Barts Health NHS
NHS Trust

LONDON CANCER
NORTH AND EAST

NHS
Royal Free London
NHS Foundation Trust

London Cancer

Hepatic Pancreatic and Biliary (HPB) Faculty

Management of Patients with Suspected Cholangiocarcinoma **CLINICAL GUIDELINES**

JULY 2014

This operational policy is agreed and accepted by:

Designated individuals

HPB Pathway Director

Dr Andrew Millar

Pancreatic Tumour Specific Group

Prof Massimo Malagó (chair, surgeon)

Dr Michael Chapman (gastroenterologist)

Mr Satya Battacharya (surgeon)

Mr Robert Hutchins (surgeon)

Dr Roopinder Gillmore (medical oncologist)

Contents

1. MDT coordinator and CNS contact details

1.1 CNS Royal Free Hospital (RFH)

Claire Frier (020 7794 0500 Extension: 31405, Bleep: 1066, claire.frier@nhs.net)

Paula Noone (020 7794 0500 Extension: 33762, Bleep: 2648, paula.noone@nhs.net)

Gemma Keating (020 7794 0500 Extension: 33838, Bleep: 2721, gemmakeating@nhs.net)

1.2 CNS Royal London Hospital (RLH)

Karen Mawire (020 35945696, Karen.mawire@bartshealth.nhs.uk)

Katie Ryan (020 35940759, Kathleen.ryan@bartshealth.nhs.uk)

Rosie Hesling (020 35945740, rosie.hesling@bartshealth.nhs.uk)

1.3 MDT -coordinator RFH

Scott Green (020 7794 0500 Ext: 35812, ScottGreen@nhs.net)

1.4 MDT -coordinator RLH

Sally Howe (020 35940762, sally.howe@bartshealth.nhs.uk, emma.grimshaw@bartshealth.nhs.uk)

2. BACKGROUND

These (DRAFT) guidelines are based upon the BSG guidelines for the treatment of cholangiocarcinoma (CCA) (Khan et al, 2012) and have been adapted to the regional environment of the London Cancer network.

2.1 Introduction

- Cholangiocarcinoma (CCA) is uncommon and often difficult to diagnose. Inappropriate early management can be detrimental to patient care.
- All cases of suspected CCA should be discussed at the specialist hepato-pancreatico-biliary multi-disciplinary meeting (sHPB-MDM).
- Ampullary cancers and distal bile duct cancers (below the common hepatic duct) are discussed in the pancreas section of the s HPB-MDM.
- Clinicians unfamiliar with the management of suspected CCA should refer patients to a local or regional specialist team.
- Initial management for all patients with CCA should be guided exclusively by the sMDT.

2.2 Definition and Classification

- Biliary tract cancer includes primary adenocarcinomas of the bile duct epithelium (cholangiocarcinoma)and gallbladder.
- Cholangiocarcinoma is classified by ICD codes byintra or extrahepatic location, (ICD-9 155.1, ICD-9 156). However, this classification less clinically useful than the commonly adopted anatomic classification below. The following classification should be used for clinical purposes within the London Cancer network
    - Intra-hepatic (IHCCA)
    - Extrahepatic perihilar CCA
    - Extrahepatic distal CCA
    - Gallbladder carcinoma
- Ampullary cancer is formally sub-classified as a biliary tract cancer but for clinical purposes will be managed as part of the pancreatic cancer guidelines.

For the purposes of good clinical practice, these cholangiocarcinoma guidelines will be divided into management of tumours at three anatomic locations

2.3 Clinical Nurse Specialists

- All patients should be allocated to a CNS to help guide the patients through their care. A direct contact number should be offered to all patients.

2.4 Oncology

- All patients should be offered oncology review if clinically appropriate
- Standard of care for chemotherapy is combination of gemcitabine and cisplatin but regimens may change based on patient related factors and future clinical trials

2.5 Nutrition

- All patients should be screened for under-nutrition using a screening tools such as simple estimate of weight loss or the MUST tool.
- Patients with suspicion of under-nutrition should be referred for dietician review.

2.6 Palliative care

- All patients who have not had successful curative surgery, or are not eligible for chemotherapy should be made aware of and offered contact details with the local palliative care team.

