory role in determining margin status, unresectability, or the presence of metastases. Frozen section margin status in intrahepatic cholangiocarcinoma is largely academic, as technical limitations dictate whether further margins are possible.

- *Role of Transplant in Hilar Cholangiocarcinoma:*
  - *Mayo Protocol* for patients with unresectable hilar cholangiocarcinoma or cholangiocarcinoma arising de novo in the setting of PSC is offered at UHN.
  - *Exclusion Criteria*—patients with intrahepatic cholangiocarcinoma, intrahepatic or extrahepatic metastases, gall bladder/below cystic duct involvement, tumor size ≥3 cm, age ≥ 65 years old, Hx of malignancy within 5 years, Hx of prior RT in upper abdo, prior hilar dissection within 12 months, any patients who underwent transperitoneal biopsy within 12 months.
  - *Original Mayo protocol*; Preoperative Radiation—40–45 Gy, with concurrent 5-FU, followed by 20–30 Gy transcatheter irradiation with iridium. Capecitabine until transplantation.
  - *UHN Mayo protocol*; Preoperative Radiation—Conformal RT boost, local regional 45 Gy + Boost 54–75 Gy, with concurrent Capecitabine, Gemcitabine + Cisplatin until transplantation.
  - *Preoperative Assessment*—staging laparotomy (patients must be node negative, negative for metastases and no evidence of locally advanced disease). Liberal endoscopic ultrasound and fine needle aspiration of regional nodes have identified occult metastatic disease prior to neoadjuvant therapy.
  - 5-year survival for patients who entered Mayo protocol is 54% and for patients transplanted is 73% [18].
  - Fallout rate is about 30% and median survival after fall out is 6.8 months [19].
- *Role of Medical Oncology*: All patients with a good performance status should be referred to a medical oncologist following resection for consideration of adjuvant systemic chemotherapy. Recent data from the phase III BILCAP trial in the United Kingdom revealed an improvement in median overall survival to 53 months with adjuvant capecitabine compared to 36 months with observation alone (Primose abstract, Ghidini et al.). Subgroup analysis reveals the benefit was present in R0 resections (HR 0.73) and R1 resections (HR 0.90) as well as node negative or node positive disease (2-year OS of 80% vs. 50%). Furthermore, those with perihilar tumors did not benefit from adjuvant therapy in this trial.
- *Quality Indicators*: Margin: tumor margin of at least 5 mm or more [13]. Pathological analysis: regional lymphadenectomy includes 12 or more LN.

Landmark Publications

Prospective RCTs regarding surgical management of this disease are few, due to the relative rarity of the disease. Surgical management is largely dictated by consensus statements formed by large high volume centers (see Table 5.6).

Table 5.6 Landmark publications

Consensus guidelines	*ESMO Clinical Practice guidelines: Biliary Cancer* Eckel et al. [22]		European guidelines
	Clinical Practice Guidelines: JSHBPS Kondo et al. [23]		Japanese guidelines
	AHPBA Summary statement: Hilar Cholangiocarcinoma Clary et al. [24]		North American guidelines
	SIGE/AIGO/AIOM/AIRO Position Paper Alvaro et al. [1]		Italian guidelines
	Study	*Methods*	*Results*
Medical oncology management	*UK-ABC-02* Valle et al. [25] *BILCAP* Primrose et al. [26] *PRODIGE 12-ACCORD 18 UNICANCER GI* Edeline et al. [27]	RCT phase 3 Conducted in 37 centers in the UK *N* = 410 patients Non-resectable, recurrent, or metastatic biliary cancer (included intra−/extrahepatic cholangiocarcinoma, ampullary, gallbladder cancer) Two groups, adjuvant Capecitibine for 24 weeks or observation alone RCT phase 3 Conducted in 44 centers in the UK *N* = 447 patients Resected gallbladder cancer or cholangiocarcinoma (included intra−/extrahepatic cholangiocarcinoma) Two groups, adjuvant Capecitibine for 24 weeks or observation alone RCT phase 3 Conducted in 33 centers in France *N* = 196 patients Resected gallbladder cancer or cholangiocarcinoma (included intra−/extrahepatic cholangiocarcinoma) Two groups, adjuvant GEMOX or observation alone for 12 weeks	Median survival was 11.7 vs. 8.1 months for the Gemcitabine–Cisplatin and Gemcitabine-alone groups, respectively (HR 0.64) Significant improvement in progression-free survival, 8 months vs. 5 months Gem-Cis vs. Gem, respectively (HR 0.63) The combination of Gem-Cis chemotherapy for advanced/metastatic disease gave an average of 3.6 months longer life than gemcitabine alone, with limited toxicity, and represents an appropriate option for treatment in these patients In the per-protocol analysis, median overall survival was 53 vs. 36 months for the capecitabine and observation groups respectively (HR 0.75) Median recurrence-free survival (ITT) was 24.4 months for capecitabine and 17.5 months for observation with a difference in months 0–24 after randomization (HR 0.75). No difference in recurrence-free survival, 30.4 vs. 18.5 months for the GEMOX and observation groups, respectively (HR 0.88) No difference in overall survival, 75.8 vs. 50.4 months for the GEMOX and observation groups, respectively (HR 1.08)

RCT randomized controlled trial, ITT intention-to-treat, GEMOX gemcitabine and oxaliplatinin

Referring to Medical Oncology

1. Resectable and unresectable disease with good performance status.

Referring to Radiation Oncology

1. R1 resection.
2. Palliative patients for consideration of symptomatic control/photodynamic therapy.
3. Locally advanced disease.

Referring to Multidisciplinary Cancer Conference (MCC)

1. R1 resection.
2. Locally advanced disease.
3. Unresectable disease.
4. All potentially resectable cases should be reviewed and treated at a high-volume HPB surgical oncology center.
5. Patients with PSC.
6. Mayo protocol candidate.

Toronto Pearls

- Strongly consider biliary decompression of future remnant liver for hilar tumor preoperatively and wait for near normal bilirubin levels if possible.
- Biliary decompression should occur prior to portal vein embolization (if required).
- Future remnant liver volume > 40% may be required.
- Caudate lobe resection should be considered in all cases, unless drainage of caudate duct into unaffected duct can be confirmed on MRCP and will not compromise surgical margin.
- Biliary infection/sepsis must be treated prior to proceeding to resection.
- Early and aggressive management of biliary infections in the postoperative period, considering drug resistant organisms if patient has had previous preopereative cholangitis and longer term antibiotic treatment AND never request a percutaneous biopsy in unresectable Klatskin's tumors if considering Mayo protocol.

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