

West Midlands Hepatobiliary

Guidelines Coversheet for Network Site Specific Group Agreed Documentation

Purpose of the Document

To ensure version control of the NSSG Guidelines for 2012/13 this will be reviewed on a regular basis by the West Midlands Hepatobiliary Group.

Document control

Document versions will be numbered, and only changed using a formal change control following approval by the NSSG, subsequent releases will be consecutively numbered; the version number appears in the footer of every page.

Version	Date Issued	Consultation*	Brief Summary of Change
V1	June 2012		
V2			
V3			
V4			

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The West Midlands Group acts as NSSG for the Greater Midlands Cancer Network, Pan Birmingham Cancer Network and Arden Cancer Network.

Colorectal Liver Metastases Guidelines

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1. Scope of the guideline

This guideline makes recommendations for the establishment of a region wide (the following cancer networks: Arden, Birmingham, Greater Midlands, Three Counties) approach to the management of colorectal liver metastases. This region wide group hosts the site specific Hepatobiliary Supra Network Group (HPB SNSSG) which is led by Greater Midlands Cancer Network.

2. Guideline background

- 2.1 Configuration of centres providing liver resection services: There are two hepatobiliary (HPB) centres within the wider SNSSG providing liver resection for metastatic colorectal cancer: The Liver Unit at the Queen Elizabeth Hospital (UHBFT) in Birmingham, currently performing around 150 resections for metastatic colorectal cancer, and the University Hospital Coventry and Warwickshire (UHCW) in Coventry performing around 30 such procedures annually. They serve a total West Midlands population of 5.2 million. Additional referrals are also received from parts of Wales and the south west of England.
- 2.2 Over the last decade, the UK has seen an increase in surgical resection of liver metastases for colorectal cancer, mainly due to the recognition by oncologists and colorectal surgeons of the potential benefits of liver resection. There is however evidence of variable referral rates for liver resection across England and Wales which suggests that not all patients are offered this treatment option (Morris et al BJS 2010). As yet there is still no one standard UK pathway for the management of metastatic colorectal cancer. The recently published NICE document on management of colorectal cancer (NICE TAG Nov 2011) also addresses this issue.
- 2.3 Colorectal cancer is the second commonest cancer, comprising 11% of new cancer diagnoses and 10% of all cancer deaths in the UK. Approximately 20-25% of patients will have clinically detectable liver metastases at the time of the initial diagnosis and a further 40 -50% of patients will eventually develop liver metastases after resection of the primary, most commonly during the first 3 years post primary surgery^{1 - 3}
- 2.4 Several large series' on resection for colorectal liver metastases (CRLM) have reported 5 year survival ranging from 25-60%, with operative mortality between 2 and 5% (4-7). Of the 28,000 patients who develop colorectal cancer annually in the UK up to 18,000 will develop hepatic metastases. If 10-20% of these lesions are potentially resectable, between 1800-3600 patients

- may be suitable for hepatic resection by conventional criteria, not including those additional patients with initially non resectable or borderline resectable disease. Of those undergoing liver resection, up to 10% of patients become candidates for redo liver resection at an interval after the primary resection.
- 2.5 The availability of effective chemotherapy as well as newer biological agents has led to patients with initially non resectable and borderline resectable liver metastases to also be considered as candidates for liver resection, with a resultant increase in liver resection activity. The wider use of minimally invasive approaches for both resection of the primary and now also for secondary liver and lung disease has also had an impact on timing for surgery, as recovery times after these procedures is much shorter.
- 2.6 The availability of additional measures such as portal vein embolisation/ligation, two stage hepatectomy, parenchyma sparing surgery and combination of resection and ablation have also increased the potential number of patients suitable for liver resection without adversely affecting outcomes after hepatic resectional surgery.
- 2.7 Recent published evidence on data collected to 2004 has demonstrated that there are variable rates of liver resection for metastatic colorectal cancer across England and Wales, ranging from 1.4 to 4.3% by health authority and 0.7% to 6.8% by referring hospital (Morris et al BJS 2010 – Figure 1). Following this publication an audit performed by the four Birmingham colorectal cancer network hospitals has shown an overall increase in referrals for liver resection see figure 2.