3. INTRA-HEPATIC CHOLANGIOCARCINOMA (IHCCA)

3.1 Clinical presentation

- Most patients with IHCCA present with vague nonspecific symptoms or with an 'incidental' finding on ultrasound or cross sectional imaging.
- Biliary obstruction is a relatively rare and late event
- Pain and weight loss suggests advanced disease or infiltration of adjacent organs

3.2 Investigation

- All patients with suspected IHCCA should have blood tests analysed including simple biochemistry (including liver function tests), FBC, INR and serum CA19.9 and AFP. Additional blood tests such as other tumour marker and IgG4 levels should be done if clinically indicated.
- Most patients will have an ultrasound at presentation; further evaluation and staging require contrast enhanced CT (arterial and portal venous phase for resectability) and/or MR (need MRCP to determine extend of stricture).
- Patients deemed potentially suitable for surgical resection should have staging CT of the chest and pelvis to exclude metastatic disease.

3.3 Diagnosis and Staging

- IHCCA most frequently arises in non-cirrhotic liver and presents as single or multiple intrahepatic tumours without evidence of other primary extra--hepatic tumours
- A biopsy is the gold standard tool to diagnose IHCCA in appropriate clinical and radiological setting.
- Review of histopathology and immunohistochemistry at the specialist HPB MDT is recommended for all cases.
- TNM staging has prognostic significance in IHCCA (see table in Appendix)

3.4 Management

- Initial management for all patients with IHCCA should be guided by the sMDT
- Indication and selection for surgical management (the only potentially curative option) is the primary initial question to be addressed by the sMDM.
- Potentially resectable cases must be discussed at sMDM and liver volumetric assessment determined when appropriate
- A plan for surgical resection will be made via the sMDM and direct review by the HPB surgery clinic.
- Unresectable patients should be considered for palliative chemotherapy as indicated by the sMDM or for symptomatic palliative treatment
- Further management may be managed by the primary responsible clinician and re-discussed at sMDM as necessary

4. EXTRAHEPATIC DISTAL CHOLANGIOCARCINOMA

4.1 Clinical presentation

- Most patients with Distal CCA present with jaundice and biliary obstruction or an incidental finding of a periampullary mass or dilatation of the extrahepatic biliary tree on imaging

4.2 Management

The diagnosis and management follow pathways that are similar to tumours of the head of the pancreas unless otherwise directed by the sMDT. See pancreatic cancer guidelines for further guidance.

5. EXTRAHEPATIC PERI-HILAR CHOLANGIOCARICNOMA (hilar CCA)

5.1 Clinical presentation

- Most patients with hilar CCA present with jaundice and biliary obstruction or an incidental finding of a mass or dilatation of the biliary tree on imaging. Some patient have pruritis
- Cholangitis is uncommon without prior biliary intervention.
- Pain and weight loss suggests advanced disease

5.2 Investigation

- All patients with suspected hilar CCA should have blood tests analysed including simple biochemistry (including liver function tests), FBC, INR and serum CA19.9. CA19-9 is elevated in approximately 75% to 85% of patients with CCA and has a specificity of 50-80%. There is no evidence that measurement of tumour markers is useful for monitoring tumour progression
- IgG4 levels shall be obtained whenever an autoimmune cholangitis is suspected (eg, with evidence of more extensive cholangiopathy, abnormal pancreas or pancreatopathy, and/or

evidence of associated distant autoimmune disease). When strongly suspected, ampullary biopsies for tissue IgG4 staining are positive in up to 70% of cases of IgG4 disease.

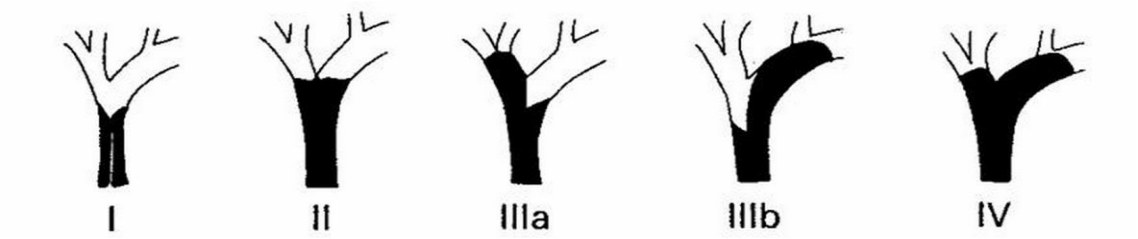
- Most patients will have an ultrasound at presentation and require contrast enhanced CT (arterial and portal venous phase to assess for resectabily) and MRCP for further evaluation and staging.
- Patients deemed potentially suitable for surgical resection should have staging CT of the chest and pelvis to exclude metastatic disease.
- PET scanning is usually not required for diagnosis or staging of CCA but may provide supportive information for some diagnostic difficulties such as the nature of distant lesions.

