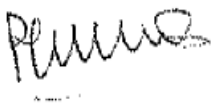
NHS England

Primary Liver Cancers

West Midlands Clinical Networks and Clinical Senate

Coversheet for Network Expert Advisory Group Agreed Documentation

This sheet is to accompany all documentation agreed by the West Midlands Strategic Clinical Network Expert Advisory Groups. This will assist the Clinical Network to endorse the documentation and request implementation.

EAG name	Hepato-Pancreato-Biliary EAG	
Document Title	Primary Liver Cancers	
Published date	December 2018	
Document Purpose	To provide guidance on the diagnosis and management of primary liver cancers.	
Authors	Dennis Freshwater, Consultant Hepatologist	
References	See Further Reading section in document	
Consultation Process	Presented and discussed at West Midlands HPB EAG 12 September 2017	
Review Date (must be within three years)	October 2020	
Approval Signatures:	**EAG Chair**  Date: 04/12/2018	**Network Clinical Director**  Date:04/12/2018

PRIMARY LIVER CANCERS

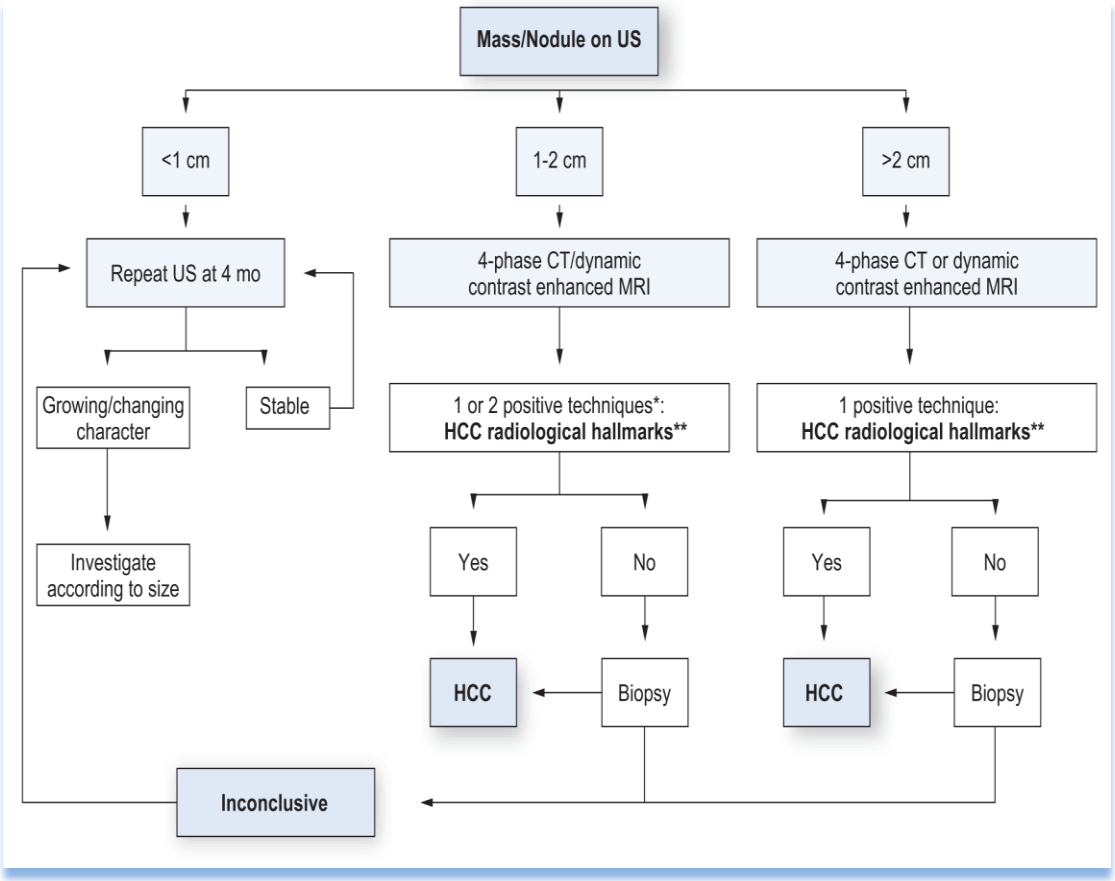
This guideline provides information on the diagnosis and management of primary liver cancers, which are divided into hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC).