Figure 1
Liver Resection for CRC metastases (Morris et al 2010)

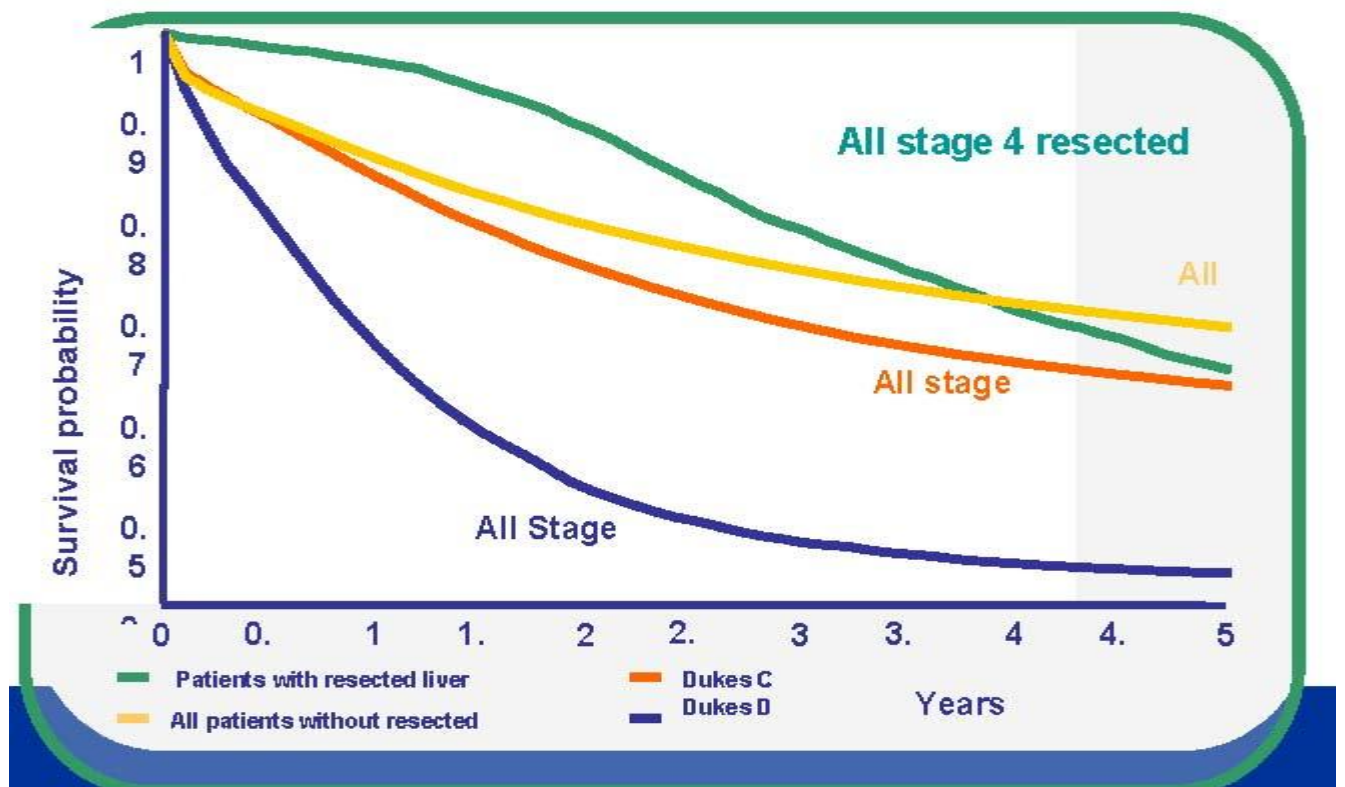


Figure 2 Total: 2005 – 2010 per Hospital (Pan Birmingham Cancer

	Total colorectal cancer presentations/ resections		Total liver resections	Proportion	
				98-04	05-10
Walsall	634	571	33	5.2%	5.7%
HEFT	2132	1832	65	3%	3.5%
UHBFT	1798	1321	75	4.2%	5.6%
SWBH	1248	1091	36	2.9%	3.3%
Total	5812	4035	209	3.6%	5.0%

