King's College Hospital NHS
NHS Foundation Trust

King's College Hospital NHS Foundation Trust
Hepato-biliary and Pancreatic Service

CLINICAL GUIDELINES FOR THE MANGEMENT OF PATIENTS WITH COLORECTAL LIVER METASTASES

as included in the Operational Policy for the care of patients
with suspected hepato-biliary and pancreatic malignancies (HPB)

South East London Cancer Network
Kent & Medway Cancer Network

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Introduction

In September 2006 King's was designated as the specialist centre for all patients with colorectal liver metastatic disease from both the SE London and Kent and Medway Cancer Networks. King's had a successful Peer Review as a Liver Resection MDT for patients with colorectal liver metastases in October 2007.

Recent advances in liver surgery and new chemotherapeutic agents have altered the approach to colorectal liver metastases (CLM) dramatically. Of the almost 50-60% of patients with colorectal cancer who develop liver metastases, it is expected that up to 40% will be amenable to resection, more than doubling the historic resection rate of 10-15%, and more than 40% of these patients will be alive and disease free at 5 years post-resection (compared to an untreated 5 year survival rate of less than 1%).

Therefore, it is recommended that the majority of patients with CLM are assessed by a specialist HPB MDT, for resection of their disease. In fact, most authorities agree that the only independent limiting factor (out with co-morbidity preclusion) for resecting CLM is the volume of the remaining functional liver.

Referral guidelines

Patients with synchronous liver metastases, with treatment for their primary disease planned/underway, should be referred to King's, following discussion at an outreach MDM, with a copy of the outreach MDM outcome and proforma for tracking purposes and to enable the advice given by the King's HPB surgeon to be logged. These patients will not be required to attend for King's outpatient review unless subsequent outreach MDM review decides this is appropriate at a later date.

Patients who have developed liver metastases subsequent to treatment of their primary, where resection of their liver disease is considered possible if downstaged, at outreach MDM, and who are awaiting/undergoing second-line chemotherapy should be referred to King's with MDM outcome and completed proforma, again for tracking purposes and to enable advice given by King's surgeon to be logged. We recognise that there may be a subsequent c.3-6 month wait while the patient completes chemotherapy.

Patients whose liver disease is deemed immediately resectable at an outreach MDM should be referred up with MDM outcome, proforma and all imaging for review at the King's liver resection MDM and review in HPB outpatients' clinic. These patients will need pre-assessing at King's.

Imaging guidelines

The patient referred to King's for management of colorectal liver metastases is likely to have had previous investigations including staging CT at the time of their original diagnosis of colorectal cancer and subsequent follow or restaging scan series. The patient may have had a PET, CT PET or MRI scan for further staging.

It is very important that when the patient is initially referred to King's for collaborative management of their hepatic metastatic disease their imaging is included in the referral. Ideally, a CD of all of their scans to date should be forwarded with the referral. Contrast enhanced CT of chest, abdomen and pelvis remains the gold standard in imaging patients with CLM and patients should be referred when this CT has been obtained. Baseline LFTs and CEA should also be part of the initial investigations

Subsequent imaging may not be required, but if it is then the following will be considered:

- Ultrasound
- CT
- MRI
- PET scan
- Imaging guided biopsy [CT or USS]
- Portal Vein Embolisation [for liver volume modulation prior to resection]

Details of techniques used are included in the Network Imaging Group protocol.

At the time of treatment for CLM, the latest axial staging imaging must not be more than 6 weeks old.

Further axial imaging in the form of MRI will occasionally be used after review of the initial CT at King's HPB MDM in cases where diagnosis is uncertain or additional information is required prior to planning surgery (i.e. vascular and/or biliary anatomy considerations).

The role of PET scanning is under evaluation worldwide and definitive results are awaited. Its use for patients evaluated at King's HPB MDM is for discussion on a case by case basis and would usually only be indicated in the setting of excluding the presence of extra-hepatic disease when liver resection is planned in the presence of unfavourable history i.e. ruptured primary, or primary tumour histology, e.g. pT4 and/or N2, or where there is suspicion of pulmonary spread.

