HPB Clinical Guidelines for Pancreatic and Periampullary Cancer, Colorectal Liver Metastases and Primary Liver Cancers 2019 (Lancs & South Cumbria)

ELHT Pancreatic and Periampullary Cancer Referral Guidelines

(Version 6 2019)

1 Criteria for diagnosis of pancreatic or peri-ampullary malignancy

Patients with any of the following should be assessed and treated for malignancy until proven otherwise. This group will include patients with ampullary tumours, duodenal tumours and distal cholangiocarcinoma.

- A mass in the head or body of the pancreas on CT or MRI
- A stricture of the distal common bile duct on ERCP or MRCP
- The combination of a dilated pancreatic duct and common bile duct on any imaging **in the absence of a visible mass.**
- An isolated dilated pancreatic duct on any imaging except where explained by clear chronic pancreatitis **in the absence of a visible mass.**
- An abnormal appearing papilla with any degree of dysplasia on biopsy or suspicion that biopsy is negative due to sampling error

Biopsy is not essential and is inadvisable where there is a potential for curative resection, except where performed endoscopically. A serum CA19-9 level can be useful evidence, especially in equivocal cases. It should be requested upon suspicion of malignancy.

2 Patient Assessment

- History and examination to assess clinical extent of disease, co-morbid disease and overall fitness including a WHO performance score.
- A specific assessment of nutritional status to include actual and percentage weight loss, body mass index and serum albumin. Creon supplements should be prescribed if there is evidence of pancreatic exocrine insufficiency.
- A CT scan is required for staging and always should be performed **before** a biliary stent is placed.
- The CT should include abdomen, pelvis and full thorax views and should be performed with intravenous contrast (see Network radiology protocols).
- Endoscopic ultrasound (EUS) may be helpful in selected but not all patients. This procedure can be combined with fine needle aspiration for cytological confirmation of the diagnosis. EUS is performed at the HPB Centre.
- A FDG-PET/CT scan should be considered if there is doubt about the diagnosis or concern that there is metastatic disease.

3 Referring to the HPB Centre

- All patients with a suspected pancreatic or peri-ampullary cancer should be referred as soon as possible to the Network HPB MDT.

- If the patient is unsuitable for or elects not to undergo further investigation and wishes to have only local palliative treatments the HPB Specialist Nurse should be informed. This can be by means of the official referral proforma (sent by email) and should include reasons for not performing further staging and the palliative treatment employed. This data will provide audit information for the cancer network.
- If the patient elects to have further staging investigations inform the HPB Specialist Nurse using the referral proforma. Include the date of CT so that MDT meeting discussion can be organised for the same week and a provisional date for an EUS, if required, and outpatient appointment can be arranged. These can be cancelled if the CT shows definite haematogenous metastases or locally unresectable disease.
- At the point of referral, if not already provided, the HPB Specialist Nurse will ask for essential information required for a complete MDT discussion. This information requires clinical understanding and should therefore be provided by either the local nurse specialist or by one of the local medical team either in the form of a letter or a completed proforma that is provided by the centre. If complete information is not available at the time of the Centre MDT meeting, this can delay treatment recommendations.
- The Network HPB MDT currently takes place on Friday mornings between 9 and 12.30 at the Royal Blackburn Hospital with facilities for video-conferencing. All referrals should reach the MDT co-ordinator by 12 noon on Wednesday to allow time for radiology review of imaging prior to the meeting.
- Urgent cases requiring advice prior to the Network HPB MDT can be discussed with any core member of the Specialist HPB MDT (see below for contact details).
- Patients deemed suitable for surgery will be allocated a provisional operation date at the MDT meeting.

4 Placement of stents and biopsies

- If possible biliary stenting should be avoided prior to surgery as the procedure risks precipitating an episode of severe acute pancreatitis which may prevent an operation taking place in a timely fashion. Furthermore instrumentation of the bile duct increases the risks of recurrent cholangitis and sepsis at the time of surgery.

  Surgery can be performed up to a serum bilirubin level of 400 μmol/l depending upon the fitness of a patient. Therefore the need for an ERCP should first be discussed with the HPB centre.

  If an ERCP is performed then a stent will be required in an obstructed biliary system to prevent ascending cholangitis. A **short** (4cm) covered self-expanding metal stent (SEMS) should be placed. The stent must be short enough not to encroach upon the common hepatic duct thereby enabling a safe surgical biliary anastomosis in the future. If the pathology leading to the biliary obstruction is inoperable then due to the better long term patency rates of metallic compared with plastic stents no further stent change will be necessary. If further definitive biopsies are required then a covered metal stent can be removed and replaced.

- It is always helpful to take biopsies at the time of endoscopic stenting either by means of brush cytology or biopsy of abnormal tissue at the ampulla or in the duodenum. Brush cytology is reported to have a sensitivity ranging from 30 – 70% and a specificity of 100%. A positive brush cytology or biopsy will avoid the need for a further invasive diagnostic investigation such as an EUS-guided FNA or percutaneous biopsy and will provide an accurate prognosis. Furthermore patients will also have the option of participating in an appropriate clinical trial.
- If a biliary stent is required, for example in the presence of cholangitis, and there is difficulty placing it endoscopically then either a combined rendezvous PTC/ERCP procedure or a PTC long plastic stent can be attempted. If the expertise does not exist for this technique locally then either the stent should be left until the radiology images have been assessed by the Network MDT or the patient should be referred to the HPB centre for stenting.
- Biopsies (other than endoscopic biopsies) should not be undertaken in any patient where resection remains a possibility. This is because of the risk of intraperitoneal or needle tract seeding. However nearly all patients with unresectable disease require biopsy for the following reasons. Up to 15 % of such lesions may not be pancreatic adenocarcinomas and therefore may have a better prognosis and may be more amenable to chemotherapy. Participation in clinical trials requires histological proof of diagnosis. For some patients, histological proof is important to help in accepting and dealing with their prognosis.
- Patients with gastric outlet obstruction and inoperable peri-ampullary or pancreatic tumours can be decompressed by either the placement of a SEMS or undergo a surgical bypass by open or laparoscopic techniques depending upon local availability and patient prognosis. The use of SEMS may allow for earlier commencement of palliative chemotherapy than after a surgical bypass.

5 Criteria for surgery

Surgical resection offers the only chance of cure for exocrine pancreatic cancers which have not metastasised, however, only 15 – 20% of patients are suitable for surgery at the time of diagnosis either because of metastases or locally advanced disease. A pancreatic cancer may be considered to be unresectable if the following are present :

- The presence of distant metastases
- Metastases to lymph nodes beyond the field of resection
- Involvement of the aorta or IVC
- Encasement of the SMA for >180° or occlusion/thrombus of this vessel
- Encasement of the coeliac axis for >180°
- SMV/portal vein occlusion that cannot be reconstructed
- The patient is unfit for surgery

Some cases may be considered as ‘borderline resectable’ however the definition of borderline is variable amongst surgeons. Features such as focal tumour abutment of the SMA, encasement of the gastroduodenal artery up to the hepatic artery or involvement of the SMV/portal vein may be considered in this category. Although technically it may be feasible

to operate on these tumours this is likely to be an incomplete resection. Therefore there may be a role for neoadjuvant treatments with chemotherapy+/- radiotherapy to try and downsize the tumour prior to surgery with a greater likelihood of a margin-negative resection. Furthermore using this pathway may improve patient selection by providing an opportunity during the pre-operative period to identify those patients with aggressive disease who rapidly develop metastases and therefore will not benefit from a major operation.
The rationale for this approach is currently being tested in a phase II randomised clinical trial comparing the current standard of care immediate surgery followed by adjuvant chemotherapy with neoadjuvant chemotherapy or chemoradiotherapy (ESPAC-5F).

6 Down-sizing chemotherapy

Until the results of clinical trials are known the current regimen of choice is FOLFIRINOX. This is a combination of four chemotherapy drugs (Oxaliplatin, Leucovorin, Irinotecan, Fluorouracil) and is used for patients with metastatic and locally advanced pancreatic adenocarcinoma, and occasionally used as a treatment to try to downsize tumours prior to surgery.

The recommendation for the use of FOLFORINOX is based upon the results of a multicenter phase II/III trial of 342 patients with metastatic pancreatic adenocarcinoma with an ECOG performance status score of 0 or 1 who were randomised to FOLFORINOX or Gemcitabine. The median OS was 11.1 months, with a median progression-free survival of 6.4 months and an objective response rate of 31.6% in the FOLFORINOX group compared with 6.8 months, 3.3 months and 9.4% in the Gemcitabine group (*Conroy et al NEJM 2011 364 1817-1825*).

This chemotherapy regimen been accepted as a first-line treatment option in patients with inoperable pancreatic cancer by the Lancashire & S Cumbria HPB NSSG.

This treatment can be very toxic and side effects can be greater than standard therapy of Gemcitabine +/- Capecitabine and therefore it is not suitable for all patients.

The following criteria should be considered before starting treatment:

- The patient has a diagnosis of inoperable/borderline pancreatic cancer, which has not been previously treated with chemotherapy for advanced disease, and
- The patient is sufficiently fit to tolerate FOLFIRINOX therapy, and
- Has an ECOG performance status of 0 or 1, and
- Has no clinically significant history of cardiac disease, and
- Has normal, or near normal, bilirubin levels

Clinicians should comply with the following:

- Patients must be treated under the supervision of an oncology member of the specialist multidisciplinary team (MDT), with the treatment decision documented by the MDT
- Patients should have a baseline CT scan of the chest abdomen and pelvis. This should be repeated at least every 8 weeks
- Patients should be reviewed clinically every cycle (2 weekly)
- If grade 2 neuropathy develops, oxaliplatin should be stopped
- Treatment may continue up to a maximum of 12 cycles, if tolerated

- Treatment should not continue beyond radiological or clinical evidence of progression
- Patients must be made aware that there are stopping criteria before treatment is initiated
- Information concerning the eligibility criteria and the results of associated CT scans must be available for audit
- Patients must have a baseline serum Ca19-9 measurement prior to treatment with subsequent serial monitoring as this tumour marker has been shown to be a good indicator of tumour response.

7 Peri-operative management

Prospective patients for surgery will be assessed by the operating surgeon and the HPB anaesthetic team which may include use of cardiopulmonary exercise testing (CPEX). Age alone is not a factor in the selection of patients for major pancreatic surgery. However patients must be fit, active, self-caring, and capable of climbing a flight of stairs without resting.

All surgical patients will be entered into an Enhanced Recovery Programme (ERP). The programme improves patient outcomes, speeding up a patient's recovery after surgery and ensures the patient actively participates in their own recovery. As part of the ERP there will be active involvement by the dietician in nutritional support immediately after surgery and after discharge from hospital. Pancreatic enzyme supplements should be started for all patients prior to surgery.

8 Adjuvant treatment

All patients following a successful surgical resection for a pancreatic cancer should be considered for adjuvant chemotherapy ideally within a local or national trial. Both Gemcitabine and 5-Fu/FA have been shown to be beneficial compared with no treatment. The combination of 6 cycles of Gemcitabine with continuous capecitabine has been show to improve overall survival compared with gemcitabine alone and should be regarded as the standard of care for suitable patients. Effects are similar in R0 and R1 subgroups. Patients gain the greatest benefit if they can complete all 6 cycles. It is worth noting that recent data suggests that FOLFORINOX may offer a significant overall survival benefit in fit patients compared to GemCap (Conroy *et al* NEJM 2018; 379:2395) and this regimen should be considered at the discretion of the oncologist. Patients will be referred to their local oncologist with an interest in pancreatic cancer on discharge from hospital.