Network) (Walsall = Walsall Healthcare NHS Trust, HEFT = Heart of England NHS Foundation Trust, SWBH = Sandwell and West Birmingham Hospitals NHS Trust)

2.8 Natural history of colorectal liver metastases

The vast majority of patients today will receive treatment for liver metastases. Earlier studies have shown that few untreated patients survive beyond 5 years, and approximately 20% of patients survive 3 years. Median survival times vary depending on extent of liver involvement ranging from <6 months for patients with multicentric disease to 21 months with a solitary metastasis (1, 3, 8). There is no data comparing resected vs. untreated patients with resectable liver metastases as it would be considered unethical not to offer surgery for resectable disease.

Guideline statements

3. Referral

- 3.1 All patients with potentially resectable liver metastases arising from colorectal cancer should be considered by the local multi disciplinary team (MDT) for a liver resection. All patients with colorectal cancer and metastases only in the liver should be referred to either the liver and hepatobiliary (HPB) MDT at the liver unit, UHBFT or at UHCW.
- 3.2 All patients being considered for a liver resection should be discussed at one of the two designated HPB MDTs.
- 3.3 The HPB MDT will consider the following for surgery. Patients with solitary or multicentric disease (no maximum number of lesions) where lesions are resectable with clear margins and an adequate residual liver volume.
- 3.4 The following are unlikely to be offered liver resection by the HPB MDT. Patients with extrahepatic disease, with the exception of resectable lung metastases and very selected cases of abdominal metastatic disease (limited resectable nodal/locoregional/adrenal)

4. Investigation and staging of colorectal liver metastases

4.1 Imaging summary for colorectal liver metastases:

4.1.1 Those with suspected or known liver metastases should be assessed with triple phase contrast CT scan.

4.1.2 MRI with liver specific contrast media should be carried out for:

- a. those being considered for liver resection
- b. patients unable to have iv contrast
- c. further evaluation of uncertain liver lesion
- d. further evaluation of suspected liver recurrence after liver resection

4.1.3 CT PET scan should be carried out for:

- a. those with T4 or N2 primary lesions who have a high risk of residual disease in the proximity of the primary surgery.
- b. those with uncertainty about extrahepatic metastatic disease.
- c. those with questionable lesions in the liver identified during follow-up after liver resection.

4.1.4 All of the above imaging should be reviewed at a HPB MDT meeting.

4.1.5 Further information on imaging is outlined below.

4.2 Biopsy of a suspicious liver lesion or likely metastasis should be avoided until imaging and clinical evaluation have determined that liver resection is not the best option. Most of these patients will have positive histology from their colonic resection. Needle biopsy of a liver metastasis may result in implantation metastases.

4.3 Contrast CT scan: the current investigation of choice is a contrast CT scan of the abdomen and pelvis, with detection rates of 68-91% (70% detection for lesions < 1cm). This has replaced ultrasonography as the preferred imaging modality . The sensitivity and specificity of CT liver will vary, depending on the equipment and contrast enhancement methods. Inclusion of the thorax in the CT will help complete pre liver resection disease staging. Pre contrast CT of the liver is not essential. Post i.v. contrast scans of the liver must be obtained as a minimum in the portal phase of enhancement i.e. approx 65-70 seconds after the start of a bolus injection of 100ml contrast injected at 2-3 ml/second. Greater volumes of contrast and higher injection rates may be preferred in some hospitals. Arterial phase imaging is not essential for detection of colorectal metastases but may help in characterisation of any uncertain lesions and in the context of fatty liver. The portal phase is the appropriate time to continue the scan through the rest of the abdomen and pelvis if that is planned. Slice thickness for liver images will vary according to

the scanner capability. As multislice CT becomes more widely available a routine thickness of 5 mm or less is suggested.

