CHOLANGIOCARCINOMA AND GALLBLADDER CANCER

Effective Date: March 2019

The recommendations contained in this guideline are a consensus of the Alberta Provincial GI Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the Outpatient Cancer Drug Benefit Program Master List.

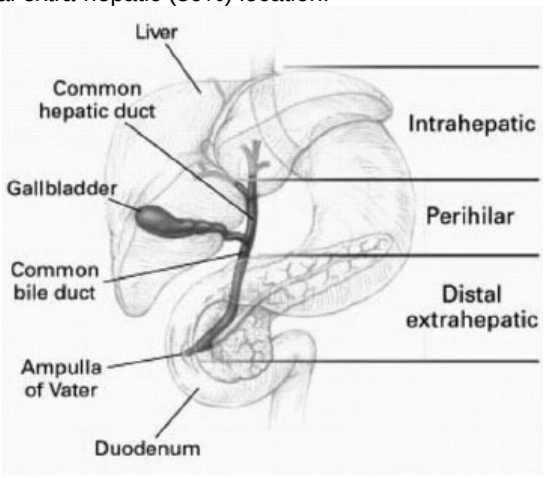
Participation of members of the Alberta Provincial GI Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial GI Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

BACKGROUND

Cancers of the biliary tract are rare tumors. Although surgery for early-stage disease may offer patients a chance for a cure, most cases are inoperable at the time of diagnosis. They often only produce non-specific symptoms (e.g.: nausea, emesis, anorexia, weight loss, abdominal pain, jaundice). Gallbladder carcinomas and cholangiocarcinomas are tumors with different biology. However, due to the relative rarity of each, they are frequently combined in clinical trials.

This guideline was developed to outline the management recommendations for patients with cholangiocarcinoma and adenocarcinoma of the gallbladder. For specific recommendations for the management of malignant biliary obstruction, please refer to the Malignant Biliary Obstruction clinical practice guideline.

Table 1. Comparison of Gallbladder Cancers and Cholangiocarcinomas.

Gallbladder Cancers	Cholangiocarcinomas
• While some gallbladder cancers are discovered incidentally at the time of a cholecystectomy, most present with late-stage disease. • Risk factors include · Cholelithiasis · Ethnicity (especially from Chile, Bolivia, or India) · Female gender · Age · Cigarette smoking · Adenomatous gallbladder polyps · Chronic inflammation of the gallbladder mucosa (e.g.: Isoniazid, primary sclerosing cholangitis, choledochal cysts, anomalous junction of the pancreaticobiliary duct, *Salmonella* or *Opisthorchis* infection) • Local extension is facilitated by the gallbladder's lack of a muscularis mucosa and submucosa, and by its direct venous drainage through the liver parenchyma to the hepatic veins. It may disseminate along the cystic duct, as well as by hematogenous, perineural, and intra-peritoneal spread.	• Present as a solid mass and/or an infiltrative lesion. • Categorized by intra-hepatic (10%), peri-hilar (60%), or distal extra-hepatic (30%) location.  • Risk factors include · Primary sclerosing cholangitis · Chronic inflammation or infection (e.g.: *Clonorchis* or *Opisthorchis* infection, choledochal cysts) · Age · Cirrhosis of any etiology, including viral hepatitis · Exposures to dioxin, vinyl chloride, and nitrosamines • Tumors grow by infiltration along biliary ducts, invasion into perineural and vascular spaces, or direct extension into adjacent structures.

GUIDELINE QUESTIONS

- What are the management recommendations for adult patients with localized and potentially resectable cancers of the biliary tree or gallbladder?
- What are the management recommendations for adult patients with unresectable or metastatic cancers of the biliary tree or gallbladder?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Gastrointestinal Tumour Team. Members of the Alberta Provincial Gastrointestinal Tumour Team include surgical oncologists, radiation oncologists, medical oncologists, hepatologists, gastroenterologists, interventional radiologists, nurses, nurse practitioners, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Gastrointestinal Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in March 2010. This guideline was revised in June 2011, October 2013, October 2016, and March 2019.

SEARCH STRATEGY

This guideline was developed to promote evidence-based practice in Alberta. It was compiled from the results of randomized controlled trials and systematic reviews, derived from an English language and relevant term search of PubMed and MEDLINE from 1990 forward. It takes into consideration related information presented at local, national, and international meetings as well as the Alberta Provincial Gastrointestinal Tumour Team's interpretation of the data. The 2019 update did not necessitate a full literature review and focused on adjuvant therapy. Recommendations were modified based on a consensus discussion at the 2019 Annual Gastrointestinal Tumour Team Meeting.