Unfortunately even with modern chemotherapy drugs the five year survival rates for patients with node negative disease is only 25 – 30% and for those with node positive disease this drops to about 10%.

9 Pathology

The examination and reporting of surgical resection specimens relating to pancreatic, ampulla of Vater and bile duct cancers will follow the guidelines issued by the Royal College of Pathologists in 2017 and will include the minimum dataset.

10 Surgical follow-up

All patients after surgery are reviewed in the HPB clinic to provide ongoing support, to identify at an early stage any complications such as pancreatic insufficiency or recurrent cholangitis and to look for disease recurrence. A dietician will be involved to provide advice on nutrition (see PEI guidelines).

Monitoring of the serum Ca19-9 tumour marker may be helpful particularly if it was raised prior to surgery.

There is no evidence that regular radiology surveillance by CT scans is of any benefit or alters outcomes.

The HPB Clinical Nurse Specialists will have regular contact with patients before and after their surgery.

11 Non-surgical oncology

Palliative chemotherapy

Patients with inoperable locally advanced or disseminated pancreatic adenocarcinoma who fulfil the following criteria should be referred to their local oncologist with an interest in pancreatic cancer for consideration of palliative chemotherapy:

- a WHO performance score of 0 – 2
- adequate bone marrow, renal and hepatic function.
- if the patient wishes to be considered for palliative chemotherapy
- the patient is aware of their diagnosis
- ideally all patients should have a biopsy proven adenocarcinoma

Patients who are being considered for palliative chemotherapy should be encouraged to enter appropriate local or national clinical trials.

The choice of chemotherapy regimen will depend upon an individual patient's performance status. If a patient is fit enough they should be considered for FOLFORINOX. Otherwise combinations of Gemcitabine and other standard cytotoxics such as Capecitabine may be appropriate. If the patient is not fit enough for combination chemotherapy then Gemcitabine alone can be used at 1000 mg/m^2 on day 1, 8, 15 , q28. Gemcitabine infusion is over 1 hour.

The ACELARATE trial is currently open at ELHT. This is a phase 3 multicentre trial comparing Acelarin (NUC-1031) with Gemcitabine in the presence of metastatic disease.

Palliative chemoradiotherapy

Patients with localised pancreatic adenocarcinoma may be candidates for palliative chemoradiotherapy if they fulfil the following criteria:

- a WHO performance score of 0 – 2
- have a biopsy proven adenocarcinoma
- have a tumour ≤ 5cm in maximum diameter on a current CT or MRI scan
- have no evidence of metastatic disease

Suitable patients should be considered for inclusion in clinical trials of chemoradiotherapy. A recent phase II randomised trial of chemotherapy (Gemcitabine and Capecitabine) followed by chemoradiotherapy if the cancer did not progress (SCALOP) has just been completed. The results were encouraging and a further trial SCALOP II which includes 5 arms involving chemotherapy alone and chemoradiotherapy at different doses +/- nelfinavir is now open.

12 Palliative care and support

Patients with pancreatic cancer will have access to specialist palliative care and support at any stage of their illness.
The level of palliative care support may vary but referral to specialist palliative care services should be based on need and not on diagnosis. Referral should be considered for:

- Complicated and uncontrolled symptoms
- Complex psychological and social issues
- Difficulties in adjusting to the diagnosis or disease progression

The subsequent care package will be dependent upon an assessment by a member of the specialist palliative care team and should be made in agreement with the patient, carers and referring team.

13 Cancers of unknown primary

Any patient with metastatic cancer from an unknown primary will be referred for discussion at the carcinoma of unknown primary (CUP) MDT.

14 Site of Investigation and Treatment

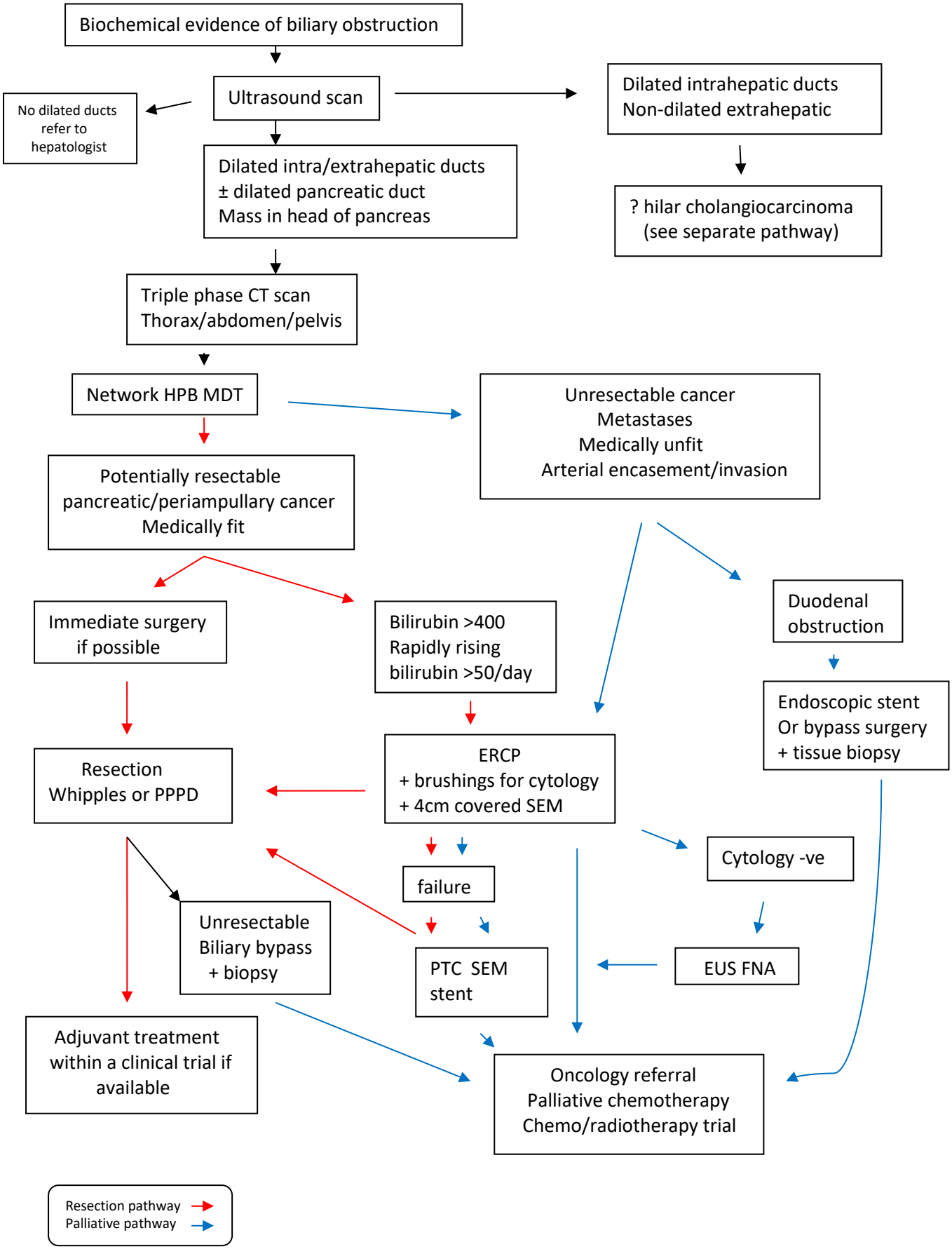
Investigations : all investigations can be performed at the local UGI unit other than PET/CT which is referred to LTHT (Preston). EUS is performed at ELHT with some capacity at BVH.

Stenting : ERCP and PTC stenting can be performed at all local UGI units after discussion with the HPB MDT – level 2 care. Complex cases can be referred to ELHT for stenting.

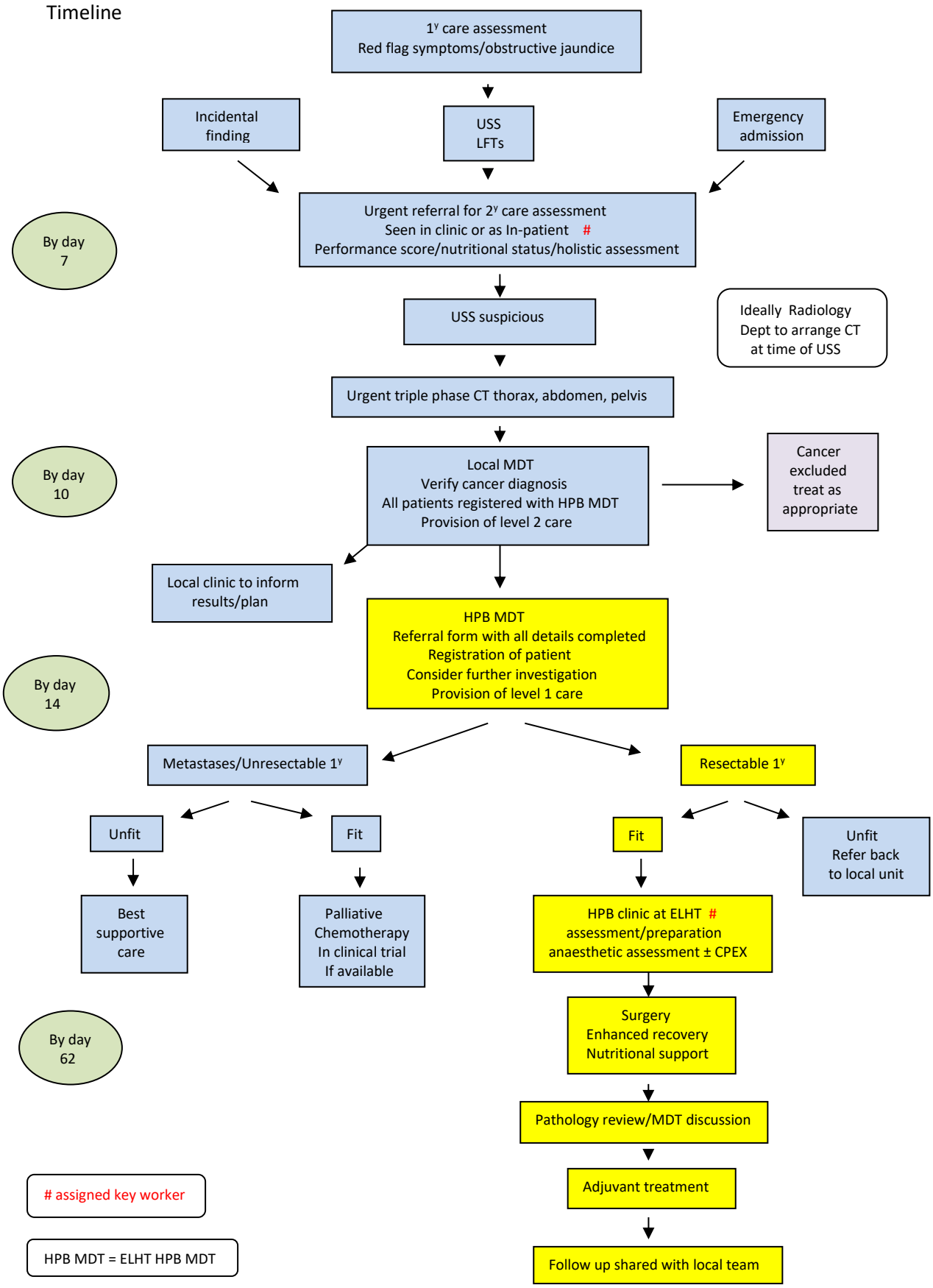
Chemotherapy : all chemotherapy can be performed at the local chemotherapy unit – level 2 care.

Surgery : all pancreatic surgery will be performed at ELHT (Blackburn) – level 1 care.