- 4.4 Ultrasonography (US): compared to contrast CT, US has a much lower sensitivity (53-82%) and specificity in diagnosing metastases⁹. In addition, US is operator dependent and has poor sensitivity for smaller lesions. US may be helpful in differentiating solid from cystic lesions, one of the potential false positives following contrast CT scans. Annual ultrasonography alone is not an effective way of screening for hepatic metastases. Ultrasound images do not give the spatial information on relationships required for a decision on whether to perform surgery. Clearly however ultrasound evidence of multiple liver metastases in both lobes of the liver will preclude surgery but non-surgical therapy may be considered.
- 4.5 Magnetic resonance imaging (MRI): MRI scan is now widely utilised in the UK in planning surgical management of liver tumours. It is helpful for patients who cannot receive i.v. contrast for CT scan. Good quality T1 and T2 weighted images are required of the liver. There should be a visible signal intensity difference between the normal liver and the spleen on the images. The parameters used will vary for each type of MRI scanner. Dual echo T2 weighted scans and contrast enhancement will help clarify the nature of uncertain lesions. The use of gadolinium or the addition of newer liver specific contrast agents may improve diagnostic accuracy, particularly in reducing false positive findings of CT. Since June 2005, the preferred pre liver resection liver imaging modality is an MRI carried out with liver specific contrast media e.g. Gadolinium, Tesla and Resovist/Primavist. MRI and CT provide information on vascular anatomy, which may help in planning surgery.
- 4.6 CT PET scanning is useful in the detection of synchronous and metachronous metastatic colorectal disease and is being increasingly used. Due to risk of a false negative result, it should not be undertaken when a patient is receiving chemotherapy and should be delayed until at least 2 weeks after completion of chemotherapy.
- 4.7 CT PET scanning may help identify suspected metastatic disease in the following:
- rising CEA post-resection with negative cross sectional imaging and colonoscopy.
 - suspected extrahepatic: eg peritoneal, skeletal, nodal and pelvic recurrent / residual disease (T4 or N2 primary or tumour perforation at presentation).
 - conventional imaging uncertainty with regards to hepatic or extrahepatic recurrence.
- 4.8 Other investigations
- 4.8.1 CEA measurement: these may be elevated in up to 90% of patients with liver metastases^{10, 11}. A rise in CEA after an initial fall may be the first indication local / distant recurrence in an otherwise asymptomatic patient (10, 11). However a rising CEA concentration may be a relatively late phenomenon in patients with liver metastases.

4.8.2 Colonoscopy (to have been performed within the last three years if patient presents with metachronous disease).

4.8.3 Bone scintigraphy is indicated in symptomatic patients with suspected bone metastases.

5. Management of synchronous liver metastases

5.1 Synchronous liver metastases are those which are detected at diagnosis or within six months of diagnosis.

5.2 Detection and Imaging: synchronous metastases are detected in approximately 20-25% of patients presenting with primary disease. A majority of such patients will have non-resectable liver disease. All patients should have a staging contrast enhanced CT chest, abdomen and pelvis around the time of their primary surgery. All patients diagnosed with synchronous disease should undergo a MRI scan with Gadolinium and liver specific contrast material (primavist/resovist) prior to undergoing liver resection. Additional CT PET scan imaging is advisable in patients with T4 or N2 disease, and suspected peritoneal, nodal, pelvic and skeletal metastases. All of the above imaging should be reviewed at a HPB MDT meeting.

5.3 Liver after primary surgery: patients with potentially resectable liver metastases should be referred for consideration of liver resection upon recovery from their primary surgery (usually within 4 weeks). In patients with potentially resectable liver lesions, the hepatobiliary centre (or the referring centre after discussion at the HPB MDT) will organise an MRI scan of the liver with liver specific contrast media and a contrast CT scan chest, abdomen and pelvis (if one has not been performed within the last 3 months) prior to resection.

