Clinical practice guidelines have been developed after multi-disciplinary consensus based on best available literature. As the name suggests, these are to be used as a guide only. The purpose of guideline is to develop the consensus opinion of cancer specialists and allied health professionals in an attempt to define best care practices and to improve care and outcomes for patients with gastrointestinal cancers. These guidelines do not replace physician judgment which is based on multiple factors including, but not limited to, the clinical and social scenario, co morbidities, performance status, age, available resources and funding considerations. Participating in clinical trials is encouraged when available.

Recommendations for drug treatment presented in the Agency’s guidelines for a cancer site may not reflect provincial cancer drug funding. Please refer to the current Saskatchewan Cancer Agency drug formulary at www.saskcancer.ca for information on cancer drug listing and funding.

Benefits and risk of the proposed treatment should be discussed with patient.

Participating in clinical trials is encouraged when available. Involvement of a multidisciplinary team is strongly recommended.

- Biliary tract and gall bladder cancers are uncommon gastrointestinal malignancies. Biliary tract cancers include hilar (Klatskin tumors), perihilar, distal (extra-hepatic), and intra-hepatic cholangiocarcinoma.
- Whereas gallbladder cancer is more common in women, the incidence of cholangiocarcinoma is slightly higher in men. The incidence of biliary tract cancers increases with age and is usually diagnosed between 50 and 70 years of age. However, patients with primary sclerosing cholangitis and those with choledochal cysts present nearly two decades earlier.
- The incidence of intrahepatic cholangiocarcinoma has been rising, while rates of extrahepatic cholangiocarcinoma are declining globally. Primary sclerosing cholangitis and choledochal cysts are the major risk factors for biliary tract cancers in the Western countries.
- The geographic variation in gall bladder cancer incidence correlates with the prevalence of gall stones. Several risk factors have been reported, many of which share a common characteristic of chronic gallbladder inflammation such as gallstone disease, gallbladder polyps and congenital biliary cysts, anomalous pancreaticobiliary junction, and chronic infection.
- More than 90 percent of biliary tract and gall bladder cancers are adenocarcinomas, squamous cell cancer is the second most common histology.

A. ASSESSMENT AND INVESTIGATIONS

- Given the complex nature of biliary tract and gall bladder cancer management, all patients should be evaluated by a multidisciplinary team including radiologists, pathologists, gastroenterologists, surgeons, medical oncologists, interventional radiologists, radiation oncologists, nuclear medicine specialists, psychiatrists and palliative care specialists (in advanced disease). When a case of biliary tract or gall bladder cancer is referred to a specialist surgeon, the surgeon should see the patient in 1-2 weeks and discuss it in
multidisciplinary conference. If a patient is ready for resection, surgery scheduling should best be targeted within 1 month and should be performed by a specialty-trained surgeon in hepatobiliary surgery at an academic center.

- Staging is based on the AJCC TNM system. T signifies depth and invasion into adjacent structures, N status describes lymph node status and M indicates metastatic disease. Hilar cholangiocarcinoma (Klatskin’s tumor) is clinically staged depending on the involvement of the hepatic ducts according to the Bismuth–Corlette classification (see section B1).
- Clinical staging involves a combination of clinical and radiological investigations outlined below. The purpose of which is to determine which patients are potentially curable and those that are not.
  - History and physical examination
  - Review of medication
  - Nutritional evaluation
  - Complete blood count (CBC), liver function test (LFT), metabolic profile and tumor markers
  - CT scan abdomen, pelvis and chest
  - MRI combined with magnetic resonance cholangiopancreatography (MRCP) is a noninvasive technique for evaluating the intrahepatic and extrahepatic bile ducts and the pancreatic duct.
  - Cholangiography: Preoperative cholangiography may be indicated either diagnostically or therapeutically for patients with biliary obstruction and can be performed by endoscopic retrograde pancreatography (ERCP) or via a percutaneous approach i.e. percutaneous transhepatic cholangiogram (PTC).
  - Endoscopic ultrasound examination: For distal bile duct lesions to visualize extent of the primary tumor and the status of regional lymph nodes. EUS-guided fine needle biopsy of tumors and enlarged nodes can also be performed. EUS with fine needle aspiration biopsy has a greater sensitivity for detecting malignancy in distal tumors than does ERCP with brushings.
  - Positron emission tomography (PET) scan: PET scan permits visualization of cholangiocarcinomas because of the high glucose uptake of bile duct epithelium and can be helpful to identifying occult metastases.
  - Laparoscopic exploration for sub-radiological metastasis is an option before definitive surgery.
  - It is reasonable to pursue surgical resection based on radiological and clinical findings, in the absence of pathological confirmation of cancer.
  - Tissue diagnosis is important for biliary strictures of clinically indeterminate origin or prior to chemotherapy or radiation therapy, particularly if the patient will be enrolling on a therapeutic clinical. Metastatic lesions can be biopsied percutaneously under ultrasound or CT guidance or during EUS.