TARGET POPULATION

The recommendations outlined in this guideline apply to adults over the age of 18 years with cancers of the biliary tree and gallbladder. Different principles may apply to pediatric patients.

RECOMMENDATIONS AND DISCUSSION

Suggested Diagnostic Work-Up

A complete diagnostic work-up provides the multidisciplinary team with the necessary information required to define and offer the optimal care to patients with biliary cancers. The multidisciplinary team should be composed of radiologists, general and hepatobiliary surgeons, gastroenterologists and hepatologists, and oncologists. The diagnostic work-up should evaluate the liver for local and vascular extension/invasion.

Unresectable or metastatic disease represents an incurable situation for which palliative options should be considered.

An abdominal ultrasound confirms biliary duct dilation, localizes the site of obstruction, and excludes gallstones. A three-phase CT scan detects the disease, locates the level of biliary obstruction, and identifies any regional lymphadenopathy or metastatic disease.

Proximal Cholangiocarcinoma and Gallbladder Carcinoma:

To establish resectability, the diagnostic work-up should define the proximal extent of the tumor in both lobes of the liver. This can be achieved with MR cholangiopancreatography (MRCP), but percutaneous transhepatic cholangiography (PTC) may be required. Patients should not undergo percutaneous biopsy prior to surgical assessment.

MR cholangiopancreatography is preferred over an endoscopic retrograde cholangiopancreatogram (ERCP) for proximal tumors because of the lower risk of septic complications. If MRCP is not possible, then PTC is preferred over ERCP. Non-interventional imaging studies (e.g.: MRCP) should precede interventional procedures (e.g.: PTC, ERCP, stent placement).

Endoechosonography obtains a biopsy to distinguish between a benign stricture and a cholangiocarcinoma.

Distal Cholangiocarcinoma:

ERCP is a useful procedure in patients with distal cholangiocarcinomas. MRCP should be reserved for those patients in whom biliary drainage is not imminently required. The other staging procedures are the same as for proximal cholangiocarcinomas.

Staging

Table 2.AJCC TNM Staging Information for Perihilar Bile Duct Cancer, Eighth Edition.

Stage	Depth of Tumour Penetration		Regional Node Involvement		Metastases	
0	T_{is}	Carcinoma *in situ*/high-grade dysplasia	N0	None	M0	Absent
I	T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue	N0	None	M0	Absent
II	T2a-b	T2a: Tumor invades beyond the wall of the bile duct to surrounding adipose tissue T2b: Tumor invades adjacent hepatic parenchyma	N0	None	M0	Absent
IIIA	T3	Tumor invades unilateral branches of the portal vein or hepatic artery	N0	None	M0	Absent
IIIB	T4	Tumor invades the main portal vein or its branches bilaterally, or the common hepatic artery; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement	N0	None	M0	Absent
IIIC	Any T	As described above	N1	1-3 positive nodes*	M0	Absent
IVA	Any T	As described above	N2	≥4 positive nodes*	M0	Absent
IVB	Any T	As described above	N_{any}	As described above	M1	Present

* Typically involving the hilar, cystic duct, common bile duct, hepatic artery, posterior pancreatoduodenal, and portal vein lymph nodes

Table 3a. AJCC TNM Staging Information for Distal Bile Duct Cancer, Eighth Edition.

Stage	TNM
0	T_{is}N0M0
I	T1N0M0
IIA	T1N1M0 T2N0M0
IIB	T2-3N1M0
IIIA	T1-3N2M0
IIIB	T4N(any)M0
IV	T(any)N(any)M1

Table 3b. AJCC TNM Staging Information for Distal Bile Duct Cancer, Eighth Edition.