5.4 Chemotherapy: patients with liver metastases who have undergone resection for their primary tumour should be considered for neoadjuvant chemotherapy, usually consisting of an oxaliplatin-based regimen, oxaliplatin with either oral capecitabine or 48 hour infusional 5FU/folinic acid (modified de Gramont regimen) in the following circumstances;

Resectable liver disease: Patients with higher risk (usually lymph node positive or T4) primary tumours are at high risk of early recurrence within the liver or outside the liver despite resection of liver metastases. The main aim of neoadjuvant chemotherapy is to reduce this risk. These patients should have 3 months of neoadjuvant chemotherapy followed by re-imaging. Following successful liver resection these patients should be considered for a further 3 months of adjuvant chemotherapy. However oxaliplatin-based chemotherapy is associated with injury to the liver parenchyma (sinusoidal dilatation, steatohepatitis) resulting in higher complication risks and in some circumstances, higher mortality. Therefore patients with lower risk (usually

lymph node negative and less than T4) primary tumours who have easily resectable liver disease should be considered for early liver resection (avoiding neoadjuvant chemotherapy) followed by adjuvant chemotherapy instead.

Borderline resectable or non-resectable liver disease: these patients should be considered for neoadjuvant oxaliplatin-based chemotherapy. The main aim is to increase the likelihood of curative resection in borderline resectable disease and to downstage non-resectable disease to become resectable, in order to improve survival in these groups of poor prognosis patients. Recent NICE guidelines (NICE TAG 2009) have recommended routine testing of the primary tumour for KRAS mutation, with the aim of adding cetuximab (monoclonal EGFR inhibitor) to oxaliplatin and infusional 5FU/folinic acid in those with no K-RAS mutations (wild type). This will achieve higher response rates compared to oxaliplatin-based chemotherapy alone, in order to improve the curative resection rate. Cetuximab should not be used with the combination of oxaliplatin and capecitabine. Patients with K-RAS mutation will not benefit from addition of cetuximab and should be offered an oxaliplatin-based chemotherapy regimen alone.

Following 3 months of neoadjuvant chemotherapy patients should be re-imaged with a CT chest, abdomen and pelvis. In the absence of disease progression on CT, patients with potentially resectable disease will require an MRI of the liver using the protocol as defined under imaging. All imaging should be reviewed by the HPB MDT to assess suitability for liver resection (16-18).

Patients who have made an insufficient response to proceed to surgery should continue treatment for a further 3 months using the same regimen, with further assessment and review by the HPB MDT at this point. Patients who have disease progression should be treated with a second-line chemotherapy regimen, usually an irinotecan containing combination with or without bevacizumab (VEGF inhibitor).

- 5.5 Liver resection before primary surgery: in general liver resection is performed at an interval after primary surgery. In the following circumstance this may be considered before primary surgery: high burden multicentric liver disease with a well controlled or small primary (usually rectal) as the metastatic disease is more likely to influence outcome
- 5.6 Resectable liver and lung metastases: liver resection is usually performed before lung resection. In some situations such as multiple lung lesions with low volume easily resectable liver disease, an approach to perform thoroscopic resection prior to liver surgery should be considered.
- 5.7 Simultaneous liver and primary resection: this approach may be considered selectively in patients with good performance status and easily resectable primary (colonic rather than rectal) and liver disease. Patient selection is crucial as the risks of both surgical procedures are compounded in this setting. This approach requires the colorectal and hepatobiliary teams to carry out a joint procedure. .

6. Metachronous liver metastases

- 6.1 Metachronous liver metastases are those occurring at an interval of greater than six months after treatment of the primary bowel lesion.
- 6.2 Detection and imaging: most patients who develop metachronous liver metastases do so within the first 3 years post bowel resection. Most liver metastases are asymptomatic till very late when surgery may not be possible. Most patients followed up at colorectal oncology units will undergo 3-6 monthly physical examinations, CEA estimation with/ without liver biochemistry, and 2 to 3 yearly colonoscopy, with an aim to identify further bowel lesions.

The detection of potentially resectable liver lesions should be one of the main aims of follow-up screening. The use of ultrasonography, CT or even MRI to detect recurrence or metastatic disease is still variable (12-14). Published national guidelines recommend annual CT scans of the chest and abdomen for the first 3 years to identify asymptomatic resectable liver metastases (Garden et al, Gut 2006). The addition of annual contrast CT scans for the first 3 years can only facilitate earlier diagnosis of resectable liver disease. McArdle reports up to 80% of hepatic metastases are identified at an asymptomatic stage with a regime of intensive liver imaging for the first 3 years after surgery (14).