B. SURGICAL APPROACHES

B1. Cholangiocarcinoma

- Surgical management of intrahepatic cholangiocarcinoma is similar to liver cancers, while distal common bile duct (CBD) cholangiocarcinoma management is similar to pancreatic head (peripapillary) cancer. Rarely, a mid bile duct tumor can be resected with a bile duct resection and regional lymphadenectomy.
- Surgery is the only curative treatment for patients with cholangiocarcinoma. Surgery cures the minority of patients with cholangiocarcinoma, with a 9–18% five year survival for proximal bile duct lesions and 20–30% for distal lesions.
Pre-operative biliary drainage of the future liver remnant (FLR) and contralateral portal vein embolization (PVE) should be considered in cases of a small future liver remnant.

Frozen section assessment of proximal and distal bile duct margins is recommended.

Thorough dissection (skeletonization of hepato-duodenum ligament) should be emphasized.

Multi-focal liver disease is generally contraindication to resection, except highly selected cases with limited multi-focal disease. Gross lymph node metastases to the porta hepatis is contraindication to resection except in highly selected cases.

For Klatskin tumors the Bismuth classification is a guide to the extent of surgery required (aim is tumor free margin of >5 mm). The basic principle is that the tumor is resected along with the involved biliary tree and the involved hemi-liver with a reasonable chance of a R0 resection, while contra-lateral liver requires intact arterial and portal inflow as well as biliary drainage.

- Types I and II: en bloc resection of the extrahepatic bile ducts and gall bladder, regional lymphadenectomy, and Roux-en-Y hepaticojejunostomy;
- Type III: as above plus right or left hepatectomy;
- Type IV: as above plus extended right or left hepatectomy.
- Segment 1 of the liver may preferentially harbor metastatic disease from hilar cholangiocarcinoma and removal should be considered with Types II–IV.
- Resection and reconstruction of portal vein or/and hepatic artery may be necessary, and is acceptable for R0 resection.

B2. Gallbladder cancer

- Principles of resection consist of radical cholecystectomy including segments IV B and V and hepatoduodenal ligament lymphadenectomy and extended hepatic or biliary resection as necessary to obtain R0 resection. In other words, if preoperative assessment confirms distance metastasis or if R0 resection is not possible palliative therapy should be considered.
- When incidentally found on routine cholecystectomy while no expertise is available, the patient should be referred to an academic center. However, if expertise is available, definitive resection should be performed with or without intra-operative frozen section to confirm the diagnosis.
- When incidentally found on postoperative pathology after cholecystectomy, review of operative note and/or communication with operating surgeon is suggested for pertinent information, such as completeness of cholecystectomy, signs of disseminated disease, location of tumor, etc. Review of pathology regarding T stage, cystic duct margin status and other margins, is recommended. Cross-sectional imaging of the chest, abdomen and pelvis should be performed. If there is no distant metastasis, lymph node metastases in the celiac axis or aorto-caval groove, radical surgery should be performed for ≥T1b tumors. Port site resection did not show to improve outcomes.
- When a gallbladder mass is found on pre-operative ultrasound, a cross-section imaging should be performed. Percutaneous biopsy is not recommended. However, laparoscopic exploration with cholecystectomy and intraoperative frozen section is useful, while definitive radical resection is prepared.

C. ADJUVANT THERAPY IN LOCALIZED DISEASE (RESECTABLE)

- The role of adjuvant chemoradiation therapy or chemotherapy for resected biliary tract cancers and gallbladder cancer has not been clearly established. Retrospective reports suggest a survival advantage for adjuvant therapy. A Japanese phase III trial involving 508 patients with resected pancreatoco-biliary cancer randomly assigned two cycles of intravenous mitomycin and 5-FU (MF) followed by maintenance oral 5-FU till disease recurrence or observation. In a sub-group of 140 patients with gall bladder cancer, 5-year
disease-free survival (20.3% vs. 11.6%) and overall survival (26 vs. 14.4%) rates were significantly better in the adjuvant therapy group compared with observation. A systemic review and meta-analysis showed an improvement in overall survival for patients who received chemoradiation or chemotherapy especially in patients with lymph node positive disease and macroscopic residual disease. There was a significant survival benefit for chemoradiotherapy (OR 0.39, 95% CI 0.23-0.66) and chemoradiotherapy (OR 0.61, 95% CI 0.38-0.99) but not RT alone (OR 0.98, 95% CI 0.67-1.43).

- As both gallbladder and biliary tract cancer present a high incidence of local failure after surgical resection, despite limited evidence a locoregional adjuvant treatment may be considered.

C1. Extrahepatic Cholangiocarcinoma

- Negative margin (R0) and node negative disease: Observation alone is appropriate, alternatively fluoropyrimidine chemoradiation or fluorouracil-based or gemcitabine-based chemotherapy for six months can be considered.
- Positive margin, or positive regional nodes: Consider fluoropyrimidine chemoradiation followed by an additional fluoropyrimidine-based or gemcitabine-based chemotherapy or fluorouracil-based or gemcitabine based chemotherapy for total six months.

