PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

GASTROINTESTINAL

BILIARY TRACT CANCERS

GI Site Group – Biliary Tract Cancers

Authors: Dr. Jennifer Knox, Dr. Mairead McNamara

These guidelines are evidence-based and thus subject to change. Some recommendations are currently funded in this jurisdiction, while others are in negotiation.

1. Introduction

Cholangiocarcinomas, which refers to cancers arising in the intrahepatic, perihilar (klatskin), or distal biliary tree and gallbladder carcinoma (GBC) are highly lethal. Cholangiocarcinomas constitute approximately 2% of all reported cancer, and account for about 3% of all gastrointestinal malignancies. Gallbladder carcinoma is the fifth most common malignancy of the gastrointestinal tract and is the most common biliary tract neoplasm, with an annual incidence in the United States of almost 10,000 and annual mortality of 3,300.

2. Screening and early detection

Conditions that are associated with an increased risk of cholangiocarcinoma include primary sclerosing cholangitis with an increased incidence in patients with inflammatory bowel disease, choledochal cysts, germline mutations in BRCA2 and mismatch repair genes, and other hepatic infections.

Gallstones increase the risk of cancers of the gallbladder and calcification of the gallbladder (porcelain gallbladder), a result of chronic inflammation, has also been associated with gallbladder cancer. Gallbladder polyps >1cm are thought to have an associated risk of malignancy. Surveillance can be recommended for polyps <1cm and cholecystectomy is recommended for polyps >1cm. However, there are no official screening recommendations for either cholangiocarcinoma or gallbladder carcinoma.

3. Diagnosis

Diagnosis of biliary tract cancers should be made on the basis of radiological investigations, MRI/CT, pathological diagnosis from a biopsy, fine-needle aspiration or biliary brush cytology. This occasionally requires more than one attempt. Benign inflammatory processes can masquerade as biliary cancer. CEA and CA 19-9 can be considered, although these markers are not specific for gallbladder cancer or cholangiocarcinomas. Final pathological diagnosis is not critical for planning surgery in patients with characteristic findings of resectable biliary cancer.

4. Pathology

More than 90% of cholangiocarcinomas are adenocarcinomas and can be divided into 3 types depending on macroscopic appearance: mass-forming, periductal, and intraductal. The AJCC and UICC staging systems (Hepatobiliary cancers) for cholangiocarcinomas and gallbladder carcinoma are available online at www.nccn.org

Approximately 80% of gallbladder cancers are adenocarcinomas and the AJCC and UICC TNM staging (Hepatobiliary cancers) is available online at www.nccn.org

5. Management

5.1 Surgery

5.1.1 Gallbladder cancer

A radical re-resection (after a complete staging including laparoscopy demonstrating resectability) is highly recommended for patients with **incidental gallbladder carcinoma** stage T1b (tumour invades muscle layer) or greater **on pathological review**.

After **incidental finding of gallbladder cancer at surgery**, staging has to be performed intraoperatively and extended cholecystectomy including en bloc hepatic resection and lymphadenectomy with or without bile duct excision has to be considered.

Resection of gallbladder cancer consists of extended cholecystectomy including en bloc hepatic resection and lymphadenectomy (porta hepatic, gastrohepatic ligament, retroduodenal) with or without bile duct excision.

5.1.2 Cholangiocarcinoma

Major hepatectomy including caudate lobectomy such as extended right lobe resection will increase resectability for stage 3 and 4 hilar cholangiocarcinomas. Pre-operative biliary drainage is often indicated prior to resection, with endoscopic stenting preferred over percutaneous drainage in potentially resectable cases where feasible. Vascular resection, including resection and reconstruction of the portal vein, increases the resectability rate of advanced hilar cholangiocarcinomas and can be performed with low perioperative morbidity. For peripheral cholangiocarcinoma, anatomic hepatic resection with/or without portal lymphadenectomy is indicated. Preoperative portal vein embolization increases the remnant liver volume in patients with estimated post-resection volumes of <25% and appears to reduce postoperative liver dysfunction.

5.1.3 Role of liver transplantation in patients with a diagnosis of biliary tract cancer

Liver transplantation is indicated under strict protocols at selected centres, for patients with early stage histologically confirmed hilar cholangiocarcinoma that are anatomically unresectable.

