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Management of colorectal cancer presenting with synchronous liver metastases.

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Introduction

Bowel cancer is the third most common cancer in the United States[1]; in Europe, colorectal cancer was the third most common cause, both of cancer and of cancer-related death in 2012.[2] The liver is the most common site of metastasis in colorectal cancer: 14-18% of patients have hepatic metastases at presentation and up to a further third will subsequently develop liver lesions.[3,4] Liver metastases in patients with colorectal cancer constitute stage IV disease in which overall 5-year survival is 6%[5]. However, stage IV bowel cancer encompasses a wide clinical spectrum of disease and those patients with surgically removable lesions confined to the liver have 5-year survival rates of 25 – 40%[5]. Such patients represent a selected but important cohort with long-term survival of approximately 17% at 10-years if the hepatic metastatic burden is removed by surgery.[6]

Patients who present with metastatic liver disease following treatment of the primary (termed metachronous disease) receive care focused on this new metastatic disease.[7,8] In contrast, the management of patients who present with liver metastases and concurrent colorectal cancer (synchronous metastasis) is more complex.[8,9] These patients may have less favourable cancer biology and thus may be less likely to become long-term survivors.[10] Logically, the management of patients with colorectal cancer with synchronous metastases can be dichotomised into those with liver and systemic metastatic disease and those with liver-limited hepatic metastases. Systemic chemotherapy is the mainstay of treatment advocated in current guidelines for patients with advanced multi-site metastatic (liver and systemic metastatic) disease of colorectal cancer origin.[8,11]

Patients with liver-limited synchronous metastases represent a complex and common clinical management problem.[12] Traditional management (referred to as the classical approach) comprised resection of the colorectal primary tumour followed by adjuvant chemotherapy with liver resection as a subsequent operation.[13,14] Advances in surgery, anaesthesia and critical care have made two alternative options feasible for patients with synchronous disease. The first is synchronous resection of the liver metastases and the colorectal primary.[12,14] This has the attraction of removing the macroscopic tumour burden at a single operation. However, the morbidity of complex liver resection combined with major bowel resection may be considerable (although arguably less than that of the two procedures undertaken as two separate operations)[15] and there is some evidence of a negative effect on progression-free survival.[14] The second option in the management of synchronous disease is

resection of the liver metastatic disease as the first step, termed the reverse or liver-first approach.[16,17] Liver-first surgery to manage synchronous colorectal cancer and liver metastatic disease has become more widely utilised because of a number of oncological and technical developments. Oncologically, the classical approach has been superseded in some locations by new approaches to pre-operative chemo-radiotherapy for rectal cancer which may require prolonged (long course) treatment before surgical resection.[18] This chemo-radiotherapy-based downstaging period creates a potential treatment window in which liver resection may be undertaken.[18] The parallel technical development of colonic stenting permits symptoms associated with rectal cancer such as partial obstruction to be palliated without recourse to urgent bowel surgery.[19]

The liver-first strategy may be oncologically advantageous if liver metastatic disease rather than the primary cancer gives rise to systemic metastasis – although this is not established.[21] A further potentially important benefit of the liver-first approach is that in selected patients with rectal tumours with a complete endoscopic, radiological and clinical response to chemo-radiotherapy, pelvic surgery may be avoided altogether.[22]

This review addresses the management of patients with colorectal cancer with synchronous hepatic metastases and examines relevant aspects of current terminology, the influence of mode of clinical presentation on management strategy, diagnostic/staging tests and the key issues of treatment options for integration of surgical management with oncological care. The role of the modern multidisciplinary team in treatment planning is emphasised with the goal being to provide a synthesis of evidence that supports holistic, personalised, treatment.

Current terminology

In current colorectal clinical practice, the term synchronous liver metastasis or metastases refers to the presence of hepatic lesions arising from a colorectal primary source and being present at the time of clinical presentation or detection of the primary.[23] It is important to appreciate that there is no clear consensus on the definition and usage of the terms "synchronous" and "metachronous". The current American Joint Committee on Cancer (AJCC) manual states that staging of synchronous disease can be undertaken up to 4 months after detection of the primary .[24] Mekenkamp's report of clinicopathological features and outcome in synchronous colorectal metastases defines synchronous disease as "occurring within 6 months of the primary diagnosis of the colorectal cancer".[25]