5.3 Diagnosis

- Hilar CCA can be difficult to differentiate from benign causes of biliary stricture such as PSC, IgG4 disease an ischaemic bile duct injuries. If there is significant clinical concern about differential diagnoses then patients require thorough evaluation to confirm or exclude these conditions
- Serum (and tissue) IgG4 levels should be measured in all patients with multifocal strictures or evidence of disease in the pancreas or other distant organs
- Consideration for reaching confirmatory tissue diagnosis should be made for each potentially resectable case but this may not be required if alternative diagnoses are unlikely and/or if tissue sampling may compromise future surgical resection fields and risk tumour seeding.
- Audit of histopathological confirmation in resected specimen should aim for confirmation of cancer in >90% of cases.
- All patients planned for chemotherapy or other systemic therapy and all patients recruited into clinical treatment trials should have confirmatory tissue diagnosis prior to commencing therapy.
- Molecular testing of tissue samples (including advanced cytological tests such as FISH) are currently not clinically useful and done only as part of research studies.
- Reporting o cytology and histopathology specimen should be carried out by specialist pathologists with reporting by a second pathologist or review at the MDM in cases diagnostic or suspicious for cancer.

5.4 Staging

- The TNM staging system is not effective or prognostically predictive in hilar CCA. The classification devised by Bismuth and Corlette (types I-IV) is still the most commonly used and clinically useful local staging system and should be reported for cases within the London Cancer network.



- MRI/MRCP is the optimal imaging to define local extent of tumour and presence of liver metastases, and accurately guides surgical resectability. It is however inferior to CT at assessing distant metastases so these modalities should be used in tandem for potentially resectable patients.
- PTBD and/or ERCP allow sampling for cytology (+/- biopsy) and also stent insertion for palliative purposes in unresectable tumours. The route of drainage should be established from the imaging. Most patients with tumour to the confluence point of the left and right main ducts are best served with bilobar percutaneous drainage (since ERCP is non steerable). Initial drainage (with brushing, biospies either endoluminal or percutaneous fluro guided onto the stricture) allows evaluation of the effectiveness of drainage (by improvement of the LFTs) prior to stent insertion, as well as exclusion of rarer pathologies such as lymphoma that would not be desirable to stent. All patients that have had previous gastric surgery which would preclude endoscopic stenting WHETHER INTRA OR EXTRAHEPATIC should have percutaneous drainage.
- Cholangioscopy may be useful for targeted tissue sampling and macroscopic assessment of extent of tumour margins. However, this currently is inaccessible and appreciating new scopes are becoming available, meeting the current demand in a timely way is difficult.
- Laparoscopy can be considered to determine the presence of peritoneal or superficial liver metastases where there is suspicion of extrahepatic peritoneal or superficial liver involvement.

5.5 Management

- Initial management for all patients with CCA should be guided by the sMDT.
- Further management may be managed by the primary responsible clinician and re-discussed at sMDM as necessary

5.6 PTD / ERCP and biliary drainage

- Urgent biliary intervention is indicated for patients with cholangitis (and occasionally severe pruritis).
- Patients without these indications should be discussed at an sMDT meeting to guide future appropriate biliary intervention
- ERCP is ordinarily the route for sampling and drainage of distal bile duct strictures up to uncomplicated hilar strictures (Bismuth classification <II)
- Patients with proximal hilar strictures beyond the primary bifurcation (Bismuth >II) usually require PTD for adequate guided drainage of appropriate liver segments as guided by the sMDM.