DIAGNOSIS AND MANAGEMENT OF HEPATOCELLULAR CARCINOMA

Algorithms for the diagnosis and management of hepatocellular carcinoma are presented, followed by the evidence for the recommendations.

Algorithm For Diagnosing Hepatocellular Carcinoma

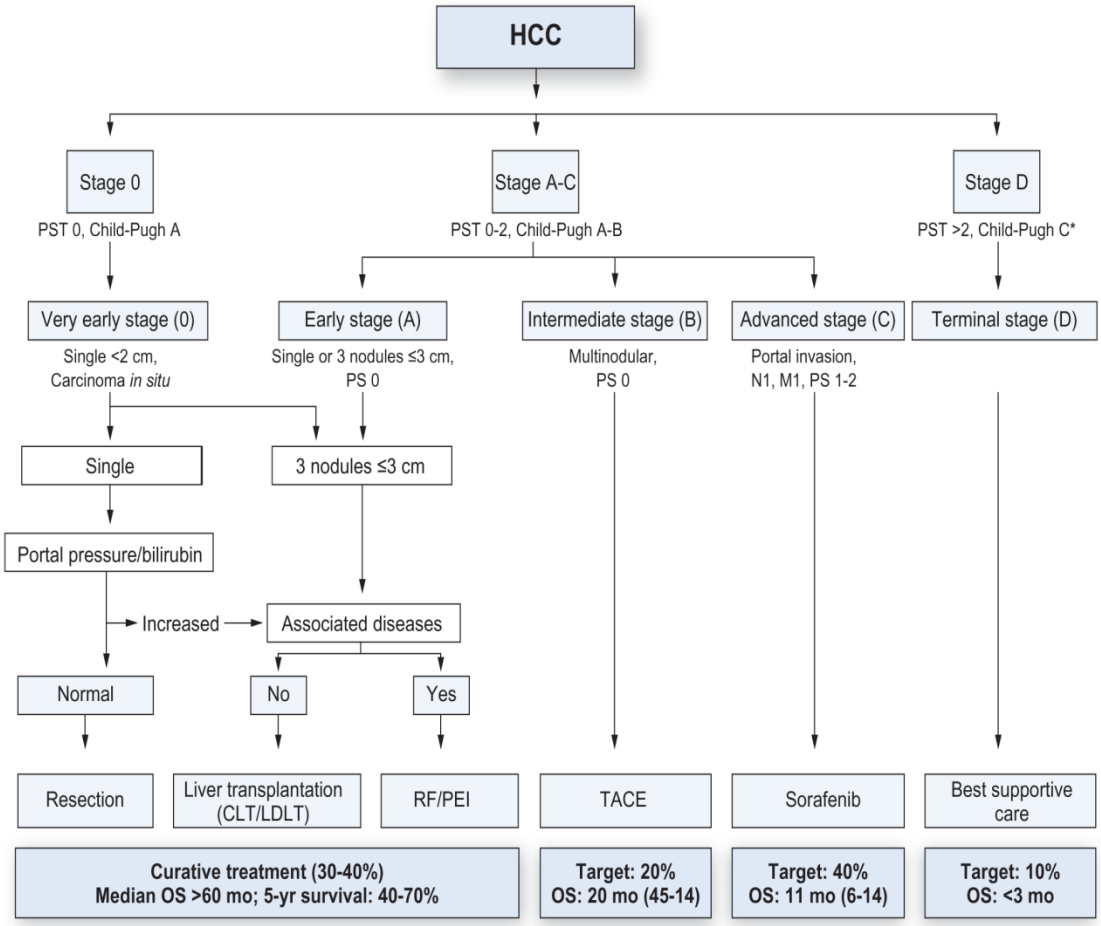
[From the clinical practice guidelines of the European Association for the Study of the Liver 2011]