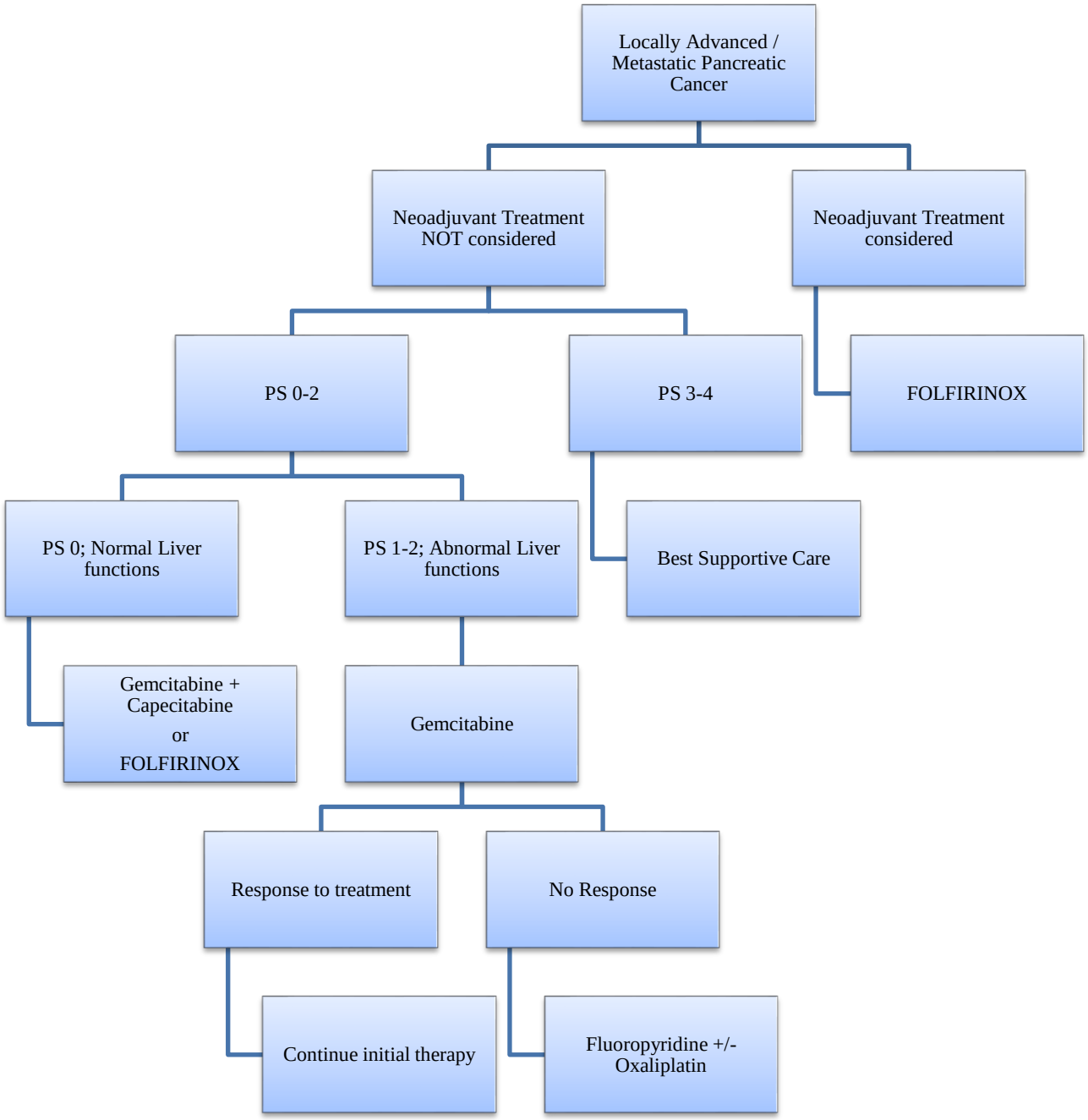
PATIENTS WITH PAINLESS OBSTRUCTIVE JAUNDICE



Clinical Pathway for Pancreatic and Periampullary Cancer



Pathway for Advanced/ Metastatic Pancreatic Cancer



Chemotherapy regimens can be accessed via this link http://www.gmlscscn.nhs.uk/index.php/networks/cancer/network-groups-meetings/lancashire-south-cumbria/chemotherapy

Whenever possible, eligible patients should be offered access to treatment as part of clinical trials

Pancreatic Cysts
(Version 3 2019)

The incidental identification of pancreatic cysts is becoming more common with the growing use of cross-sectional abdominal imaging. A small minority of cysts may harbour an early invasive cancer or high grade dysplasia and the challenge is to develop strategies to identify patients most likely to benefit from evaluation, surveillance and/or surgery for these cysts. The overall risk of malignancy in incidental cysts is thought to be low at 0.01% but certain cyst characteristics increase this risk (*infra vide*). Literature reports state no risk of malignancy in serous cystic neoplasms, simple cysts and lymphoepithelial cysts.

Types of Pancreatic Cyst

Pancreatic cysts can be classified into inflammatory fluid collections, non-neoplastic pancreatic cysts and pancreatic cystic neoplasms (PCN) which account for just over half of the cysts. Rarely solid pancreatic tumours can present as a pancreatic cyst.

Inflammatory fluid collections - develop following local complications of acute pancreatitis and include acute peripancreatic fluid collections, pseudocysts, acute necrotic collections in the setting of necrotising pancreatitis and walled-off pancreatic necrosis which is a mature encapsulated collection of pancreatic necrosis containing liquid and solid elements.

Non-neoplastic pancreatic cysts – include true benign epithelial cysts, retention cysts due to obstructed side branch ducts in chronic pancreatitis, lymphoepithelial cysts which may be difficult to differentiate from a PCN.

Pancreatic cystic neoplasms – can be classified into 4 subtypes :

Serous cystic tumours – most of these lesions are serous cystadenomas. The main types include microcystic serous cystadenomas and oligocystic serous cystadenomas. The latter variety may be difficult to distinguish from a MCN or side branch IPMN. These are benign lesions which extremely rarely can become malignant and do not require surgery unless symptomatic. They may be seen as part of von Hippel-Lindau disease (VHL) an inherited autosomal dominant syndrome.

Solid pseudopapillary neoplasms (SPN) – typically occur in young women under the age of 35 and have a malignant potential (approximately 16%) and should be resected. Even in the presence of metastases surgical debulking may prolong survival.

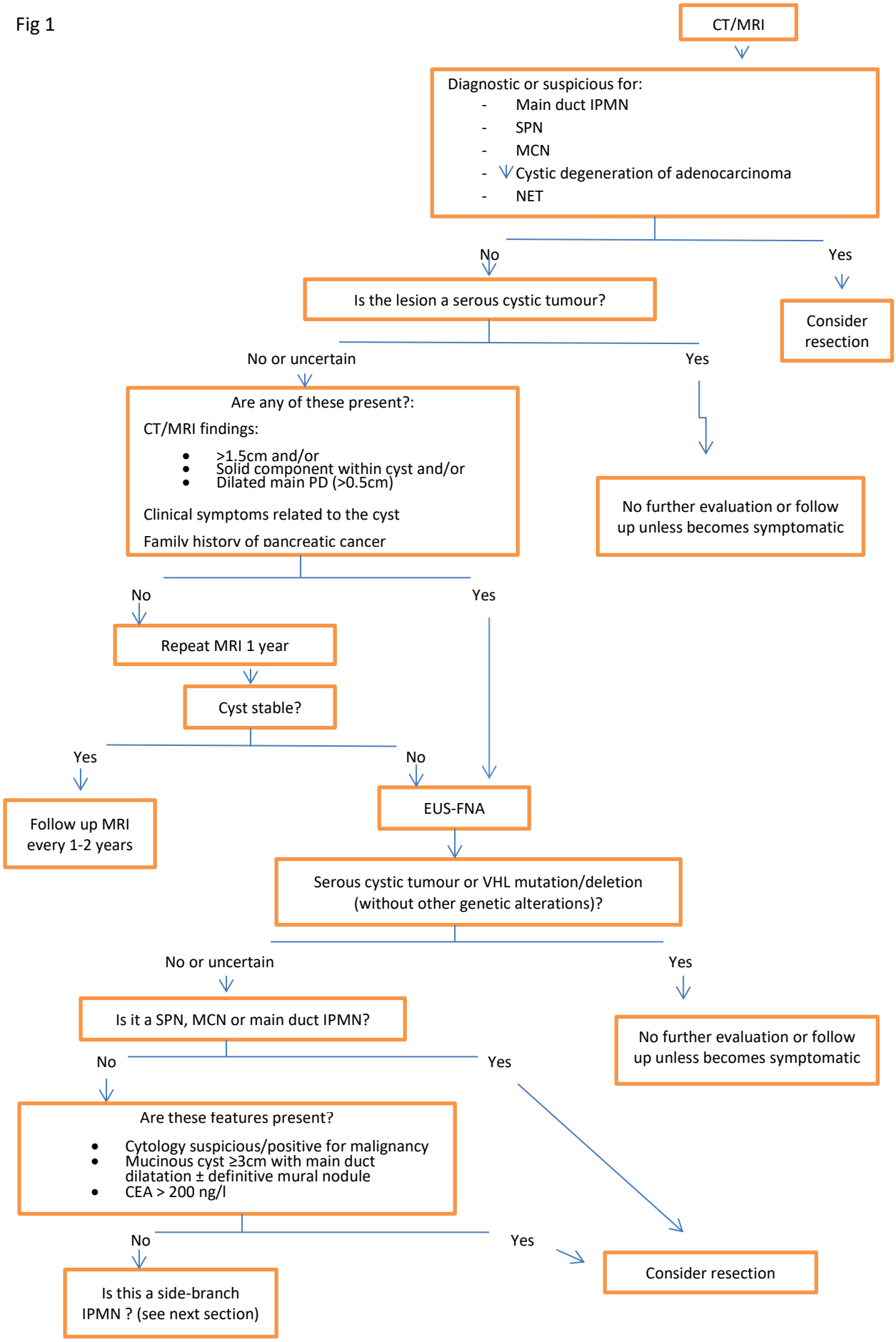
Mucinous cystic neoplasms (MCN) – occur most commonly in women and are usually located in the body and tail of the pancreas. They do not communicate with the pancreatic duct and contain ovarian-like stroma in contrast to IPMN. These lesions have significant malignant potential of 10% to 17% and patients should be offered surgery if fit enough.

Intraductal papillary mucinous neoplasms (IPMN) – see next section

Cystic pancreatic neuroendocrine tumour- are uncommon but account for 13-17% of pancreatic NETs, they are often a component of a large tumour with cystic degeneration but mall NETs with cystic change also occur. There is a 6-31% risk of malignancy.

An algorithm for the management of pancreatic cysts is shown in figure 1.

Fig 1


CT/MRI
Diagnostic or suspicious for:
- Main duct IPMN
- SPN
- MCN
- Cystic degeneration of adenocarcinoma
- NET
No
Yes
Is the lesion a serous cystic tumour?
Consider resection
No or uncertain
Yes
Are any of these present?:
CT/MRI findings:
>1.5cm and/or
Solid component within cyst and/or
Dilated main PD (>0.5cm)
Clinical symptoms related to the cyst
Family history of pancreatic cancer
No further evaluation or follow up unless becomes symptomatic
No
Yes
Repeat MRI 1 year
Cyst stable?
Yes
No
Follow up MRI every 1-2 years
EUS-FNA
Serous cystic tumour or VHL mutation/deletion (without other genetic alterations)?
No or uncertain
Yes
Is it a SPN, MCN or main duct IPMN?
No further evaluation or follow up unless becomes symptomatic
No
Yes
Are these features present?
Cytology suspicious/positive for malignancy
Mucinous cyst ≥3cm with main duct dilatation ± definitive mural nodule
CEA > 200 ng/l
No
Yes
Consider resection
Is this a side-branch IPMN ? (see next section)

Intraductal papillary mucinous neoplasm of the pancreas (IPMN)

IPMN is defined as intraductal mucin-producing neoplasms involving the main pancreatic duct or its side branches that lack the ovarian stroma characteristically seen in mucinous cystic neoplasms. It is the only radiologically identifiable lesion in the pancreas that is known to be a precursor to invasive cancer. The natural history of these lesions is not yet entirely clear but there does appear to be an opportunity to prevent the development of an invasive pancreatic adenocarcinoma.