5.2 Adjuvant therapy

A recent systematic review and meta-analysis looking at the impact of adjuvant therapy (chemotherapy or chemoradiotherapy) on survival of biliary tract cancer patients indicated that the greatest benefit for adjuvant therapy was in those with lymph node positive disease and R1 disease (Horgan et al., 2012). This review suggested that for node positive disease, the evidence supports chemotherapy as an adjuvant approach and that the addition of radiation has no proven benefit. Prospective clinical trials are underway. **Until further data, appropriate patients will be considered for adjuvant**

5-FU or gemcitabine-based chemotherapy. Currently there is no data supporting adjuvant therapy for intrahepatic biliary cancers.

Additive fluorouracil-based chemotherapy has been associated with a small survival benefit after *noncurative resection* of gallbladder cancer. The National Comprehensive Cancer Network guidelines suggest adjuvant concurrent 5-FU-based chemoradiotherapy in patients with positive margins, carcinoma in situ at the margins, or positive lymph nodes after resection for cholangiocarcinoma followed or not by additional fluoropyrimidine or gemcitabine–based regimens. See guidelines for hepatobiliary cancers on www.nccn.org

Postoperative treatment after noncurative (R2) resection of cholangiocarcinoma remains controversial, and both supportive care and palliative chemotherapy and/or radiotherapy may be taken into consideration.

5.3 Treatment of unresectable biliary tract cancers

Palliation of jaundice by appropriate endoscopic or percutaneous stenting of the biliary tree or by operative biliary-enteric bypass is indicated. Considerations should be given to best stenting techniques and devices to provide longer term decompression and therefore the chance to receive further therapies. Metal prostheses are generally preferred for patients with a life expectancy of greater than 3 months since they present fewer complications (occlusions) than plastic endoprostheses. Metal prostheses are preferred for patients with a life expectancy of greater than 3 months since they present fewer complications (occlusions) than plastic endoprostheses.

Urgent biliary drainage and broad-spectrum antibiotics are crucial in patients with cholangitis due to obstructive jaundice.

The UK ABC-02 trial established a new standard of care in the treatment of advanced biliary cancers and cisplatin (25 mg/m^2) followed by gemcitabine (1000 mg/m^2), administered day 1 and 8 every three weeks for 8 cycles is now an appropriate first-line option for the treatment of patients with advanced biliary cancer (Valle et al., 2010) and this is funded in Ontario. Patients can also be treated until progression or with drug holidays and surveillance. For select patients where cisplatin/gemcitabine is contraindicated other platinum-based or gemcitabine-based combinations are appropriate, however one may be limited by funding issues.

Patients who have an impressive and durable response to chemotherapy can be considered for "consolidative" approaches such as surgical resection or radiotherapy although level of evidence supporting these approaches in advanced disease is limited.

5.4 Second line chemotherapy in advanced biliary tract cancer

The benefits of second line chemotherapy in advanced biliary tract cancer are unclear. A recent large retrospective study indicated that outside a clinical study, patients with a

good performance status (PS 0-1) progressing after cisplati/gemcitabine may be considered for a 5-fluorouracil (5-FU) based doublet such as FOLFIRI or 5-FU alone or gemcitabine plus capecitabine or erlotinib (Walter et al., 2012). Enrollment on appropriate clinical trials is strongly supported or consideration of palliative radiotherapy where symptomatic.

5.5 Oncology Nursing

Refer to general oncology nursing practices

6. Palliative therapy

Best supportive care measures should be administered to patients with unresectable/inoperable disease who are not candidates for other therapies.

7. Supportive Care

7.1 Patient Education

Refer to general patient education practices

7.2 Psychosocial Care

Refer to general psychosocial oncology care guidelines

7.3 Symptom Management

Refer to general symptom management care guidelines

7.4 Clinical Nutrition

Refer to general clinical nutrition care guidelines

7.5 Palliative Care

Refer to general oncology palliative care guidelines

8. Follow-up Care

Follow up of patients undergoing resection of **cholangiocarcinoma** or **gallbladder carcinoma** include consideration of imaging studies every 6 months for 2 years. Re-evaluation according to the workup should be considered in the event of disease progression.

Response evaluation during treatment for **advanced biliary tract cancer** is recommended after two or three cycles (8-12 weeks) of chemotherapy by clinical evaluation, subjective symptom evaluation, blood tests and repeating the initially abnormal radiological or ultrasound examinations.

9. References

Horgan AM, Amir E, Walter T et al. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. J Clin Oncol 30: 1934-1940, 2012.

Valle J, Wasan H, Palmer DH et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 362: 1273-1281, 2010.

Walter T, Horgan A, McNamara M et al. Feasibility and benefits of second-line chemotherapy in advanced biliary tract cancer: a large retrospective study. Eur J Cancer 49: 329-335, 2013.