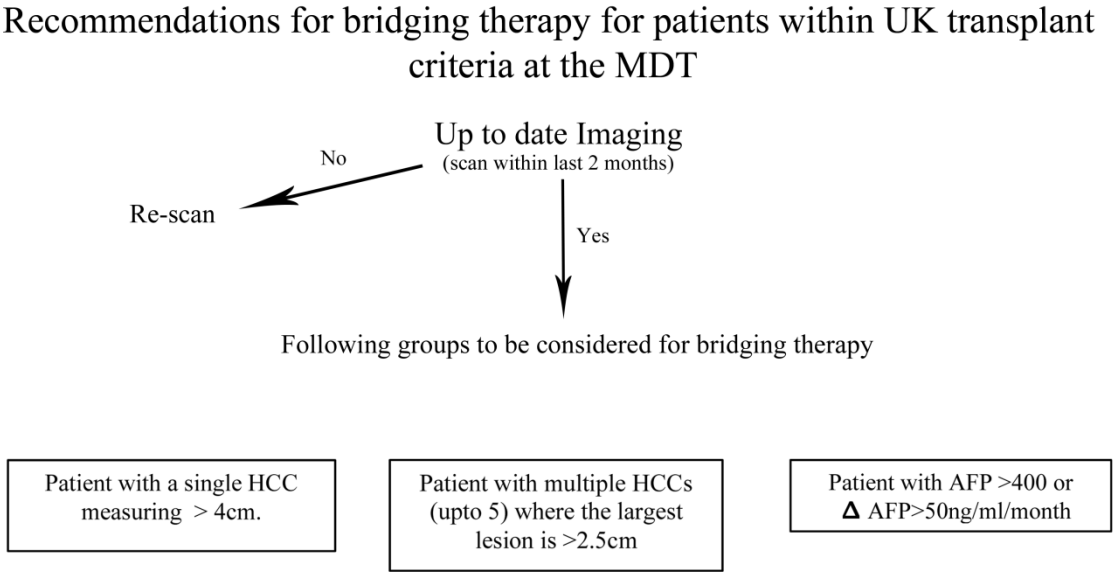


*One imaging technique only recommended in expert centres with appropriate imaging protocols.
**HCC radiological hallmark: arterial hypervascularity and venous/late phase washout.

All cases of suspected or confirmed hepatocellular cancer should be discussed at a specialist HPB MDT to determine the most appropriate management, taking account of the patient's performance status

Barcelona Clinic Liver Cancer (BCLC) Staging System and Treatment Strategy for Hepatocellular Carcinoma





Factors which influence waiting time on the list need to be taken into consideration such as patient's blood group and whether a patient is suitable for DCD or DBD grant. Bridging therapy is with trans-arterial chemo-embolisation (TACE).

Introduction

This guideline explains the diagnosis and management options for HCC and are drawn from the national and international guidelines. Approximately 40% of patients are currently considered for curative therapies (transplantation, resection, or ablation), 35% are considered for non-curative therapies (TACE or sorafenib), and 25% suitable for best supportive care including palliation of symptoms.

Levels of Evidence According to Study Design and end-points

Study design

Level 1: Randomized controlled clinical trials or metanalyses of randomized studies

i) Double-blinded

ii) Non-blinded treatment delivery

Level 2: Non-randomized controlled clinical trials

Level 3: Case Series

i) Population-Based, consecutive series

ii) Consecutive cases (not population-based)

iii) Non-consecutive cases

End Points

A. Total mortality (or overall survival from a defined time)
B. Cause specific mortality (or cause-specific mortality from a defined time)
C. Carefully assessed quality of life
D. Indirect surrogates
    i) Event free survival
    ii) Disease-free survival
    iii) Progression-free survival
    iv) Tumour response rate

Surveillance

Patients with known cirrhosis, and who are likely to benefit from early detection, of HCC should be entered into surveillance programs (**Evidence 3**).

Non-cirrhotic hepatitis-B patients with high viral loads, prior to treatment, and family history of HCC should be considered for surveillance (**Evidence 3**).