Literature reports malignancy risk of 38% to 68% for main duct IPMNs (MD-IPMNs), 38% to 65% risk for mixed-IPMNs, 12% to 47% risk for branch duct IPMNs (BD-IPMNs). Therefore it is recommended that patient's with main duct IPMN should be considered for surgical resection if deemed fit. The extent of the surgery will depend upon the location of the affected duct within the pancreatic gland but may involve anything from a segmental resection to a total pancreatectomy.

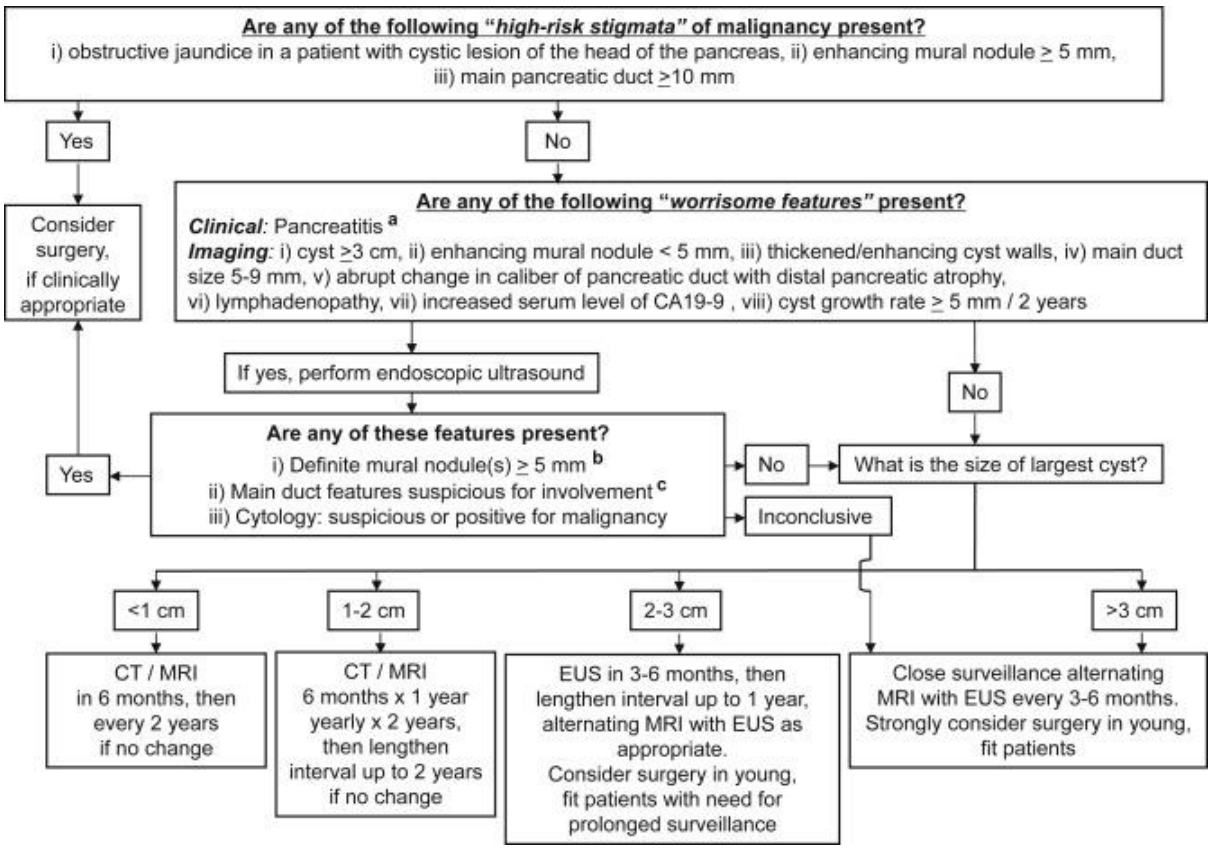
Side-branch IPMN's are usually identified as small cystic lesions in the pancreas with a prevalence of 2-3% in healthy, asymptomatic individuals who have had a CT or MRI scan of the abdomen. They are far more common than main duct IPMN's and are usually managed by surveillance in most HPB centres. However there has been ongoing debate about the best strategy for dealing with these lesions with recommendations ranging from aggressive surgical resection[1] to the conservative approach adopted in the American Gastroenterology Association guidelines[2]. The European Study group on cystic tumours of the pancreas produced guidelines in 2013 which were revised in 2018 and the International Association of Pancreatology produced guidelines following a consensus symposium in Fukuoka, Japan in 20132 which were revised in 2017. The main features on prediction of malignancy are shown in the table below:

Selected features of BD-IPMNs for predicting high risk of malignancy by the guidelines

Fukuoka 2017	European 2018	AGA 2015
High-risk stigmata • Obstructive jaundice• • Enhancing solid component • MPD ≥10 mm Worrisome features • Cyst >3 cm • Thickened/enhancing cyst wall • MPD 5-9 mm • Abrupt change in PD caliber with distal pancreatic atrophy • Lymphadenopathy • Increased serum level of Ca 19-9 • Cyst growth rate >5mm/2yrs	High-risk features • Jaundice • Enhancing mural nodule >5mm or a solid component • Dilated MPD>10mm Increased risk • MPD 5-9.9mm • Cyst Growth rate> 5 mm/year • Serum level Ca 19-9 >37U/ml • Presence of symptoms • enhancing mural nodules<5mm • cyst diameter >40mm	High-risk features • Cyst >3 cm • Associated solid component • Dilated MPD

It is clear from the literature that the optimum management for this condition is evolving. However the decision to treat side-branch IPMN's in particular with surgery needs to balance the morbidity and mortality against the cumulative lifetime risk of developing malignancy. In addition long term surveillance of these pancreatic lesions needs to take into account the patient's age-adjusted cumulative risk for malignancy and their fitness for surgery. In the future set criteria such as the Charlson co-morbidity index score may help to guide decisions for individual patients. Given the current evidence currently we have adopted the revised international consensus Fukuoka guidelines produced by the International Association of Pancreatology in 2017[3]. An algorithm summarising the clinical management of side-branch IPMN is shown in fig 2. These recommendations were introduced to avoid too many unnecessary surgical resections for benign pancreatic lesions. However the indications for surgery and surveillance are likely to change as more information about this condition is published and the guidelines will be updated accordingly.

Fig 2 (Adapted from Tanaka et al[3])



Alogorithm for the management of suspected BD-IPMN
a pancreatitis may be an indication for surgery for relief of symptoms. b differential diagnosis includes mucin. Mucin can move with change in patients position, may be dislodged on cyst lavage and does not have Doppler flow and FNA of nodule include lack of mobility, presence of Doppler flow and FNA od nodule showing tumour tissue. c presence of any one of thickened walls, intraductal mucin or mural nodules is suggestive of main duct involvement . In their absence main duct involvement is inconclusive.

EUS-FNA of cystic lesions

Endoscopic ultrasound guided fine needle aspiration provides high quality imaging and a means to sample pancreatic lesions. Cyst fluid should be assessed for viscosity by visual inspection ‘string sign’ and sent for analysis for cytology, CEA level and amylase level. Cytology usually reveals a paucicellular specimen however with appropriate staining mucin can be identified. FNA of mural nodules may increase cytology sensitivity. The CEA level is the most accurate tumour marker for diagnosing a mucinous PCN. Using a cut-off level of 192 ng/l has a sensitivity of 73% and a specificity of 83%.
Other molecular markers including mutations in KRAS, GNAS and TP53 are under investigation but their clinical application is still to be determined.

REFERRAL GUIDELINES FOR PATIENTS WITH COLORECTAL LIVER METASTASES

(Version 10 2019)

Surgical resection offers the only potentially curative option for patients with liver only metastatic colorectal cancer. Appropriately selected patients treated by surgery will have five year relapse-free survival rates of about 30% and five year overall survival rates of between 45 - 50%.

Indications for referral

All patients with liver metastases from a primary colorectal cancer should be considered for a liver resection and referred for discussion at the HPB MDT unless the patient has uncontrollable extrahepatic disease such as :

- non treatable primary tumour
- widespread pulmonary disease
- unresectable loco-regional recurrence
- peritoneal disease
- extensive nodal disease, such as retroperitoneal, mediastinal or portal nodes
- bone or CNS metastases

or the patient is unwilling to have further treatment or is unfit for further treatment.
Patients with more than 5 liver metastases scattered throughout the liver are less likely to benefit from surgery but each case should be looked at individually.

Staging investigations at presentation of primary

It is presumed that all patients will have undergone a staging CT scan of the chest, abdomen and pelvis with intravenous contrast (ideally at a maximum collimation of 5mm) for the primary colorectal cancer.
The whole of the colon will have been visualised.
A baseline CEA measurement should be performed.

Liver biopsy

Biopsy of a suspicious liver lesion or likely metastasis should **not** be performed unless first discussed at the HPB MDT. Most of the patients will have positive histology from the colorectal primary. Needle biopsy of a liver metastasis may result in implantation metastases.

Referrals to the HPB MDT

To avoid unnecessary delays for the patient all referrals to the HPB MDT should include all relevant information about the patient. This will include the initial oncology annotation, past medical history, performance status, details of treatment (chemotherapy, radiotherapy, surgery etc), histology, date of scans and where performed, tumour markers and relevant blood tests.

Synchronous liver metastases

Patients found to have liver metastases at the time of their initial presentation with a primary colorectal cancer should be discussed at the HPB MDT.

Unless the patient required an emergency colonic resection for the primary a PET/CT scan and a liver MRI scan with a liver specific contrast agent should be performed **before** starting chemotherapy or resection of the primary or before chemo-radiotherapy of rectal tumours.

Patients with potentially resectable liver disease and who have undergone radical resection of the primary tumour should be considered for adjuvant chemotherapy (eg FOLFOX) prior to liver resection.

The management of patients with synchronous liver metastases and a relatively asymptomatic colorectal primary can be approached by three different strategies. All the options can be prefaced with a course of neoadjuvant chemotherapy (currently FOLFOX4 for up to 6 cycles – see Network colorectal chemotherapy guidelines).

- The classical approach of resection of the primary tumour followed by liver resection for the metastatic disease.

- Simultaneous resection of both the primary tumour and the liver metastases (see below)

- The reverse approach of liver resection prior to the colorectal resection.

There are advantages and disadvantages to each approach. However, the decision regarding operative strategy should be prioritised based on whether the primary is causing symptoms, followed by which of the two sites presents the greatest oncologic risk. The best management will need to be tailored to the individual patient's circumstances and therefore it is essential that all patients are discussed at the HPB MDT.

Following completion of all surgery patients should be considered for a further 6 cycles of adjuvant chemotherapy (eg FOLFOX4).

Synchronous liver and primary resection

Most patients will have the liver disease resected at a different time to the primary tumour. However in some circumstances it may be appropriate to resect all the disease at one operation. In general provided the patient is fit a right sided colon resection can be combined with any liver resection other than an extended hemihepatectomy. Only a minor liver resection of a peripheral segment/ left lateral segmentectomy/or metastectomies should be considered with a left sided colon resection when it may be more likely that the patient will need a stoma.