In a review on effectiveness of follow-up, earlier practice targeted detection of local recurrence (reflecting residual disease left at primary surgery) or metachronous primary tumours (relatively uncommon), with minimal impact on survival (14). Follow-up is better directed to detect asymptomatic liver metastases which are much more common, and are confined to the liver in a quarter of patients (14). There are only two randomised studies to date with numbers too small to show a survival advantage in patients undergoing intensive follow-up imaging, with limited data on the cost effectiveness of aggressive screening (12, 13). Shoemaker et al reported that the addition of yearly CT, colonoscopy and chest radiography had limited impact on survival compared to a standard follow-up protocol including 3 monthly history, physical examination, CEA, LFTs, 5 yearly colonoscopy, and CT and chest radiology as indicated (12). A meta-analysis of published follow-up studies suggests that regular imaging to identify recurrence has an impact on survival for metastatic cancer, reporting a 9-13% reduction in cancer related mortality if CT and frequent CEA are used (15), and a benefit similar to the use of adjuvant 5FU in patients with node positive primaries.

- 6.3 Liver resection timing: following diagnosis, patients with resectable disease on completion of staging as defined by the HPB MDT should be considered for surgical resection without commencing chemotherapy. Adam et al (22) in a study of 1471 patients clearly showed no benefit of perioperative chemotherapy in patients undergoing liver resection for solitary metachronous liver metastases. Liver resection should be performed as soon as possible. There is good data from large liver resection studies showing excellent outcomes with 5 year survival in excess of 50% after resection for smaller,

solitary metastatic lesions (4-7). These outcomes decrease to 25-40% 5 year survival for patients with larger or multiple liver lesions.

- 6.4 Chemotherapy and liver resection: in some patients the HPB MDT might decide that the disease is only borderline resectable or completely irresectable and that down staging chemotherapy is necessary prior to re-staging and further HPB MDT review.

Patients with metachronous metastatic disease should be treated with an oxaliplatin-based regimen unless they have previously received oxaliplatin as part of their adjuvant chemotherapy. In these circumstances and irinotecan-based regimen would be recommended. The K-RAS status of the primary tumour should be tested and patients with no mutations (wild-type) considered for addition of cetuximab according to NICE 2009.

Re-staging of the liver under these circumstances should be using the MRI protocol as defined under imaging above. These images should be reviewed by the HPB MDT before deciding about surgery or completion of a further 6 cycles of chemotherapy.

In patients with resectable metachronous disease who undergo successful liver resection the evidence for 'adjuvant' therapy is very limited and a decision to recommend chemotherapy will be based on the pathology of the resected disease and the individual patient. The outcomes of a multicentre randomised trial (23) studying neoadjuvant and adjuvant oxaliplatin/5FU based chemotherapy (EPOC1) has shown a trend towards improved survival and an increased disease free interval after liver resection on an intention to treat basis. Per protocol patients in the same study showed a significantly improved overall and disease free survival, although this was not one of the primary end points. A follow-up trial is currently underway looking at combination cetuximab and oxaliplatin based neoadjuvant chemotherapy in KRAS wild type patients with resectable and borderline resectable disease (EPOC2). To facilitate better patient care, all chemotherapy treatment should be administered at the referring hospital, managed by an oncologist from the referring colorectal MDT.

6.5 Liver resection after chemotherapy: in patients where successful downstaging has been achieved and confirmed at a liver HPB MDT, liver resection should be offered at an interval of 6 weeks to allow partial resolution of the hepatotoxic effects (sinusoidal obstruction syndrome) of oxaliplatin. Patients receiving irinotecan based chemotherapy are more likely to develop steatohepatitis. This time interval also helps avoid the potential impairment of wound healing which has been described after the use of the VEGF inhibitor bevacizumab.