- A decision as to whether a patient requires biliary drainage for jaundice is usually guided by the sMDT as some cases (particularly distal CBD strictures) may be treated with pancreato-duodenectomy in the presence of significant but acute jaundice whereas patients undergoing liver resections or with a longer period of jaundice usually require effective relief of jaundice (bilirubin < x3 –x3 ULN) prior to surgery.
- Metal stents should not be deployed for hilar strictures prior to an MDT decision being made on resectability.
- The site (Right vs Left, sectorial or segmental) and extent of PTBD drainage should be directed by the sMDT once a possible surgical indication and plan have been drafted
- Patients due to have palliative treatments such as chemotherapy usually require effective drainage of jaundice (bilirubin < x2-x3 ULN)) before commencing other palliative treatments.
- Some complex hilar strictures with multiple intrahepatic sub-segmental obstructions may not be amenable to effective biliary drainage. Such cases need careful consideration on appropriateness of intervention before attempting high risk drainage procedures.
- In inoperable patients with distal biliary strictures, metal stents have greater patency rates and are associated with fewer ERCPs, shorter hospital stay and fewer complications, compared to plastic stents.
- Removable fully covered SEMS are suitable for drainage of distal strictures of suspected CCA with or without prior confirmatory tissue diagnosis but should not be deployed across hilar strictures.
- Uncovered SEMS are suitable for palliation of hilar strictures but should only be used in patients with confirmed tissue diagnosis or as directed by the sMDM

5.7 Tissue Diagnosis

- Positive histology and cytology are often difficult to obtain, but are essential for confirmation of a diagnosis of CCA and are particularly important in patients who are not proceeding to resection and for those entering clinical trials.
- Tissue diagnosis should however not delay surgery for a suspected resectable cancer.
- It is usual to obtain biliary brushings at ERCP but this is positive in only approximately 40% of CCA cases. Negative cytology does not exclude malignancy.
- Other options to obtain a tissue diagnosis are EUS-FNA/core biopsy, fluorscopically directed intra-biliary or percutaneous biopsies, or laparoscopic biopsy.
- There is a risk of tumour seeding with some techniques, so surgical assessment of resectability should be established prior to a biopsy or FNA being performed.
- Cholangioscopy allows direct visualisation of tumour within the major ductal systems and aids directed tissue biopsy with a higher rate of confirmatory tissue diagnosis than is achieved using standard ERCP techniques. Cholangioscopy should be considered for cases where initial sampling is non diagnostic in order to maximise accuracy of diagnosis.

5.8 Histology

- Histology should be reviewed at the sMDT prior to determining definitive management. If determined unresectable, this is not necessary prior to further intervention and would protract patient length of stay.
- All surgical resection specimens from both intrahepatic and extrahepatic cholangiocarcinomas need to be reported in a systematic manner. Surgical margins should be adequately sampled, because it has been shown that local recurrence is related to involvement of the margins. Lymph node groups must be specifically identified and it should be noted that peri-pancreatic nodes located along the body and tail of the pancreas are considered sites of distant metastasis.

5.9 Surgery

- Radical (R-0) surgery is the only curative treatment of hilar CCA. Potentially resectable cases should be discussed at sMDM prior to embarking on any kind biliary intervention as some interventions or complications may affect resectability.
- Patients should be assessed for suitability for surgery after staging and anaesthetic review in the surgical centre unless otherwise agreed locally
- Lymph node involvement is present in 30-40% of all patients eligible for surgical treatment and is associated with poor surgical outcome. However N1 hilar CCA may still often be considered suitable for surgical managment.
- Potential portal vein and/or hepatic artery involvement impact negatively on outcomes but do not necessarily render patients unresectable.
- N2 disease is considered as distant metastasis (M1) and surgery is contraindicated (see diagram in appendix for description of nodal disease).
- A plan for surgical resection will be made via the sMDM and direct review by the HPB surgery clinic at which time important surgical issues such as route for biliary drainage, measurement of liver volumes, vascular involvement and target bilirubin will be decided.
- The routine use of pre-operative biliary drainage (PTBD) is highly recommended, particularly in patients with cholangitis. The use of metal stents is indicated only by the sMDM
- Liver biopsy (non lesional) is indicated if bilirubin levels do not respond to optimal biliary drainage (PTBD) and appropriate antibiotic therapy. Persistent or increasing hyperbilruubinemia (> x3 ULN) is a high risk for postoperative liver insufficiency and shall be considered a relative contraindication to surgery