Individual cases will need to be discussed with the HPB and Colorectal teams.

Metachronous liver metastases

Follow up after resection of the primary colorectal cancer will be according to local protocol but it is recommended that a CT scan of the chest, abdomen and pelvis should be performed as a minimum in the 2 years following completion of treatment of the primary.

Patients found to have liver metastases during follow up should be discussed at the HPB MDT prior to any further treatment.

If there is no obvious extrahepatic disease patients should have a PET/CT scan. If this also confirms there is no extrahepatic disease patients should then have a MRI scan with a liver specific contrast agent prior to liver resection.

Currently it is unclear whether there is any benefit in giving neoadjuvant chemotherapy to patients with resectable disease. A randomised trial of peri-operative FOLFOX4 (EPOC) showed an improved progression-free survival (the primary end point) but did not improve overall survival (a secondary end point) when compared with surgery alone. A sub-group analysis suggested that patients with good performance status (PS) and a high CEA may benefit from peri-operative chemotherapy whereas those with a poor PS (≥1) and a low CEA are less likely to benefit.

Treatments will need to be tailored to individual patients and therefore the merits of peri-operative chemotherapy should be discussed between the HPB team and the oncologist.

After discussion at the HPB MDT patients who have been referred for liver resection should have their original scans sent to the HPB surgical unit prior to surgery.

Chemotherapy

Neoadjuvant chemotherapy should be considered for patients with liver tumours that are borderline for resection in order to try to downsize these tumours and achieve a R0 resection. These patients should have a PET/CT scan and if there is no evidence of extrahepatic disease they must also have a liver MRI scan with a liver specific contrast agent prior to chemotherapy because:

- These imaging modalities are complementary
- Liver metastases occult in one modality may be apparent in the other
- Initially unidentified liver metastases may ‘disappear’ after chemotherapy and potentially will be missed and left behind at the time of surgery

All these patients should be discussed at the HPB MDT.

A further staging CT scan should be performed after 3 months of chemotherapy and the patient re-discussed at the HPB MDT.

Patients should be carefully monitored during chemotherapy treatment and as soon as the metastases become resectable they should proceed to surgery without waiting for the best

radiographic response to chemotherapy, Delaying surgery and continuing chemotherapy may lead to pathological changes in the liver including chemotherapy-associated steatohepatitis (CASH) and sinusoidal obstruction syndrome (SOS). This leads to a significantly higher post-operative morbidity and mortality. It is important that there is close collaboration between the patient's oncologist and HPB surgeon.

There is some evidence to suggest that there may be a role for adjuvant chemotherapy when the resected metastasis is >5cm in size or there are poor prognostic features such as vascular invasion, tumour emboli, multiple tumours, node positive primary, disease free interval of <12months, or if the patient has not received any previous chemotherapy for metastatic disease. However a randomised trial of adjuvant chemotherapy with modern chemotherapy such as oxaliplatin is still awaited.

The place of biological agents such as cetuximab, bevacizumab and panitumumab have yet to be fully determined. For instance although the addition of cetuximab to chemotherapy in patients with operable colorectal liver metastases increases the pre-operative response rate the progression-free survival is much worse in cetuximab treated patients (new EPOC study 2013). Their role in the management of colorectal cancer is outlined in the Network Colorectal Chemotherapy guidelines.

https://www.healthierlsc.co.uk/canceralliance/chemotherapy-protocols/colorectal-chemotherapy-protocols-algorithms

Patients who develop new liver metastases or new sites of extrahepatic disease while on chemotherapy will have a poor prognosis and should not undergo liver resection unless a response to other therapy can be demonstrated.

10 – 15% of patients with initially unresectable liver metastases may eventually become suitable for surgery with chemotherapy. However, long courses of chemotherapy increase the potential for liver toxicity and peri-operative morbidity.

Liver surgery after chemotherapy

Surgery should be delayed until at least 4 weeks after the last cycle of FOLFOX and for at least 6 weeks after the last dose of cetuximab/bevicuzumab to reduce the risks of post-operative complications.

Assessment and Liver Surgery

Patients for a liver resection will be assessed by a hepatobiliary anaesthetist at ELHT who may arrange a CPEX test depending upon the patient's fitness.

Suitable patients will be selected for laparoscopic liver resections.

All patients will be entered into an enhanced recovery programme (ERP) for their surgery. Further information will be provided at the HPB clinic where patients will be introduced to their key worker.

Bilobar Liver Metastases

Patients with bilobar disease will be considered for staged liver resections and if necessary portal vein embolisation (PVE) to promote liver hypertrophy and ensure safer major resections.

Portal Vein Embolisation

Pre-operative PVE is a valuable adjunct particularly for tumours on the right side of the liver. Following liver surgery an adequate future liver remnant (FLR) is necessary to avoid post-operative liver failure. Patients with a predicted marginal FLR (ie <30% in the presence of a normal liver, <35% in those with non-alcoholic steatohepatitis, and <40% in those with cirrhosis or a remnant liver to body weight ratio>0.5) may benefit from PVE. However, the response to PVE will depend upon any underlying liver dysfunction and systemic disease such as diabetes mellitus. The need for PVE will be assessed at the HPB MDT and the procedure if required arranged at ELHT.

In addition Associating Liver Partition and Portal Vein Ligation for Staged hepatectomy (ALLPS) may be a useful technique for suitable patients.

Ablative therapy

Patients not suitable for liver resection (e.g. extensive co-morbidity, patient choice, irresectable tumours) may be offered ablative treatment (microwave ablation). There is no evidence to support the value of ablative therapies in colorectal liver metastases that can be resected. However ablative therapy may be indicated for awkwardly placed metastases in combination with liver resection. This would be assessed at the HPB MDT and the procedure arranged at ELHT.

Pathology

Detailed assessments will be performed of all resected liver specimens according to the guidelines and datasets published by the Royal College of Pathologists. Results will be discussed at the HPB MDT.

Clinical Trials

All patients will be offered the opportunity of participating in a clinical trial where available. The HPB surgical lead will review the list of colorectal liver metastases trials on behalf of the HPB MDT in conjunction with the colorectal oncologists.

Audit

All patients will be entered into a central database and the results audited. Complications will be recorded and graded according to the Clavien-Dindo classification of surgical complications.

Follow up after liver resection

Follow up after liver resection will be for a minimum of 5 years. A baseline CT scan of chest, abdomen and pelvis should be performed 4 - 6 months after surgery depending upon whether the patient received adjuvant chemotherapy and then at 12, 18 months and 2 years, and then on an annual basis for a total of 5 years. These scans can be performed at the patient's local hospital but should be reviewed by the HPB MDT. CEA levels should be measured at each clinic visit. Out patient reviews can be 4 monthly in the first two years, 6 monthly for the third year and then on an annual basis. Follow up will be shared between the HPB team and the oncology or colorectal team.

Approximately 70% of patients who undergo a liver resection will eventually develop recurrent disease of which 20 – 30% will be isolated to the liver. Repeat hepatic resection or ablation therapy as well as chemotherapy can be considered and therefore these patients should be discussed at the HPB MDT.

Patients will remain under the care of the local colorectal team for surveillance colonoscopy according to local protocol.

Cancers of unknown primary

Any patient with metastatic cancer from an unknown primary will be referred for discussion at the carcinoma of unknown primary (CUP) MDT.

Site of Investigation and Treatment

Investigations : all investigations can be performed at the local colorectal unit other than PET/CT which is referred to LTHT (Preston). Liver MRI scans can be arranged either locally or at ELHT (Blackburn).

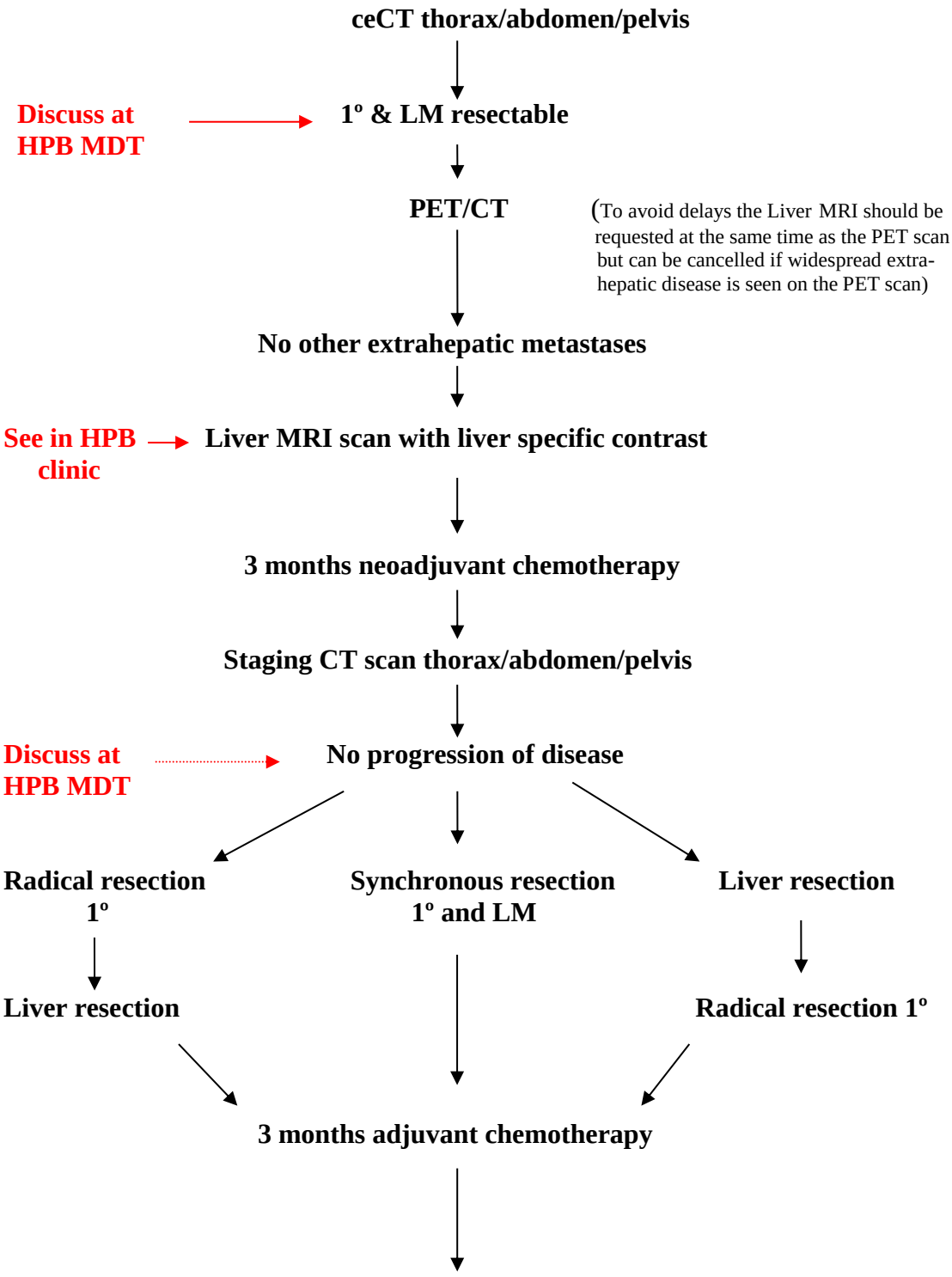
Chemotherapy : all chemotherapy can be performed at the local chemotherapy unit – level 2 care.

Surgery : all liver surgery will be performed at ELHT (Blackburn) – level 1 care.