Other investigative measures such as EUS, image guided biopsy and laparoscopic biopsy can also be used when there are specific clinical needs.

Intra-luminal staging remains within the spectrum of responsibilities of the colorectal team treating or who have treated the primary tumour.

Pre-operative evaluation

Any liver resection irrespective of the extent or the mode (laparoscopic or open) should be considered as major surgery. In addition, the majority of these patients would have undergone various periods of systemic chemotherapy. Therefore, appropriate cardiovascular, respiratory and nutritional assessment is mandatory.

These patients should be assessed by an anaesthetist at King's prior to their admission for surgery and based on this evaluation of peri-operative risk additional investigations may be requested.

Every patient coming in for a liver resection should have the following baseline investigations done:

FBC, U&Es, clotting profile, LFTs, tumour markers (CEA and CA19.9), chest x-ray, ECG, cross-match of appropriate amount of blood, screen for nosocomial pathogens and the first stage of consent taken by a member of the surgical team.

Surgical planning

The exact type of liver resection should have been discussed and decided at King's HPB MDM prior to surgery. Operative strategies can and should change according to intra-operative findings. However, the following principles should be observed:

I. Complete tumour clearance with clear resection margins; when anatomically feasible the rule of 1cm should be observed
II. Full evaluation of the liver with intra-operative USS, as this can add to intra-operative resection planning and uncover previously undetected lesions. With the role of laparoscopic staging rapidly evolving it is anticipated that this modality will also be part of the final evaluation prior to resection.
III. Planning for resection should (if possible) take into account the ¨mapping¨ of the disease at the time of presentation, as there is growing evidence that even lesions with complete radiological response to chemotherapy can re-grow if no definitive treatment is applied. When this is not possible (due to remnant functional liver mass) alternative strategies should be adopted (e.g. RFA or closer post-operative surveillance).
IV. Contraindications for liver resection at the time of the final assessment remain the presence of peritoneal spread and porta-hepatis nodal involvement
V. Where the liver resection is following a course of chemotherapy provisions should be made for a ¨wash-out¨ period of 4-6 weeks between the completion of chemotherapy and surgery.

Additional strategies to increase resectability:

Portal vein embolisation (PVE)
When, on CT volumetric studies, the expected remnant functional liver mass after the proposed hepatectomy would be marginal, or inadequate, percutaneous right portal vein embolisation should be explored as a mode to induce compensatory hypertrophy of the unaffected part of the liver, thus facilitating an extended right hepatectomy. If satisfactory response is achieved then resection is scheduled no later than 6-8 weeks after the PVE.

Two-stage hepatectomy
For patients with bi-lobar multi-nodular disease when complete removal of all tumours is thought not possible with a single procedure a two-stage approach can be adopted by first resecting the most tumour laden lobe. Allowing for a period of 6 weeks for regeneration of the remnant liver, resection is then completed with removal of part of the remaining liver lobe. This approach can be combined with PVE prior to the first stage and/or RFA of the remnant tumours at either stage.

Laparoscopic liver resection
In recent years there has been a very dynamic expansion in the application of laparoscopic techniques in HPB surgery. There is now enough data to support its role in the treatment of patients with CLM. Although almost any type of liver resection can be performed laparoscopically there is not wider consensus for a blanket application of the method, owing predominantly to the lack of long-term survival data.

At King's every patient with CLM who requires resection of up to 2 liver segments in anatomically favourable sites is considered for laparoscopic liver resection. It is envisaged that as experience and data accumulate, the spectrum of this mode will increase.

Radio-Frequency Ablation (RFA)
Although resection remains the gold standard for treatment of CLM the availability of RFA can significantly add to the treatment options particularly for patients who:

I. Are not candidates for liver resection due to poor performance status

II. Have multi-focal disease that cannot be resected (even after the implementation of the previously discussed pre-operative strategies)

III. Have recurrent disease in their liver remnant that will not tolerate further resection

IV. Are not willing to undergo liver resection, but would accept a less invasive mode of treatment

V. Require consideration of RFA in combination with liver resection when parenchyma sparing is required as means of control of otherwise irresectable disease

VI. Finally, as a part of a two-stage hepatectomy, as outlined above

RFA will be delivered either percutaneously or intra-operatively (laparoscopic or open) based on individual patient needs.