Patients on the transplant waiting list should be screened for HCC in order to detect and manage tumour progression and help to define priority policies for transplantation. (**Evidence 3D)**

Surveillance for HCC in high risk populations should be performed using ultrasonography every 6 months. (**Evidence 2D**)

Current biomarkers such as Alphafetoprotein (AFP) are suboptimal for routine clinical practice. (**Evidence 2D**)

Recall Policy

In cirrhotic patients, nodules less than 1cm in diameter detected by ultrasound should be followed every four months in the first year and 6 months thereafter. (**Evidence 3D)**

In cirrhotic patients, diagnosis of HCC for nodules of 1-2cm in diameter should be based on non-invasive criteria or biopsy-proven pathological confirmation. (**Evidence 2D**)

In cirrhotic patients, nodules more than 2cm in diameter can be diagnosed for HCC based on typical features on one imaging technique. In case of uncertainty or atypical radiological findings, diagnosis should be confirmed by biopsy. (**Evidence 2D**)

Diagnosis of HCC

The diagnosis of HCC can be based on non-invasive criteria or pathology. (**Evidence 2D**)

Pathological diagnosis of HCC is based on the recommendations of the International Consensus Panel. (**Evidence 2D)**

Non-invasive criteria can only be applied to cirrhotic patients and are based on imaging techniques obtained by 4-phase multidetector CT scan or dynamic Primovist-enhanced MRI. While one imaging technique is required for nodules beyond 1cm in diameter, a more conservative approach with two techniques is recommended in sub-optimal conditions. (**Evidence 2D).**

Staging Systems

To best assess the prognosis of HCC patients it is recommended that the staging system takes into account tumor stage, liver function and physical status. The impact of treatment should also be considered when estimating life expectancy. Currently, the Barcelona Clinic Liver Cancer (BCLC) system is the only staging system that accomplishes these aims. (**Evidence 2A**). It is recommended to perform a Chest CT to rule out extrahepatic spread.

Treatment of HCC

All HCC patients need to be discussed at a dedicated HPB MDT meeting where a decision is made by the multi-disciplinary team as to the best form of therapy for a given patient, dependent on their: general fitness, underlying disease, hepatic reserve, presence of portal hypertension. Patients will also have access to clinical trials and advanced therapies.

Patients with suspected HCC should be diagnosed and assessed for treatment within the 62 day target.

Liver transplantation

Liver transplantation should be considered in cirrhotic patients with a solitary lesion less than 5cm or up to five lesions of 3cm or less. **(Evidence 2A)**. Other patients to be considered are those with a single lesion greater than 5cm but less than or equal to 7cm diameter where there has been no evidence of tumour progression (volume increase by <20%; no extrahepatic spread; no new nodule formation) over a 6 month period. Locoregional therapy +/- chemotherapy may be given during that time. Loco-regional therapy should be considered for all waiting list patients (**Evidence 2**). In general the waiting times for transplantation for patients with HCC are short. Therefore, no priority is given for solitary tumours < 2cm in diameter. Patients with more advanced HCC may be given priority following discussions in the transplant listing meeting.

Additional guidelines have recently been agreed by the Liver Advisory Group (LAG) for the United Kingdom with regard to Alpha-fetoprotein levels. In a recent multi-centre study to identify prognostic markers which would improve on the current Milan Criteria, an AFP of greater 1000ng/ml was associated with a high risk of recurrence at 5 years (Duvoux et al Gastroenterology 2012). **In light of these findings, LAG have decided that AFP>1000 ng/ml is a contra-indication to listing for liver transplantation.**
Patients on waiting list will require 3 monthly re-staging using an appropriate imaging modality which should have been decided at the time of listing for transplantation.

Bridging therapy for patients being considered for transplantation

The benefit of bridging therapy in HCC patients in terms of post transplant survival or drop out rates from the waiting list have not been studied in randomized control studies. This is acknowledged in the EASL guidelines where the evidence is taken from observational studies and cost effectiveness studies. Despite this, bridging therapy for patients with HCC in the form of local ablation or chemoembolization is

used in most liver transplant centres for patients on the waiting list. EASL guidelines suggest **'treating patients waiting for transplant with local ablation, and as a second choice with chemoembolization when waiting times are estimated to exceed 6 months'.**

In view of the above we have taken the approach that patients who are referred that have tumour size which is close to exceeding transplant guidelines, (with well preserved liver function) should undergo bridging therapy in parallel to being referred for transplantation, Furthermore, those patients who have tumour characteristics which predict high rate of drop out (high AFP or AFP velocity) should also be considered for bridging therapy. Several studies have suggested an AFP >400 or high AFP velocity (15-50ng/ml/month) is associated with high risk of recurrence and drop out from the waiting list.

