Agreed Guidelines and Patient Pathways for Colorectal Cancer (Liver Metastases)

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
- 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 (e.g. 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 (e.g. FOLFOX4).

Synchronous liver and primary resection

Most patients will have the liver disease resected separately after removal of 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 hemi hepatectomy. 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 n 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. This is 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 or tumour emboli. 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 aflibercept 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 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 resection which is now standard for lesions in the left lateral segments.

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 (i.e. <20% in the presence of a normal liver, <30% in those with non-alcoholic steatohepatitis, and <40% in those with cirrhosis) will 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 (radiofrequency 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. Mr Chang 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. Outpatient 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 LTHTR (Preston). Liver MRI scans can be arranged either locally or at ELHT (Blackburn).

Chemotherapy: all chemotherapy can be performed at the local colorectal 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 2006 and the latest peer reviewed publications. The guidelines will be reviewed annually to take into account new studies and research.

Communication with the HPB team

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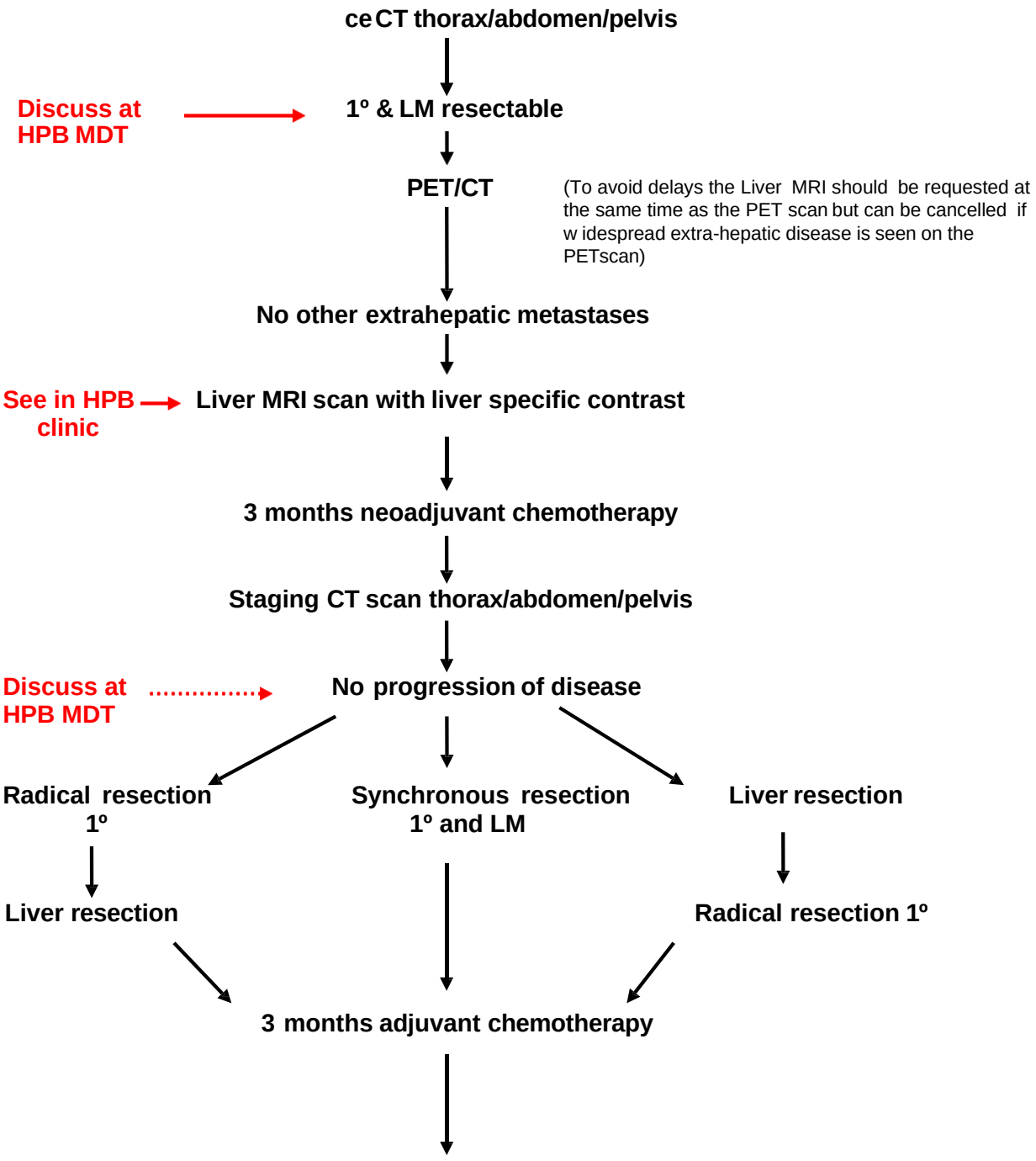
SYNCHRONOUS LIVER METASTASES (LM)



Follow up ceCT (thorax/abdomen/pelvis) at 4-6 months
Joint follow up in Oncology & HPB clinics
Colonoscopy screening by CR team

METACHRONOUS LIVER METASTASES (LM)