Synchronous liver lesions

There is sufficient evidence to support the simultaneous treatment of the primary colorectal tumour and the CLM. Emerging evidence may support dual surgical approach in low volume/solitary CLM. However, most centres avoid combining a major liver resection (more than 3 liver segments) with left-sided or pelvic colectomies due to increased risk for post-operative liver failure and/or septic complications from anastomotic leaks (see guidelines below).

It is pertinent to note however that the long-term prognosis is not influenced by simultaneous surgery and the vast majority of data reflect results from the staggered approach.

In the same context major liver resections should not be combined with other major GI tract procedures (i.e. reversal of covering stomas).

Liver and pulmonary metastatic disease

The simultaneous presence of liver and lung colorectal metastases does not preclude the surgical treatment of both sites. If by thoracic criteria the pulmonary disease is resectable then the CLM should be assessed for treatment and this should be completed prior to the lung resection(s). The advent of RFA for pulmonary metastases can further enhance the therapeutic options for this group of patients.

Resection with (neo-) adjuvant chemotherapy

As much as chemotherapy has transformed the treatment of CLM and has been the key factor in the increase in the resectability rate, the ideal protocol is yet to be defined. The length and the agents will depend on:

I. the presentation (synchronous vs. metachronous)
II. any previous chemotherapy treatment and observed response rate
III. any previous liver resection
IV. the disease free interval

Current evidence suggests that a staggered approach (chemotherapy-surgery-chemotherapy) may offer the best results for patients treated for their CLM for the first time.

Guidelines for combined HPB and other surgical interventions

We have agreed guidelines for the management of patients who require a HPB surgical intervention in combination with other surgery:

Surgeon from another Trust operating at King's

The patient is admitted under the King's HPB consultant who takes full responsibility for the care of that patient, even if the HPB part of the operation is the more minor.

King's HPB surgeon operating at another Trust

The patient is admitted under the local Trust consultant who takes full responsibility for the care of that patient. If the HPB part of the operation is the more major then that surgery should not be taking place off site.

No pancreatic resections or liver resections for colorectal liver metastases can be undertaken off site as this would contravene the IOG.

Surgeon from within King's operating with King's HPB team

The surgeon performing the more major part of the operation should agree to admit the patient under their name, to one of their wards and take overall responsibility for the operation.

Combined liver and other organ resection when consultants from other specialties are involved:

Liver surgery and colonic resection

As a rule, when the liver resection is of >2 segments, or is 2 liver segments but is combined with RFA, the index consultant will be the HPB surgeon.

When the colonic resection is left sided or a pelvic resection the liver resection is commonly ≤ 2 liver segments and the index surgeon is the colorectal surgeon.

When only operative RFA ≤3 lesions, is performed then the colorectal surgeon is the index surgeon.

If the RFA is to <3 lesions then the index surgeon is the HPB surgeon.

N.B. these are general guidelines that it is hoped will help clinicians in decision making. When the clinical situation indicates a need for deviation it is expected that appropriate discussions will take place between the clinicians involved, confirmed in MDM(s) if necessary.

It is important to stress however, that one clinician will always be identified as the index surgeon.

Pathology

Description and sampling of the tumour are carried out in compliance with the guidelines issued by the Royal College of Pathologists (RCPath) in 2007 (minimum dataset for histopathological reporting of primary and metastatic carcinoma). The specimen is measured and weighed. Location and size of the tumour are noted. When relevant specimens are photographed. The relationship between tumour and resection margin is noted and the distance of the tumour from the resection margin is measured macroscopically. The margin usually considered during macroscopic examination, sampled and assessed microscopically is the hepatic transection margin unless indicated otherwise by the surgeon.

Tumours are graded into well, moderately and poorly differentiated. The presence of necrosis, invasion of vascular/biliary structures, liver capsule and peri-hepatic tissue is noted.