The following patients should be considered for bridging therapy:

1) **Single tumour >4cm**
2) **Multiple HCCs (up to 5) where the largest lesion is 2.5cm.**
3) **AFP>400 or tumour velocity (Δ AFP) >50ng/ml/month**

It is important to highlight that other factors which influence waiting time on the list need to be taken into consideration such as patient's blood group and whether a patient is suitable for DCD or DBD grant. These issues can be discussed at the HPB MDT or listing meeting.

Living donor transplantation can be offered for HCC within the above stated transplant criteria.

Down staging for Liver Transplantation

At present, down-staging of HCC allowing listing for liver transplantation is not permitted under UK liver transplant selection criteria. However, as discussed in the section on liver transplantation, locoregional therapy may be given to try to prevent tumour progression during the waiting period. As part of a UK Blood and Transplant service evaluation, the regional liver MDT will utilise the criteria proposed by Duvoux et al including number and size of tumours as well as AFP values to determine those suitable for transplantation.

Surgical Resection

Patients can be offered surgical resection if they are non-cirrhotic or have cirrhosis but still have well preserved liver function (**Evidence 2A)**. These procedures should be undertaken in units with expertise in hepatic resection and management of liver failure and in consultation with a liver transplant unit. In Birmingham resections are being carried out in non-cirrhotic patients with large HCCs falling outside the

transplantation criteria, and a few cirrhotic patients who have well preserved hepatic function with small, technically resectable tumours.

Percutaneous Ablation

Radiofrequency ablation (RFA) has been shown to be effective therapy particuarly in HCCs less than 3cm in diameter (**Evidence 2A).** Percutaneous ethanol injection (PEI) has been shown to be inferior to RFA in local tumour control. PEI still has a potential role in the treatment of small lesions difficult to treat with RFA. In tumours < 2cm BCLC stage 0 both techniques can achieve complete response in more than 90% of cases. According to EASL guidelines it is still an open question whether RFA can compete with surgical resection as a first-line treatment for patients with small solitary HCCs.

Management of single HCCs <2cm

Resection is considered as first line therapy for cirrhotic patients with small lesions <2cm who have Child A cirrhosis without significant portal hypertension (platelet > 100,000 and HVPG <12) and AFP <100. If these patients have lesions which are technically difficult for resection they should be considered for local ablative therapy. However, since surgery can make subsequent transplantation very difficult the majority of these patients end up being treated by ablation.

Transarterial Embolization and Chemoembolization

Transarterial Chemoembolization (TACE) is recommended as first line non-curative therapy for non-surgical patients with large and/or multifocal HCC who do not have vascular invasion or extrahepatic spread (**Evidence IA**).
Pre or post-TACE adjuvant therapy is not recommended at present (**Evidence 2A**). However, there are a number of trials, of adjuvant treatment, now open in Birmingham so all such patients should be discussed with the Oncology team.