Depth of Tumour Penetration		Regional Node Involvement		Metastases	
T_{is}	Carcinoma *in situ*/high-grade dysplasia	N0	None	M0	Absent
T1	Tumor invades the bile duct wall with a depth less than 5 mm	N1	1-3 positive nodes	M1	Present
T2	Tumor invades the bile duct wall with a depth of 5-12 mm	N2	≥4 positive nodes		
T3	Tumor invades the bile duct wall with a depth of greater than 12 mm				
T4	Tumor involves the celiac axis, superior mesenteri artery, and/or common hepatic artery				

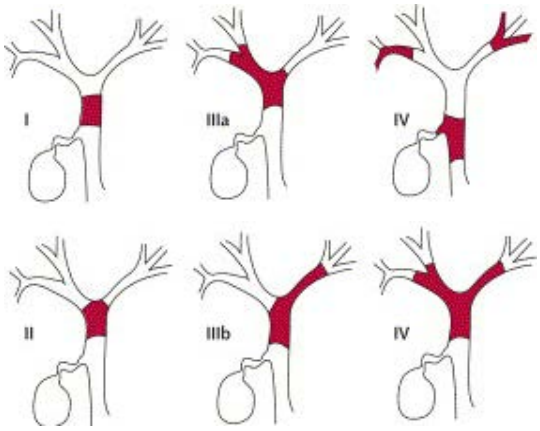
Table 4. AJCC TNM Staging Information for Intrahepatic Bile Duct Cancer, Eighth Edition.

Stage	Depth of Tumour Penetration		Regional Node Involvement		Metastases	
0	T_{is}	Carcinoma *in situ* (intraductal tumor)	N0	None	M0	Absent
IA	T1a	Solitary tumor ≤5 cm without vascular invasion	N0	None	M0	Absent
IB	T1b	Solitary tumor >5 cm without vascular invasion				
II	T2	Solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion	N0	None	M0	Absent
IIIA	T3	Tumor perforating the visceral peritoneum	N0	None	M0	Absent
IIIB	T4	Tumor involving local extrahepatic structures by direct invasion	N0	None	M0	Absent
	Any T	As described above	N1	Regional lymph node metastasis present	M0	Absent
IV	Any T	As described above	N_{any}	As described above	M1	Present

Table 5. AJCC TNM Staging Information for Gallbladder Cancer, Eighth Edition.

Stage	Depth of Tumour Penetration		Regional Node Involvement		Metastases	
0	T_{is}	Carcinoma *in situ*	N0	None	M0	Absent
I	T1	Tumor invades the lamina propria or muscular layer	N0	None	M0	Absent
IIA	T2a	Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum)	N0			
IIB	T2b	Tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver	N0	None	M0	Absent
IIIA	T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts	N0	None	M0	Absent
IIIB	T1-3	See above	N1	Metastases to 1-3 regional lymph nodes	M0	Absent
IVA	T4	Tumor invades the main portal vein or hepatic artery or invades two or more extrahepatic organs or structures	N0-1	Metastases to 0-3 three regional lymph nodes	M0	Absent
IVB	Any T	See above	N2	Metastases to ≥4 regional lymph nodes	M0	
IVB	Any T	See above	N_{any}	See above	M1	Present

Figure 1. Bismuth-Corlette Classification of Biliary Strictures



Type I: Tumour located distal to the confluence of the left and right hepatic ducts (confined to the common hepatic duct)
Type II: Tumour involves the bifurcation of the common hepatic duct but without extension into the right and left hepatic ducts
Type III: Tumour involves the bifurcation of the common hepatic duct and either the right (IIIa) or left (IIIb) hepatic duct
Type IV: Tumour involves both right and left hepatic ducts or displays multifocal growth

Goals of Therapy

To render the patient free of disease, to delay or prevent recurrence, and to improve or prolong survival.

Recommendations

All patients without overt metastatic disease should be referred to a hepatobiliary surgeon or surgical oncologist for assessment of resectability.

Table 6. Recommendations for the Management of Patients with Adenocarcinoma of the Gallbladder or Cholangiocarcinoma.