The possibility of integrating electronic templates into the histopathology reporting system is being considered for the update of the system, which should take place in 2009.

All resection specimens are discussed at the weekly MDT meeting.

Oncology (10-2D-216)

Patients with potentially resectable colorectal liver metastases are considered for peri-operative chemotherapy with an oxaliplatin containing regimen.

Cape-Ox Capecitabine 1000 mg/m^2 twice daily for 14 days
Oxaliplatin 130 mg/m^2 day 1
Repeated every 21 days

Oxaliplatin modified deGramont schedule:

Oxaliplatin	85 mg/m^2	day 1
Leucovorin	200 mg/m^2	day 1
5FU bolus	400 mg/m^2	day 1
5FU infusion	2400 mg/m^2	over 46 hours

Repeated every 14 days

Chemotherapy for patients given as a combination treatment with metastatectomy is managed by either the core oncology member of the liver resection MDT, or by an oncologist from the referring colorectal MDT following discussion and treatment planning in the liver resection MDT.

Clinical Trials

<u>Resectable liver metastases</u>

NEW EPOC- A prospective randomised open label trial of oxaliplatin/irinotecan plus fluoropyrimidine versus oxaliplatin/irinotecan plus fluoropyrimidine and cetuximab pre and post operatively in patients with resectable colorectal liver metastases requiring chemotherapy

Irresectable liver metastases

BOXER – a phase II trial of capecitabine, oxaliplatin and bevacizumab in patients with non-resectable liver metastases from colorectal cancer

FOXFIRE

Due to start 2010 – a trial of SIR-spheres +/- chemotherapy for patients with irresectable liver metastases form colorectal cancer.

Follow-up

Following a liver resection for CLM at King's patients will be seen in King's HPB outpatient clinic 2-3 weeks post-discharge. By then plans for further treatment should be in place with their local oncologist. If there are no active surgical/ hepatological issues the patients can be discharged from further HPB follow-up. Referral back to the specialist liver MDT would be triggered by evidence of disease of recurrence within the remaining liver on surveillance CT scans.

In cases where further surgery (i.e. a staged hepatectomy) or other interventional procedures (i.e. RFA) or in cases where there is known residual disease within the liver, these patients will continue to attend King's HPB outpatient clinics until all active issues are resolved.

Although the issue of post-liver resection baseline CT scan is still a matter for debate it is appropriate for these patients to have a CT scan locally 4-6 weeks after their resection when post-operative changes have diminished and regeneration would be expected to have mostly completed. It would also roughly match the initiation of their adjuvant chemotherapy (when appropriate).

The CT surveillance should follow a 6 monthly pattern for the first 3 years following liver resection, as the bulk of recurrences are observed during that timeframe and a12 monthly pattern thereafter until 5 years post-resection. These surveillance CTs should be promptly sent for review at King's MDM.

Clinical examination, LFTs and tumour markers should complete the surveillance protocol. It is hoped that the above will be facilitated locally.

All HPB malignancies:

Inoperable disease:
Patients who are not candidates for any type of surgery due to disease extent should have their endoscopic palliation ± chemotherapy and, when the need arises, palliative care locally. This should be organised in a manner that saves further centre outpatient visits unless the required procedures/treatments cannot be offered locally. Follow up should be provided by local oncologists (when appropriate), referring physicians and general practitioner.

Unfit for surgery:
Medically unfit patients should receive whatever care is appropriate (chemotherapy, palliative care) locally without further coming to the centre outpatients. Referring physicians/oncologist/general practitioner should provide their follow up.

Palliative Care:
For patients who would benefit from palliative care team only, this should be provided locally. Efforts should be made for these patients to avoid centre outpatients – even at the referral stage – and their palliative care should be organised following initial MDM discussion.

It is important to note that survival data (disease recurrence, mode of disease progression) obtained during the follow up of patients with pancreatic cancer assessed and /or treated at King's College Hospital, should be communicated back to King's College Hospital for appropriate completion of patient records.