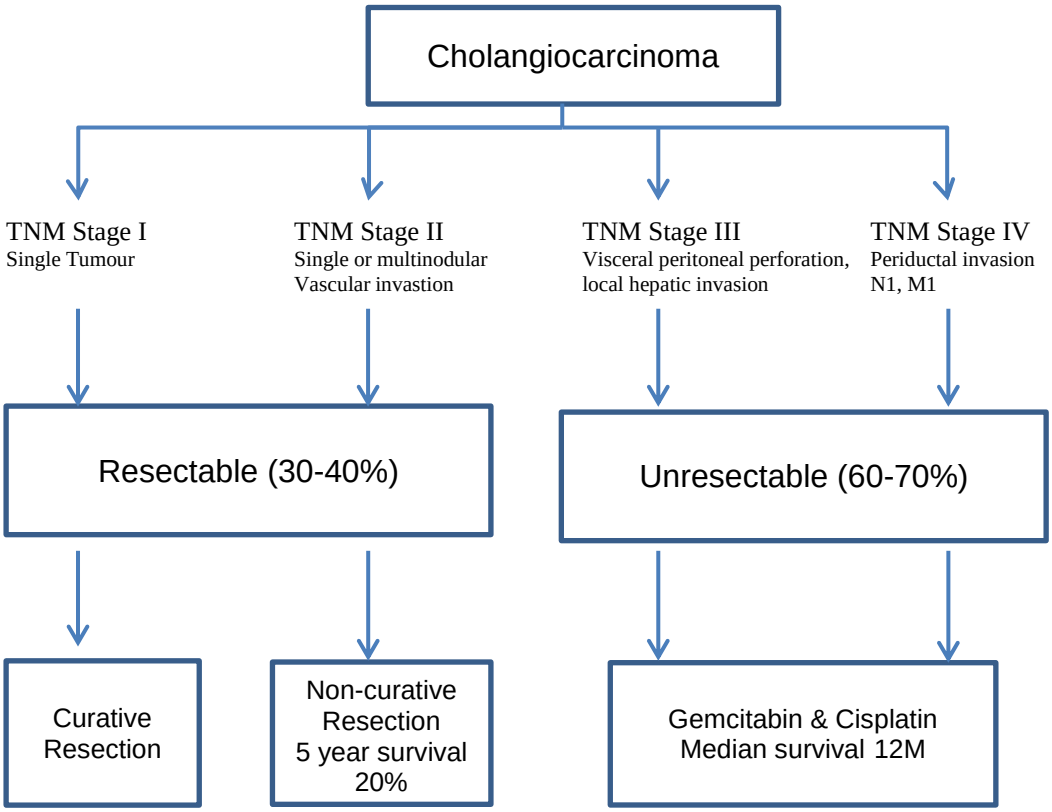
Systemic Therapies

The oral multi-tyrosine kinase inhibitor, Sorafenib, is the current systemic therapy for HCC and is indicated for patients with well preserved liver function (Child-Pugh A) and advanced tumours or those tumours which have progressed following transarterial chemoembolization **(Evidence 1A)**. There are no available second-line treatments for patients with intolerance or failure to sorafenib but there are a number of trials now open in Birmingham so all such patients should be discussed with the appropriate oncology team.

DIAGNOSIS AND MANAGEMENT OF CHOLANGIOCARCINOMA

Adapted from BSG and EASL guidelines. Please see BSG and EASL guidelines for background evidence leading to the recommendations. An algorithm for the management of cholangiocarcinoma is presented, followed by the evidence for the recommendations.

Algorithm for management of cholangiocarcinoma



Epidemiology

Cholangiocarcinoma (CC) is the second commonest primary liver tumour worldwide, after hepatocellular carcinoma (HCC). Incidence and mortality rates for intrahepatic CC have risen steeply and steadily across the world over the past few decades with concomitant falls in extrahepatic CC rates. Since the mid-1990s, more deaths have been coded in England and Wales due to CC than to HCC. CC kills approximately 1500 people annually in the UK, with approximately equal numbers of men and women.

Risk Factors

There are several established risk factors for CC, but
these account for <30% of all cases. Most cases of CC are sporadic. Known risk factors include:
Primary sclerosing cholangitis (The commonest risk factor
Cirrhosis of any cause
Chronic viral hepatitis B or C
Chronic intraductal stones
Caroli's disease
Liver flukes

A combination of recent cohort, population-based, case-control and observational studies from around the world suggest that obesity, diabetes, fatty liver disease, alcohol, smoking, IBD without PSC and polymorphisms of genes coding for carcinogen metabolism, DNA repair, inflammation and biliary transporters may also be risk factors.