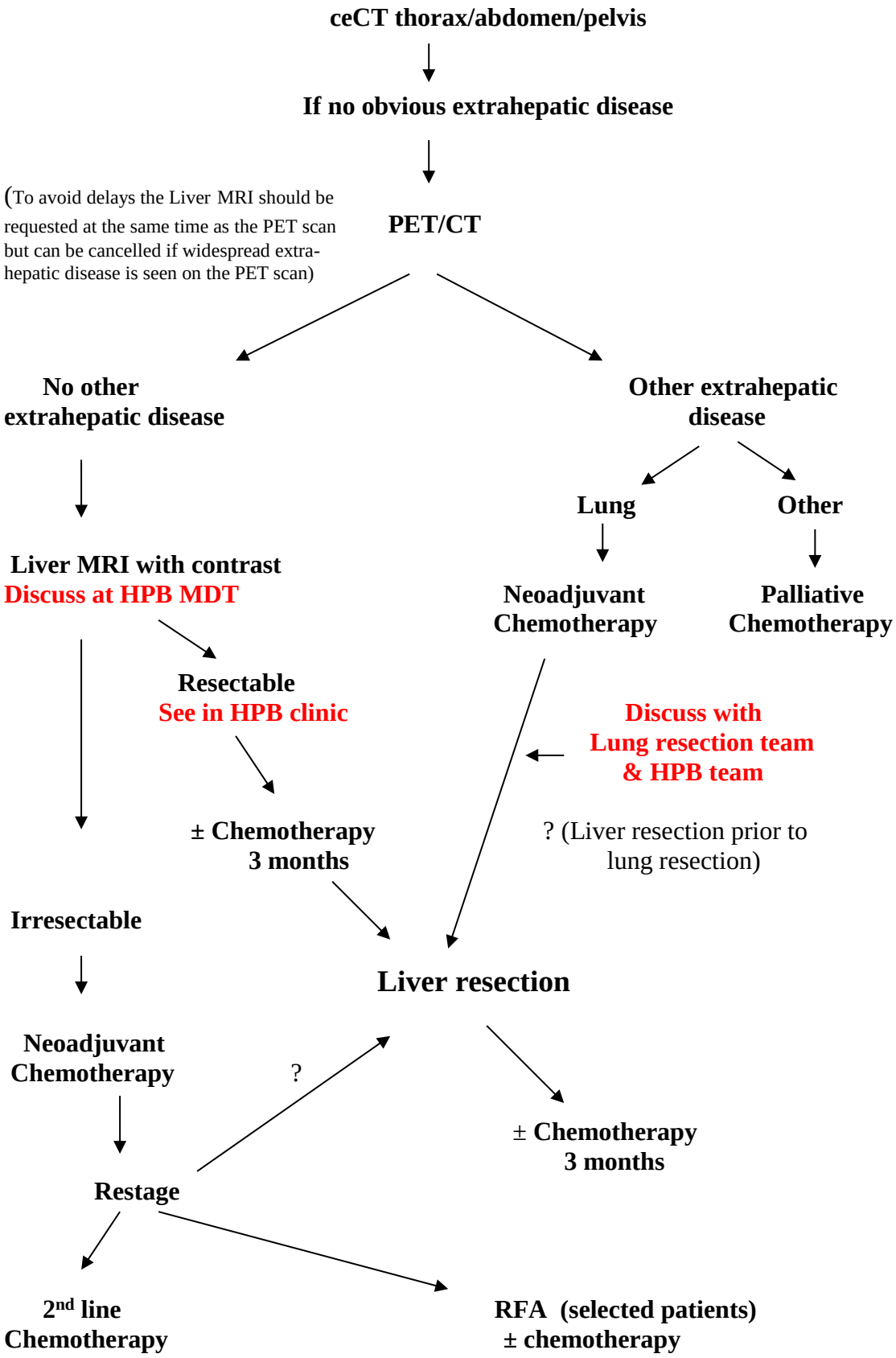
Ablation: all ablative therapy will be performed at ELHT (Blackburn) – level 1 care.

These guidelines are based upon the BSG 'Guidelines for resection of colorectal cancer liver metastases' published in August 200, ESMO consensus guidelines for the treatment of patients with metastatic colorectal cancer' published 2016, and the latest peer reviewed publications. The guidelines will be reviewed annually to take into account new studies and research.

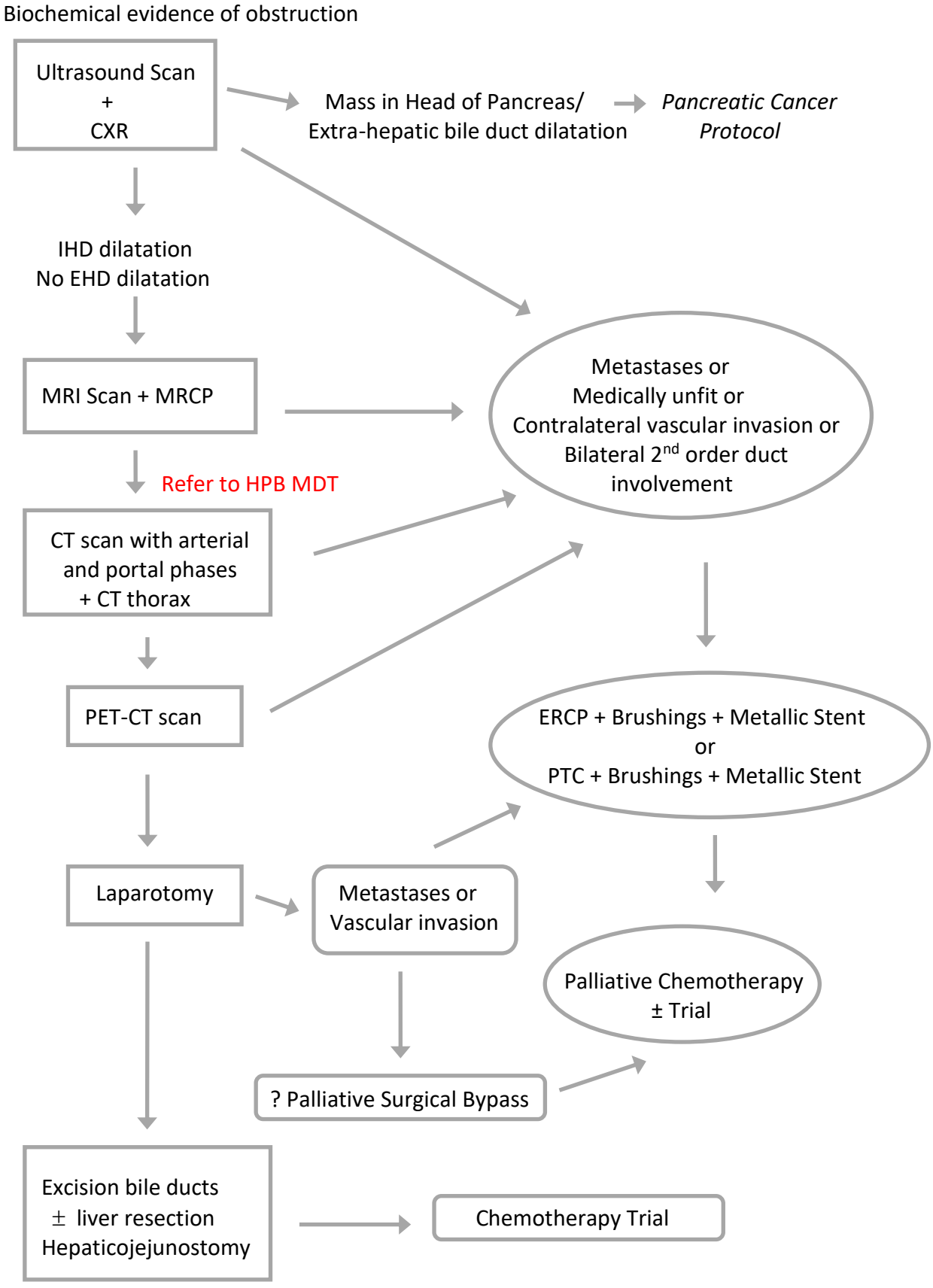
SYNCHRONOUS LIVER METASTASES (LM)



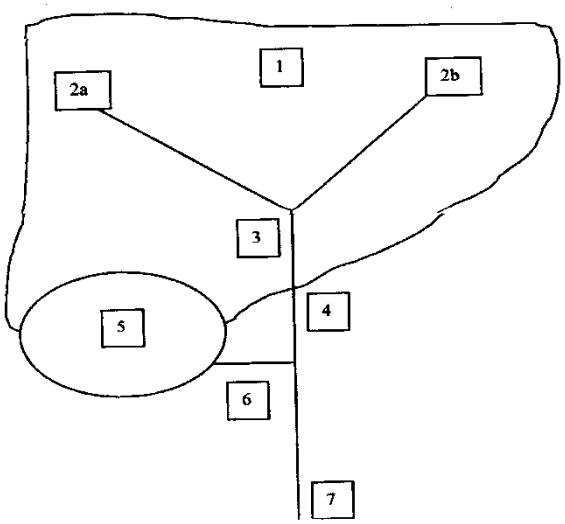
METACHRONOUS LIVER METASTASES (LM)



OBSTRUCTIVE JAUNDICE -
SUSPECTED HILAR CHOLANGIOCARCINOMA



Notes on cholangiocarcinomas



Intrahepatic Cholangiocarcinoma

1= peripheral cholangiocarcinoma

2a,b= right & left hepatic ducts

3= confluence of right & left hepatic ducts (Klatskin tumours)

Extrahepatic

4= common hepatic duct

5= gallbladder

6= cystic duct

7= common bile duct

Diagnosis

There are no diagnostic blood tests for cholangiocarcinoma but Ca19-9 should be checked as it is raised in up to 85% of patients.

After an initial ultrasound screening patients should have a combined MRI and MRCP. A good quality MRI scan gives information on liver and biliary anatomy, local extent of tumour and presence of liver metastases.

A staging CT scan of the thorax and abdomen with arterial and portal phases will exclude metastases and may indicate the extent of hilar vascular involvement.

A PETCT scan can be helpful in excluding the presence of distant metastases.

If there is doubt about the diagnosis an ERCP can be performed to obtain bile fluid and brushings for cytology. A stent should then be placed to try to avoid subsequent cholangitis. Alternatively a spyglass procedure may be undertaken which may provide biopsy material for histology.

Stenting

Stents should be avoided prior to assessing surgical resectability except in the presence of acute cholangitis. It is essential that all patients are discussed with the HPB MDT or one of the HPB surgeons before considering biliary drainage.

Plastic stents are often used for palliation but if the estimated survival is expected to be greater than 6 months then metal stents should be used. This should be discussed with the HPB MDT.

Surgery

Surgery is the only curative treatment though only a minority of patients are suitable for resection. For hilar tumours an en bloc resection of the extrahepatic bile ducts, plus a right or left hepatectomy plus excision of segment 1.

Distal cholangiocarcinomas are managed by pancreaticoduodenectomy.
Intrahepatic cholangiocarcinoma is treated by resection of the involved segment or lobe of the liver.
All surgery to be performed at ELHT (level 1 care).
Patients should be considered for adjuvant chemotherapy in a clinical trial setting after successful surgery.