C2. Intrahepatic Cholangiocarcinoma

- Negative margin and node negative disease: Observation alone is appropriate.
- Microscopic margins (R1) or positive regional nodes: Consider fluoropyrimidine chemoradiation or fluoropyrimidine-based or gemcitabine based chemotherapy for six months.

C3. Gallbladder Cancer

- For T1a or T1b N0 disease observation alone is appropriate. For tumor greater than T1b or node positive disease considers fluorouracil-based chemoradiation or fluorouracil or gemcitabine-based chemotherapy.

D. NEOADJUVANT THERAPY

- Neoadjuvant therapy is not recommended for surgically resectable disease. However, if restaging in patients with locally advanced disease shows potentially resectable tumors (conversion therapy), resection should be considered.

E. FOLLOW UP AFTER SURGICAL RESECTION

There is lack of evidence that early detection of asymptomatic recurrence by imaging study or tumor marker may be associated with better clinical outcome or survival. Follow-up investigations should be individualized based on stage of the cancer, adjuvant treatment provided, performance status, and clinical signs and symptoms. There is lack of level 1 evidence with respect to optimal follow up of patients with biliary tract and gall bladder cancer who are treated with curative intention.

- In patients treated with curative intent consider history and physical examination every 3–6 months for the first 3 years then every 6–12 months for the next 2 years and annually thereafter. All patients should be educated to seek medical attention if they developed abnormal symptoms.
• Laboratory testing including CBC, serum chemistry, LFT, and tumor marker (CEA, CA19-9) as clinically indicated.
• Routine imaging studies and endoscopic examination are not recommended and can be performed as clinically indicated.

F. MANAGEMENT OF LOCALLY ADVANCED UNRESECTABLE NONMETASTATIC DISEASE OR R2 RESECTION (RESIDUAL DISEASE)

• Between 50 and 90 percent of patients with cholangiocarcinoma present with locally unresectable disease. The optimal management of these patients is controversial, and there is no internationally-embraced standard approach.
• The options for patients with locally advanced gall bladder and biliary tract cancers include fluoropyrimidine chemoradiation or gemcitabine-based (such as gemcitabine/cisplatin combination) or fluoropyrimidine-based chemotherapy.
• For patients with unresectable intrahepatic cholangiocarcinoma, nonsurgical methods of tumor ablation which may provide adequate local palliation. Patients who are unsuitable for other treatments may be considered for chemoembolization. There are a few case series suggestive of a benefit of ablation therapy in this group of patients.

G. MANAGEMENT OF ADVANCED DISEASE

G1. Systemic therapy

G1A. First line therapy

• For patients with metastatic biliary tract and gallbladder cancer, the combination of cisplatin/gemcitabine chemotherapy is considered to be standard first line systemic therapy. This is based on the result of a randomized clinical trial (ABC-02 study) which showed an improvement in outcomes of patients with locally advanced or metastatic biliary tract and gallbladder cancer treated with combination therapy. In this trial, 410 patients with locally advanced (25 percent) or metastatic bile duct (n = 242), gallbladder (n = 148) or ampullary (n = 20) cancer were randomly assigned to eight courses of cisplatin (25 mg/m²) followed by gemcitabine (1000 mg/m² on days 1 and 8, every 21 days, or gemcitabine alone (1000 mg/m² days 1, 8, 15, every 28 days). At a median follow-up of 8.2 months, median progression free survival (8 versus 5 months) and median overall survival (11.7 versus 8.1 months) were better with combination therapy.
• Other fluorouracil-based or gemcitabine based chemotherapy regimens are additional options in metastatic biliary tract or gallbladder cancer. Monotherapy with gemcitabine or capecitabine/5-FU can be considered in patients who are not a candidate for combination therapy.

G1B. Second line therapy

• There is no standard 2nd line therapy. In patients with good performance status 5-FU/capecitabine or taxanes based therapy may be considered following progression on cisplatin/gemcitabine.

G2. Supportive Care

• Palliation of jaundice can be accomplished by endoscopic or percutaneous stenting of the biliary tree or by operative biliary-enteric bypass.
• Percutaneous transhepatic biliary drainage is recommended if endoscopic treatment is not possible.
• Prophylactic antibiotics to reduce rates of cholangitis in patients receiving an endoscopically placed plastic or metal stent for long-term palliation of obstructive jaundice after the first episode of cholangitis may be considered.
• Palliative radiotherapy should be considered for symptom management on a case by case basis.
• Palliative care team should be involved, early in patients care, for pain and symptoms management. Nutrition and psychosocial support should be provided to the patients and their family.

H. REFERENCES

Additional resources

www.nccn.org

www.cancer.gov

www.bccancer.bc.ca

www.esmo.org

www.uptodate.com

Canadian Cancer Trial www.canadiancancertrials.ca/Default.

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