Diagnosis

Clinical Features

Perihilar or extrahepatic CCs typically present with features of biliary obstruction (jaundice, pale stool, dark urine and pruritus). Cholangitis is unusual without prior biliary instrumentation. CC is usually advanced at presentation, particularly with more proximal intrahepatic and perihilar tumours obstructing one duct. These often present with systemic manifestations of malignancy including malaise, fatigue and weight loss. Some cases are detected incidentally as a result of scans performed for other indications.

Blood tests

No blood tests are diagnostic for CC. Liver function tests often show an obstructive picture. Aminotransferases are frequently normal but may be markedly raised in acute obstruction or cholangitis. Prolonged biliary obstruction can cause a reduction in fat soluble vitamins and an increase in prothrombin time. In advanced disease, non-specific markers of malignancy such as albumin, erythrocyte sedimentation rate, C-reactive protein and haemoglobin may be altered.

Serum Markers

Carbohydrate antigen (CA) 19-9 and CA-125 are the most used serum tumour markers. Overall, their sensitivity and specificity are low and they are not helpful for monitoring disease progression. They may be useful in conjunction with other diagnostic modalities. CA19-9 is elevated in up to 85% of patients with CC with a sensitivity of 40-70%, specificity of 50-80% and positive predictive value (PPV) of 16-40%, depending on cut-off values. CA19-9 elevation frequently occurs in PSC and other causes of non-malignant obstructive jaundice, but persistently raised levels of CA19-9 after decompression suggest malignancy. Therefore CA19-9 should only be measured after biliary decompression (**Evidence 2**). CA19-9 does not discriminate between CC, pancreatic or gastric malignancy. Furthermore, 10% of individuals lack Lewis antigen and cannot produce CA19-9. CA-125 is detectable in up to 65% of patients with CC. In a chemotherapy trial setting, a raised baseline CA-125 was found to be prognostic for survival. CA-125 is often raised in parenchymal liver disease and may not be helpful in this context. AFP is also unhelpful in the diagnosis of cholangiocarcinoma. Therefore, diagnosis of CC should not rely on serum markers alone (**Evidence 2**).

IgG4 Cholangiopathy

IgG4 cholangiopathy can mimic features of CC and should be excluded in suspected cases of CC by testing for increased IgG4 in serum and biliary samples (**Evidence 2**).

Imaging

Imaging is the main diagnostic modality for CC. The recommendation is that suspected cases of CC should undergo combined MRCP and contrast MRI and CT (**Evidence 2**). EUS (preferred) or ERCP should be considered where tissue samples are required, but this should not normally happen before decisions regarding resection have been made (**Evidence 2**).

USS USS offers specificity and negative predictive value of 90%, but sensitivity and PPV are only 50% through detection of ductal dilatation and associated mass lesions. These findings on USS should prompt more definitive imaging.

MRCP In a retrospective study, MRCP had superior sensitivity (96%), specificity (85%) and accuracy (91%) compared with ERCP (80%, 75% and 78%, respectively) for differentiating between CC and benign stricture.

MRI MRI with liver specific contrast is the optimal imaging investigation for suspected CC. In addition to avoiding radiation, MRI delineates hepatobiliary anatomy, local extent of duct involvement by MR cholangiopancreatography (MRCP), parenchymal abnormalities including the presence of liver metastases and hilar vascular involvement (MR angiography). However, MRI is inferior to CT for detecting distant metastases, particularly in the lungs and bone, and therefore a staging CT will still be needed in confirmed cases of CC.

EUS Endoscopic ultrasound (EUS) allows good views of the distal extrahepatic biliary tree, hilar lesions, gall bladder, regional lymph nodes and vasculature. EUS facilitates fine needle aspiration of distal lesions and nodes which can enhance the sensitivity and PPV of CC detection to nearly 100%. However, the negative predictive value is low, which does not permit exclusion of malignancy following a negative biopsy.

PTC PTC can be useful for perihilar CC, as it allows clear delineation of the biliary anatomy and access for endobiliary biopsy.

Patients with suspected CC should be diagnosed and assessed for treatment within the 62 day target.

Staging & Discussion

Studies obtained for the initial diagnosis may also provide staging information. However, to rule out metastatic disease, contrast CT of the abdomen, chest and pelvis should be carried out on all patients, particularly if resection is being considered (**Evidence 2**). The results of all investigations should be discussed at a hepatobiliary multi-disciplinary team (MDT) meeting to confirm diagnosis and plan treatment options, prior to biliary drainage.