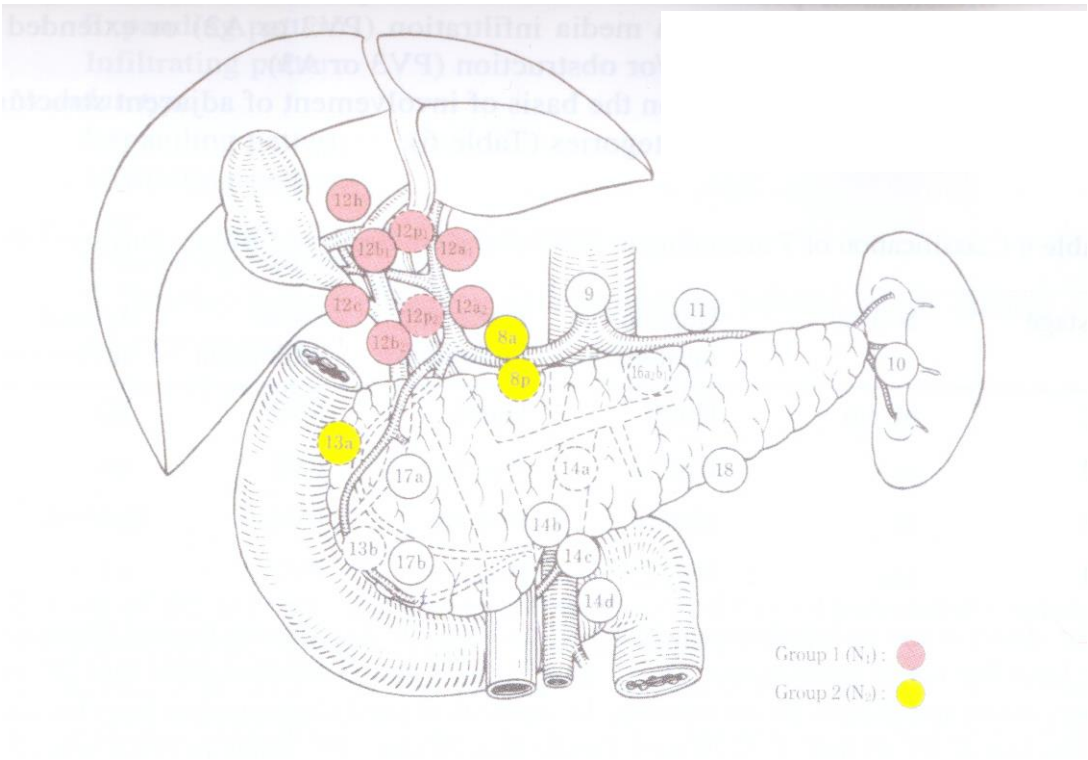
5.10 Palliative treatments

- Symptoms related to biliary obstruction in unresectable disease may be palliated by insertion of a biliary endoprosthesis, rather than a surgical bypass. Stenting procedures resulting in adequate biliary drainage improve survival
- Non surgical candidates shall be offered effective biliary drainage with internalized stents as indicated at the sMDM, unless patients are suitable only for terminal palliative care
- Unresectable patients should be considered for palliative chemotherapy as first line treatment for most patients if clinically appropriate
- Following the ABC-02 study, in patients with advanced disease and good performance status, the standard of care for palliative chemotherapy is gemcitabine and cisplatin chemotherapy.
- There is currently no evidence to support post-surgical adjuvant therapy outside a trial setting.
- There is little evidence to support the use of other chemotherapy regimens or radiotherapy, but further studies are ongoing and patient participation should be encouraged, particularly in the setting of recurrent disease.

Close liaison between oncological, palliative care and surgical teams is essential

6. Appendix

Hilar Cholangiocarcinoma Lymph node mapping



TNM Staging of Intrahepatic Cholangiocarcinoma (IHCCA)

TNM definitions	
Primary tumor	
T1	Solitary tumor, without vascular invasion
T2	Solitary tumor with vascular invasion or multiple tumors, none >5 cm
T3	Multiple tumors >5 cm or tumor involving a major branch of the portal or hepatic vein(s)
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum
Regional lymph nodes	
N0	No regional lymph node metastases
N1	Regional lymph node metastases
Distant metastases	
M0	No distant metastases
M1	Distant metastases
Stage grouping	
Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage IIIA	T3, N0, M0
Stage IIIB	T4, N0, M0
Stage IIIC	Any T, N1, M0
Stage IV	Any T, any N, M1