7. Pathological assessment of liver resection specimens

Pathology has an important role to play in the evaluation of liver resection specimens. Detailed assessments are carried out by experienced liver pathologists according to the guidelines and datasets published by the Royal College of Pathologists and the findings discussed at a pathology based MDT meeting. Because histology is not used routinely in the pre-operative investigation of suspected metastatic colorectal cancer, examination of liver resection specimens is useful in audit and quality, assurance of imaging studies. It is also involved in the audit and quality assurance of liver surgery, in assessing the effects of pre-operative chemotherapy on tumour necrosis or shrinkage and in making decisions regarding subsequent patient management. Examination of uninvolved liver may identify changes related to chemotherapy-induced liver injury and/or the presence of co-existent liver disease.

8. Follow-up after liver resection

- 8.1 All patients are followed up at 1 and 3 months post surgery by the hepatobiliary unit. Subsequently they are followed up 3 monthly for the first year, 6 monthly thereafter up to 5 years post liver resection, with alternate appointments between the oncology and surgical teams.

NICE Colorectal (Nov 2011) recommend a minimum of 2 scans in first 3 years. Follow-up imaging includes a CT scan of the chest, abdomen and pelvis at 6 month intervals for two years and yearly there after for a further three years, together with serial CEA estimations.

Post operative care is shared between surgeons and oncologists at referring hospitals.

If follow-up imaging identifies potentially resectable metastatic liver disease, these patients should be referred back immediately to the HPB MDT (2F-304).

- 8.2 Written information: written material for liver resection service for colorectal liver metastases and other treatment options is available for all patients at the HPB unit outpatient area (2F-307).

9. Options for non resectable disease

The choice of treatment for patients with nonresectable disease is chemotherapy. Patients undergoing surgery for planned liver resection may be offered radiofrequency ablation (RFA) if multicentric nonresectable disease is found at laparotomy. RFA has replaced cryotherapy as the physical ablative treatment of choice in terms of ease of application and reduced morbidity. RFA is also indicated in selected patients with nonresectable CRLM not responding to second line chemotherapy.

10. Patient information and counselling

- 10.1 All patients, and with their consent, their partners will be given access to appropriate written information during their investigation and treatment, and on diagnosis will be given the opportunity to discuss their management with a clinical nurse specialist who is a member of the relevant MDT. The patient should have a method of access to the hepatobiliary team at all times.
- 10.2 Access to psychological support will be available if required. All patients should undergo an holistic needs assessment and onward referral as required.

11. Palliative care

Palliative care services will be made available to all patients as deemed appropriate by the MDT.

12. Clinical trials

- 12.1 Wherever possible, patients who are eligible should be offered the opportunity to participate in National Institute for Health Research portfolio clinical trials and other well designed studies.
- 12.2 Where a study is only open at one Trust in the Network, patients should be referred for trial entry. A list of studies available at each Trust is available from Pan Birmingham Cancer Research Network. Email: PBCRN@westmidlands.nhs.uk.
- 12.3 Patients who have been recruited into a clinical trial will be followed up as defined in the protocol.