Inoperable disease

Patients with inoperable disease should be considered for chemotherapy clinical trials. In the absence of a suitable trial patients who fulfil the following criteria should be referred for consideration of palliative chemotherapy :

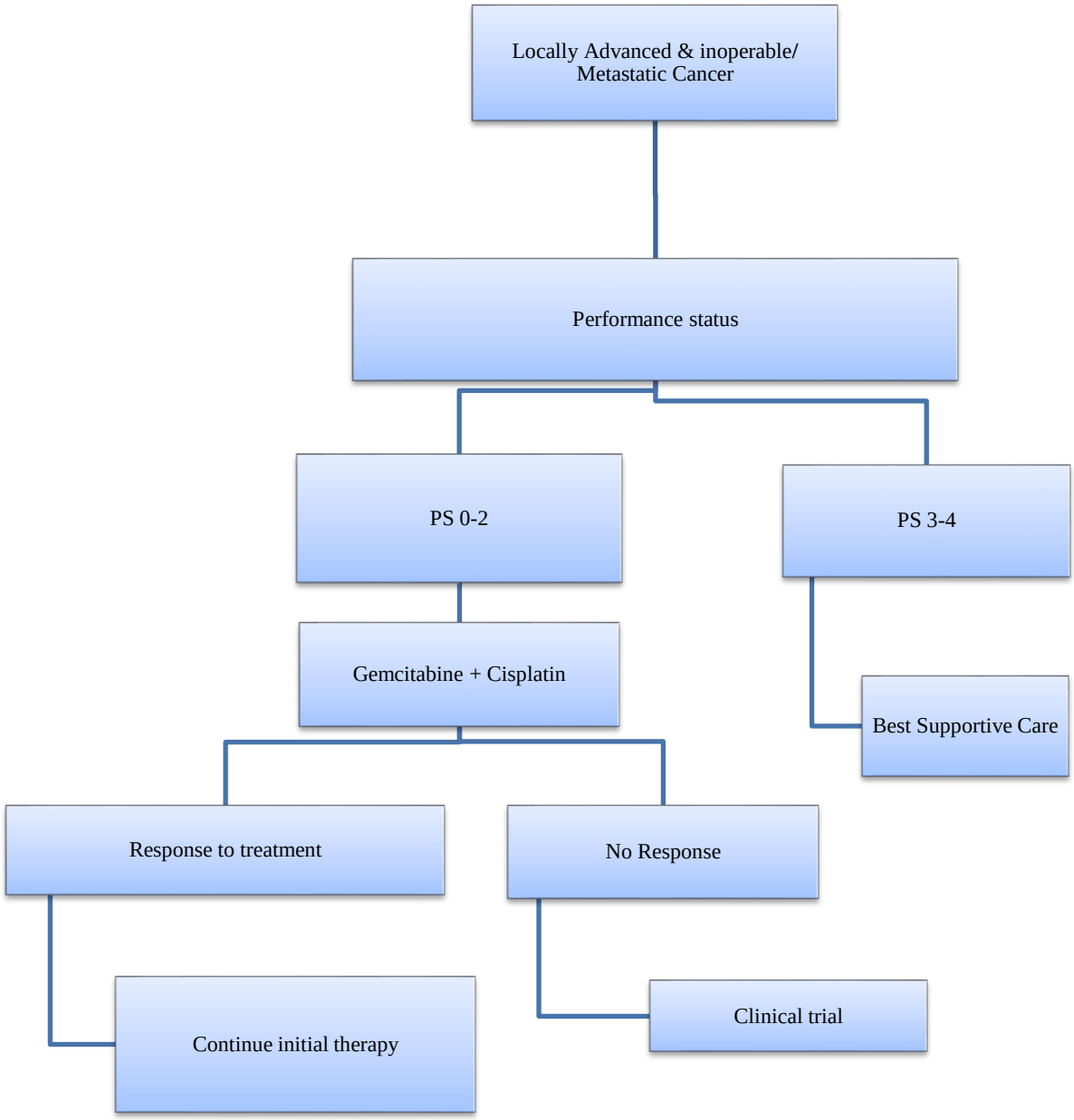
1 a performance score of 0-2
2 adequate bone marrow, renal and hepatic function
3 a life expectancy >12 weeks
4 if they wish to be considered for chemotherapy
5 ideally all patients should have histological or cytological proven cancer

A combination of gemcitabine, cisplatin or single agent gemcitabine can be used. Second line oxaliplatin/5-FU/LV treatment has shown to improve OS compared to BSC (in patients pre treated with gemcitabine) and may be regarded as a standard of care in patients who have progressed on first line gemcitabine. Treatments can be provided at ELHT, LTHT, MBUH, BVH (level 2 care).

Gallbladder Cancers

Patients who have suspicious radiological features of gallbladder cancer should be discussed at the HPB MDT prior to any decision about surgery.
Patients found to have a gallbladder cancer on histology after a cholecystectomy should be discussed at the HPB MDT with the original operation note, a baseline CT thorax, abdomen and pelvis and review of the histology by the ELHT HPB pathologist. As long as there is no evidence of metastatic disease further surgery in the form of a liver resection, lymphadenectomy +/- bile duct excision should be considered for patients with T1b – T3 disease.

Algorithm for advanced cholangiocarcinomas and gallbladder cancer

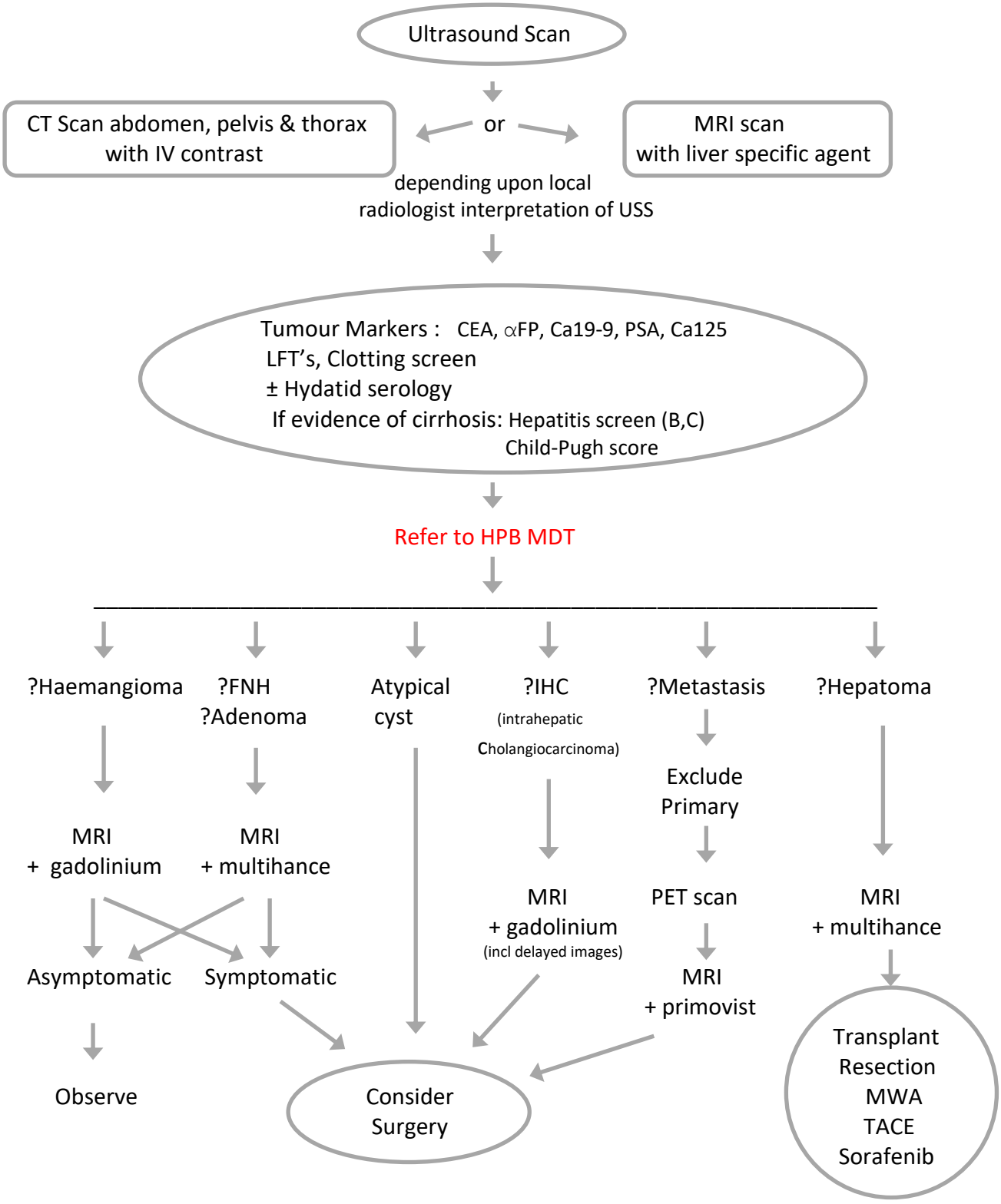


Chemotherapy regimens can be accessed via this link
https://www.healthierlsc.co.uk/canceralliance/chemotherapy-protocols/upper-gi-hpb-

Whenever possible, eligible patients should be offered access to treatment as part of clinical trials.

PATIENTS WITH A SOLITARY LIVER LESION

<u>NO BIOPSY</u> OF LESION UNTIL DISCUSSED WITH AN HPB SURGEON



- **No biopsy** if considering curative surgical resection
- Consider resection of liver lesion if no extrahepatic metastases

Investigation of Solitary Liver Lesions

For some liver lesions an ultrasound scan may be adequate for diagnosis but where further information is required and a second line investigation is necessary then this will depend upon the local radiologist's initial interpretation of their findings and the clinical information. The decision for MRI or CT should be made by the local radiologist. For example if there is concern that the liver lesion is a metastasis then a dynamic CT scan of the thorax, abdomen and pelvis may be appropriate to not only characterise the liver lesion but also to look for a primary. However if the lesion is thought to be a haemangioma a MRI with multiple phases of contrast is more appropriate especially when considering radiation dose.

If there is any doubt then the case can be discussed at the Network HPB MDT prior to deciding if CT or MR is the better imaging modality.

It is important to remember that percutaneous liver biopsies can lead to seeding of tumours. Therefore if curative surgery is to be contemplated for a liver lesion biopsies should be avoided unless first discussed with the HPB team.

Hepatocellular Carcinoma (HCC)

The incidence of primary liver cancers is increasing in our region which may be related to the high levels of excess alcohol intake and prevalence of chronic viral hepatitis in our population. There is also an increasing issue with obesity and non-alcoholic fatty liver disease (NAFLD). At present surveillance of high risk groups should include 6 monthly liver USS.

The management of hepatocellular carcinoma in our Cancer Network is based upon the revised national guidelines issued in March 2009 (*UK guidelines for the management of suspected hepatocellular carcinoma (HCC) in adults. SD Ryder. March 2009 version*) which are an update on the 2003 guidelines, the *Guidelines for liver transplantation for HCC* (www.uktransplant.org.uk/ukt/) and the EASL clinical practice guidelines : management of hepatocellular carcinoma (J of Hepatology 2018; 69;182-236).

The outlook for a patient with HCC depends upon a combination of tumour stage, underlying liver function and their performance status. The heterogeneous nature of HCC has made it difficult have a unifying staging system however the Barcelona Clinic for Liver Cancer (BCLC) system is a widely used to predict survival in untreated patients and is a good guide for clinical decision-making (fig3). In addition we will be increasingly using the CT/MRI LI-RADS® v2018 criteria and diagnostic algorithms for patients with cirrhosis, chronic hepatitis B infection and current or prior HCC.

Surgery

Surgery remains the only potentially curative treatment and either a liver transplant or liver resection should be considered initially. Liver transplantation may be appropriate for patients with cirrhosis and a small tumour (a single lesion ≤5cm or up to 3 lesions of ≤3cm) or if there is a single tumour >5cm and ≤7cm where there has been no tumour progression

over a 6 month period. Locoregional therapy ± chemotherapy can be given during that time. Early discussion with and referral to the Leeds transplant centre is recommended in suitable cases.