Stage	Recommendations
Localized and Potentially Resectable Disease	**Adenocarcinoma of the Gallbladder:**[1-5] • If a gallbladder cancer is suspected pre-operatively, an attempt at laparoscopic resection is contraindicated. Refer patients to a hepatobiliary surgeon or surgical oncologist. • For patients with $T_{is\text{-}1a}N_0M_0$ disease identified incidentally at pathologic review of the cholecystectomy specimen, no further therapy is necessary provided an "R_0" margin (microscopically negative) is achieved[6-8]. Resection of the laparoscopic port sites is recommended[9-11]. • When an "R_0" (microscopically negative) margin is anticipated for $T_{2\text{-}3}N_0M_0$ disease, a hepatobiliary surgeon or surgical oncologist may consider a partial hepatectomy with peri-portal lymph node dissection. Consider a laparoscopy to exclude previously unrecognized peritoneal metastases before proceeding to laparotomy[12]. The role of radical surgery is controversial for T_{1b} tumors. **Cholangiocarcinoma:**[13-15] • Assessment for resectability should precede instrumentation (e.g.: ERCP, PTC) and biopsy. • Resectability depends upon the extent of tumor within the biliary tree and hepatic parenchyma as well as the absence of invasion into the vasculature, unilateral hepatic lobar atrophy with contralateral extension of disease into the segmental bile ducts, regional lymphadenopathy, and metastatic disease. • For tumors that involve the confluence of the bile ducts, an "R_0" resection involves excision of the tumor, regional lymphadenectomy, cholecystectomy, and (often) partial hepatectomy (possibly to include the caudate lobe). • When an "R_0" (microscopically negative) margin is anticipated, lesions distal to the cystic duct require a pancreaticoduodenectomy. Multidisciplinary assessment by hepatology, radiology, and hepatobiliary surgery is crucial. Patients who are poor candidates for surgical resection may be offered locoregional therapy or other approaches.
	• The BILCAP trial demonstrated an improvement in overall survival (OS) in the per protocol analysis for patients randomized to 8 cycles of capecitabine versus observation after complete resection of cholangiocarcinoma or gallbladder, median OS was 53 months for Capecitabine and 36 months for Observation, HR 0.75 (95%CI 0.58- 0.97; p = 0.028). In this trial, patients with ECOG PS ≤2, were randomized 1:1 to Capecitabine (1250 mg/m2 D1-14 every 21 days, for 8 cycles) or observation [n=447, resection margins: R0 in 279 (62%) and R1 in 168 (38%); 207 (46%) were node-negative. In the intent to treat population, there was a clinically relevant improvement in OS (median OS 51 months with capecitabine versus 36 months for observation, HR 0.80, $CI_{95\%}$ 0.63-1.04; p = 0.097). Sensitivity analyses with adjustment for nodal status, grade of disease and gender indicated HR 0.71 (95%CI 0.55 -0.92 p < 0.01)[16,17]. The dose of capecitabine may be determined by institutional and regional practices.
Unresectable or Metastatic Disease	• Offer palliative maneuvers to maintain and/or improve quality of life. Once resection has been deemed impossible, relieve biliary obstruction (if possible) by stent placement via either ERCP or PTC. In certain circumstances, radiotherapy or palliative surgery may be considered. • Tissue diagnosis is important to confirm the histology and for potential involvement in clinical trials. Patients with adenocarcinoma of the gallbladder, cholangiocarcinoma, and combined hepatocellular-cholangiocarcinoma are treated similarly, although the prognosis may vary according to the subtype. • In patients with adequate biliary drainage, acceptable liver and kidney function, and a reasonable performance status (ECOG ≤ 2), the administration of up to eight twenty-one day cycles of Cisplatin 25 mg/m^2 IV and Gemcitabine 1,000 mg/m^2 IV on days one and eight prolongs progression-free survival from 6.5 months to 8.4 months (HR 0.72, $CI_{95\%}$ 0.57-0.90, p = 0.003) and overall survival from 8.3 months to 11.7 months (HR 0.70, $CI_{95\%}$ 0.54-0.89, p = 0.002) when compared to Gemcitabine alone[18].

Table 7. ECOG Performance Status Scale

ECOG	Description of Performance Status
0	Fully active and able to carry on without restriction.
1	Unable to carry out physically strenuous activities but ambulatory and able to complete work of a light or sedentary nature.
2	Ambulatory and capable of all self-care but unable to complete work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care and/or confined to a bed or chair for more than 50% of waking hours.
4	Completely disabled. Unable to carry out any self-care. Totally confined to a bed or chair.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
CI	confidence interval
CT	computed tomography
ECOG	Eastern Cooperative Oncology Group
ERCP	endoscopic retrograde cholangiopancreatogram
HR	hazard ratio
IV	intravenous
MR	magnetic resonance
MRCP	magnetic resonance cholangiopancreatography
PTC	percutaneous transhepatic cholangiography
TNM	tumour-node-metastasis

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2021. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

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