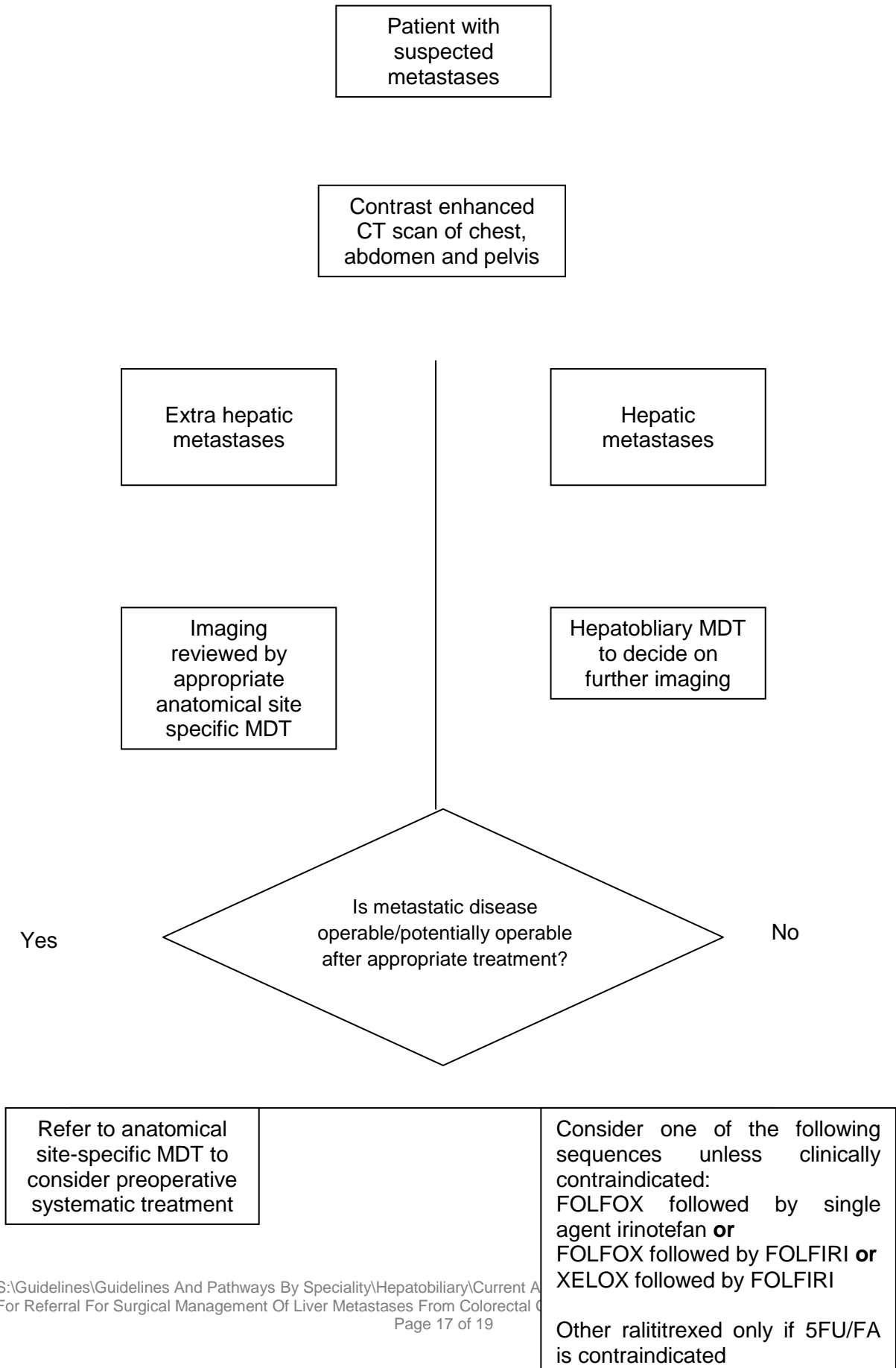
13. Exceptionality

There is preliminary data suggesting improved response rates of chemotherapy given pre liver resection when this is combined with bevacizumab (20). Current NICE guidelines only approve cetuximab based treatment for patients with wild type KRAS status and borderline respectable metastatic liver cancer (24,25,26).

14. Monitoring of the guideline

Implementation of the guidance is being evaluated with a prospective audit of HPB surgery with the “supra-network region” and is an ongoing audit topic for audit by the SNSSG for 2012\2013.

15. Liver Resection for metastatic CRC: Management Pathway (NICE TAG Nov 2011)



16. Conclusions

Liver resection is a safe established procedure that offers a cure in up to 30-50% of selected patients with colorectal liver metastases. In the UK, an increasing proportion of patients with metastatic colorectal cancer are being referred for liver resection.

Follow-up aimed at earlier diagnosis of liver metastases, referral to a multi disciplinary hepatobiliary team and the use of peri-operative oxaliplatin based chemotherapy may improve the long-term outcome in a significant proportion of these patients. The availability of KRAS status based downstaging chemotherapy has allowed this treatment option to become available to additional patients with borderline and initially non respectable disease.

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