Hepatic resection can be carried out in highly selected patients with hepatic cirrhosis and well-preserved liver function (Child-Pugh A) and is the primary treatment in all patients with HCC and a non-cirrhotic liver. Resection in the presence of cirrhosis will depend upon three variables. These include liver function assessed by Child-Pugh stage, model for end-stage liver disease (MELD) score, indocyanine green kinetics (ICG), and liver stiffness measurements; the presence of clinically relevant portal hypertension; and the extent of the resection required. Liver surgery to be performed at ELHT (level 1 care).

Non-surgical management

Local ablation techniques
Radiofrequency ablation (RFA) and Microwave ablation (MA) have been shown to be effective therapy in HCC <3cm in diameter. Percutaneous ethanol injection (PEI) may also have a role in small lesions difficult to treat by RFA or MA. These treatments will be performed at ELHT (level 1 care).
Currently external beam radiotherapy is under investigation and trial results are awaited.

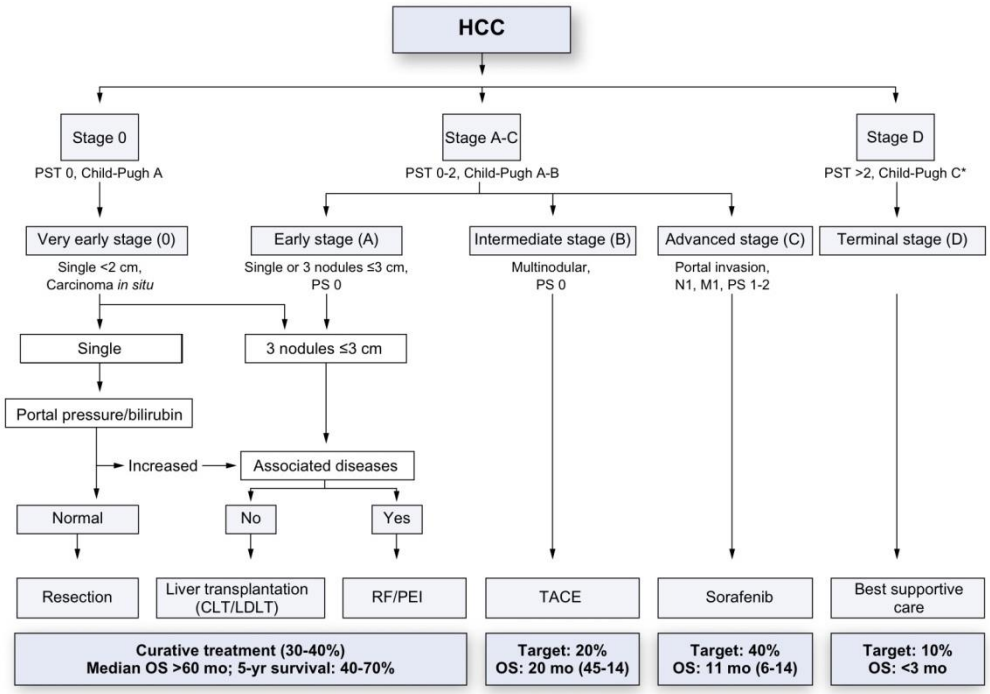
Transarterial Chemoembolisation (TACE)
Chemoembolisation using gelfoam-lipiodol particles or with DC Beads (drug-eluting beads) has been shown to increase survival in selected patients with good liver reserve in the order of 16 – 20 months when compared with best supportive care. Absolute contraindications include decompensated cirrhosis (Child-Pugh ≥B8), severely reduced portal venous flow, tumour burden >50% total liver volume, renal impairment (creatinine clearance <30ml/min) and technical contraindications to intra-arterial treatment. It is contraindicated in the presence of extrahepatic disease. Relative contraindications include segmental or sub-segmental portal vein thrombosis and thrombocytopenia. Doxorubicin is usually used with TACE and therefore patients receiving multiple TACE sessions should have an echocardiogram to check the left ventricular ejection fraction. The cumulative dose should not exceed 450 mg/m^2. TACE treatment is performed at ELHT (level 1 care).

Systemic Treatment
Sorafenib (a multikinase inhibitor) is licensed for patients with advanced HCC who are fit enough to consider systemic chemotherapy (performance score of 0-2, no worse than Child-Pugh A liver impairment). However the Cancer Drug Fund have stipulated that before a patient receives treatment they require a confirmed histological diagnosis unless a liver biopsy is considered to be high risk or technically not feasible in which case this needs to be documented at the HPB MDT, the lesion also has to meet diagnostic radiological criteria and the case has to be audited.
Lenvatinib is also a recommended alternative option for untreated HCC (Child-Pugh A and PS of 0-2). Whilst Regorafenib may be used as second line systemic treatment for those who have had Sorafenib if the Child score is A and PS remains 0-2.
Chemotherapy can be delivered at ELHT, LTHT, MBUH, and BVH (level 2 care).

Liver Transplant referral

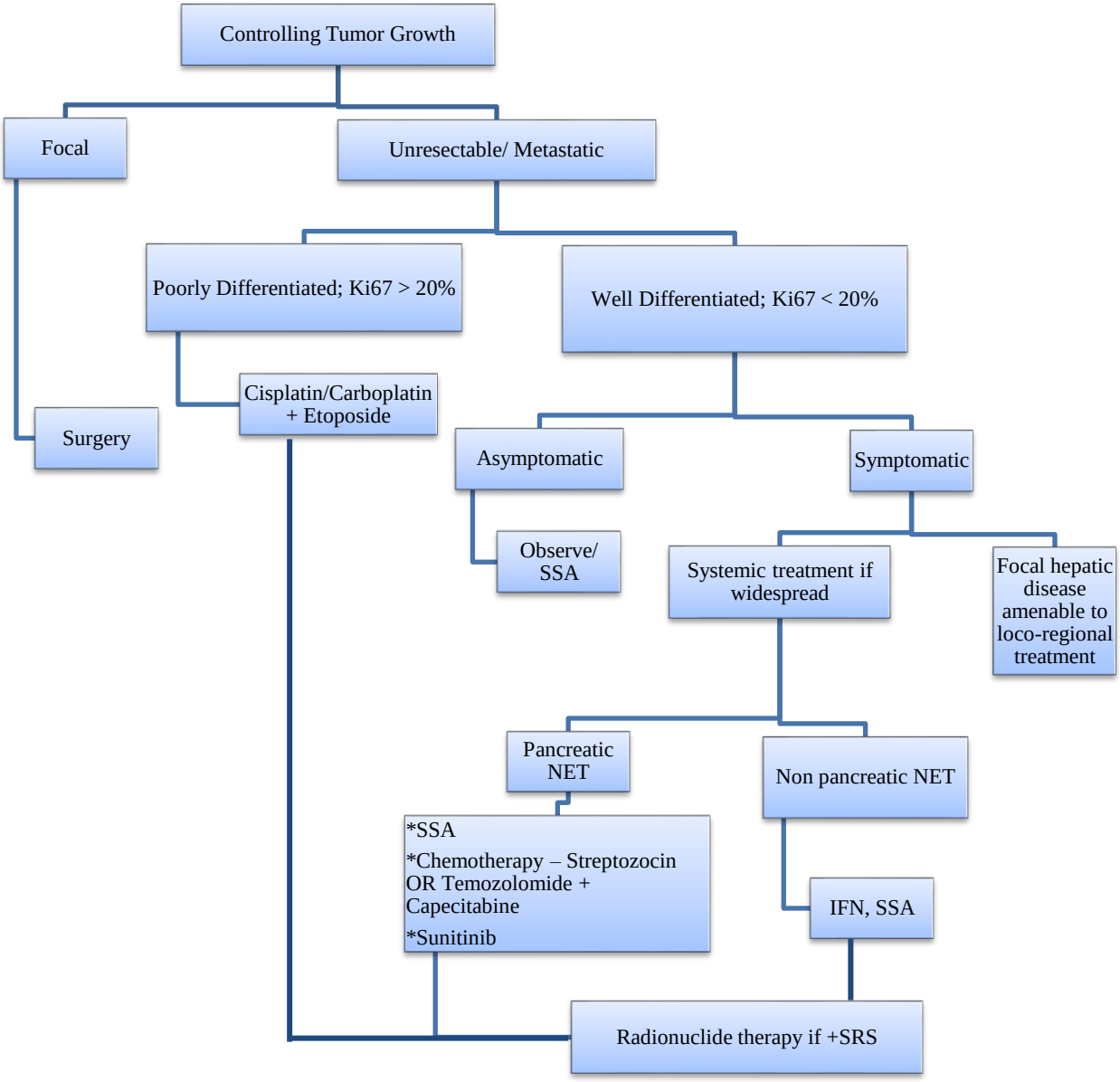
Patients with acute liver failure, cholestatic liver disorders, chronic hepatitis, various miscellaneous conditions and those with liver malignancy such as hepatocellular carcinoma and epithelioid haemangioendothelioma should be considered as potential liver transplant candidates. Discussion with and referral to the Leeds transplant centre is recommended in suitable cases.

Figure 3. Barcelona Clinic for Liver Cancer staging classification and treatment schedule updated 2011



Clinical Practice Guidelines

Pathway for Neuroendocrine Tumors



SSA - Somatostatin Analogue
NET - Neuroendocrine Tumor
IFN - Interferon
SRS - Somatostatin Receptor Scintigraphy / Octreotide Scan
BSC - Best Supportive Care

Whenever possible, eligible patients should be offered access to treatment as part of clinical trials

Communication with the HPB team

HPB MDT Co-ordinator :
Ross Dawson (ross.dawson@elht.nhs.uk)
Direct telephone no 01254 734635

HPB Specialist Nurses :
Elaine Atkinson (elaine.atkinson@elht.nhs.uk)
Joanne Thomas (joanne.thomas@elht.nhs.uk)
Cristina Veneziale (christina.veneziale@elht.nhs.uk)
Direct telephone no 01254 734967

HPB Secretary :
Jane Metcalfe (jane.metcalfe@elht.nhs.uk)
Direct telephone no 01254 734019
Facsimile 01254 736318

HPB Surgeons :
David Chang (david.chang@elht.nhs.uk)
Colin Harris (colin.harris@elht.nhs.uk)
Ambareen Kausar (ambareen.kausar@elht.nhs.uk)
Daren Subar (daren.subar@elht.nhs.uk)
Asma Sultana (asma.sultana@elht.nhs.uk)

EUS gastroenterologists :
Vishal Kaushik (vishal.kaushik@elht.nhs.uk)
Yogi Reddy (yogi.reddy@elht.nhs.uk)
Ash Banerjee (ashwini.banerjee@elht.nhs.uk)

Hepatologists :
Yogi Reddy (yogi.reddy@elht.nhs.uk)
Ioannis Gkikas (ioannis.gkikas@elht.nhs.uk)

ERCP gastroenterologists :
Yogi Reddy (yogi.reddy@elht.nhs.uk)
Ioannis Gkikas (ioannis.gkikas@elht.nhs.uk)
Damien Lynch (damien.lynch@elht.nhs.uk)
Chris Meaden (christopher.meaden@elht.nhs.uk)
Ash Banerjee (ashwini.banerjee@elht.nhs.uk)

Royal Blackburn Teaching Hospital
Haslingden Road
BB2 3HH
Telephone no **01254 263555**
Individuals can be contacted through mobiles via switchboard who have the HPB on-call rota

These guidelines include recent information and recommendations based on current clinical evidence and will be updated annually or when new evidence becomes available.