Treatment

Decisions on the treatment pathway to be adopted for an individual patient must be decided by a dedicated hepatobiliary MDT, taking account of the patient's performance status. The treatment options below are for information only.

Resectable Tumours

Resection, which should be guided by medical risk rather than age, involves a major operative procedure and requires appropriate surgical and anaesthetic experience. Surgical treatment depends on the site and extent of bile duct involvement by tumour. Intrahepatic CCs are usually treated by resection of the involved segments or lobe of the liver. Distal CCs are managed by pancreatoduodenectomy, as with ampullary or pancreatic head cancers. Major hepatectomy for hilar CCs carries a considerable risk of hepatic insufficiency if there is a small future liver remnant. Portal vein embolisation of the liver lobe to be removed is a safe method for increasing the future liver remnant and permits potentially curative hepatic resection to be carried out. Pre-operative biliary drainage of the future liver remnant is usually necessary and our preferred approach is via percutaneous transhepatic biliary drainage.

Liver Transplantation

At the time of writing, liver transplantation for CC is not approved by the Liver Advisory Group in the United Kingdom due to the previous high recurrence rates of CC following transplantation.

Adjuvant Chemotherapy

Patients with a completely resected cholangiocarcinoma or gallbladder cancer should be offered six months of adjuvant capecitabine chemotherapy based on the results from the phase 3 BILCAP clinical trial. (Evidence 1A).

Stents for Palliation

Most patients with CC have unresectable disease. In such patients, a study from the USA found that endoscopic stenting cost significantly less and was associated with longer survival than surgical treatment (19 vs 16.5 months), suggesting that endoscopic stenting is the procedure of choice for palliative biliary drainage (**Evidence 3D**). Metal stents are generally preferred over plastic stents due to the longer time to obstruction, and at present there is no convincing data of superiority of covered versus uncovered metal stents. The decision on whether to place a stent via ERCP or PTC should be taken by a hepatobiliary MDT taking into account the facilities and expertise available.

Chemotherapy

Until recently, chemotherapy for CC had poor results and studies were small and disparate. In 2010, a new standard of care in unresectable BTC was established with the reporting of the UK NCRI ABC-01 and ABC-02 trials. These found CisGem treatment to be cost-effective compared with Gem monotherapy, giving a median survival of 11.7 months, and is the recommended chemotherapy treatment

(**Evidence 1A**). Following progression on Gemcitabine and Cisplatin chemotherapy, there is no standard second line chemotherapy and patients should be considered for clinical trials.

Further Reading

European Association for the study of the Liver clinical practice guidelines for HCC management
www.easl.eu/_clinical-practice-guideline/issue-7-april-2012-management-of-hepatocellular-carcinoma

American Association for the study of Liver Disease clinical practice guidelines
www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/HCCUpdate2010.pdf

British Society of Gastroenterology guidelines for the management of hepatocellular cancer
www.bsg.org.uk/clinical-guidelines/liver/guidelines-for-the-diagnosis-and-treatment-of-hepatocellular-carcinoma-hcc-in-adults.html

Clavien PA, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A; OLT for HCC Consensus Group. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncol. 2012 Jan;13(1):e11-22. doi: 10.1016/S1470-2045(11)70175-9.

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Llovet JM et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008 Jul 24;359(4):378-90.

European Association for the Study of the Liver guidelines for the diagnosis and management of cholangiocarcinoma
http://www.journal-of-hepatology.eu/article/S0168-8278(14)00067-1/abstract

British Society of Gastroenterology guidelines for the diagnosis and management of cholangiocarcinoma
http://www.bsg.org.uk/clinical-guidelines/liver/guidelines-for-the-diagnosis-and-treatment-of-cholangiocarcinoma-an-update.html

Primrose JN, Fox R, Palmer DH, et al. Adjuvant Capecitabine for Biliary Tract Cancer: The BILCAP Randomized Study. J Clin Oncol. 2017;35 (suppl; abstr 4006).