The term metachronous metastasis is used to describe lesions presenting at a time point remote from that of the presentation of the primary colorectal cancer.[26] In addition to the lack of clarity in the usage of these terms there may also be differences in the cancer biology of synchronous and metachronous metastases.[27,28] Precise use of disease descriptors is required in order to allow for comparison of reporting. For example, before the term metachronous metastasis is used it is important to know whether there was adequate imaging of the liver at the time of index presentation of the colorectal primary tumour (as otherwise synchronous lesions may have been missed). Further, current knowledge of the molecular biology of colorectal cancer does not preclude patients with apparent metachronous metastases having clinically occult "synchronous" micrometastatic hepatic lesions at the time of presentation of the primary tumour with these lesions only becoming clinically apparent at a later stage.[29,30]

Thus the following definitions are suggested for practical use:

Synchronous hepatic metastases of colorectal origin: liver lesions with the radiological imaging characteristics (on cross-sectional imaging comprising any of CT [computed tomography], MR [magnetic resonance scanning] or ^{18}FDG-PET [^{18}fluoro-deoxyglucose positron emission tomography]) of colorectal liver metastases present either at the time of detection of the primary bowel tumour or detected within 6 months of time of presentation. More stringent criteria would define synchronous disease as present at the time of index clinical presentation

(provided that there has been adequate staging) and that any disease detected at a later stage is metachronous but it must be appreciated that the terms are not currently used with this degree of precision.

Synchronous metastases can be further divided into liver-limited hepatic lesions (where adequate full-body cross-sectional imaging has confirmed that there is no radiologically detectable disease outwith the primary tumour and the hepatic metastatic burden) and systemic disease (where there is disease distributed beyond the liver, typically lung but also peritoneal and omental metastases). Patients with systemic disease may not always have liver metastases.

Metachronous hepatic metastases are defined as liver lesions with radiological imaging characteristics consistent with colorectal origin but detected more than 6 months after presentation of the primary where there has been adequate cross-sectional imaging of the liver in the preceding time period. This last caveat is important in making the distinction between patients who present with late-declared metastases and those in whom synchronous metastases have not been detected because of limited or inadequate staging.

Influence of mode of clinical presentation on treatment strategy

The mode of clinical presentation has a substantial practical influence on the subsequent treatment strategy.[31,32] Logically, mode of presentation can be divided into asymptomatic and symptomatic categories with the latter being further dichotomised for treatment planning into urgent and non-urgent presentations.[32,33]

Asymptomatic or pre-symptomatic patients with hepatic metastases can be detected in colorectal cancer screening programmes.[34,35] The report of the first 1 million people screened in the UK(screening offered to adults between the age of 60 and 69 years and based on positive faecal occult blood tests) showed that some 3% had Dukes D disease.[former reference 20]

Liver metastases can also present as “cancers of unknown primary (CUP)”.[36] True CUP comprises about 3 – 5% of all cancer diagnoses and is more common in older people.[37] Liver lesions from a clinically occult primary cancer are typically adenocarcinoma in the majority and the most common primary sources include the breast, colon, prostate, stomach, pancreas and lung.[37] CUP lesions of colorectal origin will typically have characteristic

radiological appearances (see below). The key to management of liver lesions presenting without a known primary is the performance (for JMM: I am referring to the general fitness of the patient; oncologists use scores such as the Karnofsky score to assess "performance status" – can change it if you feel it is unclear) status of the patient: extent of further investigation and subsequent treatment is influenced by this. If a solitary liver lesion presents as CUP in a patient with a relatively well preserved performance status, endoscopic investigations of the upper and lower GI tract to locate the primary are logically the next series of investigations with biopsy of the liver being avoided. In contrast, in frail patients, without gastrointestinal symptoms, with poor performance status and with bi-lobar liver lesions, percutaneous ultrasound- or CT-guided biopsy of the hepatic lesion(s) will help to establish the diagnosis (for JMM: Agree that this paragraph is a bit of a stretch but Lisa Hutchison at Nature specifically wanted a paragraph on management of carcinoma of unknown primary so I was not going to argue!)..

The nature of symptomatic presentations have a profound influence on the options for staging and neoadjuvant treatment. For example, patients who present with peritonitis from perforated colon cancer require treatment directed at resuscitation and salvage surgery.[38] Typically, in this setting there can be little or no pre-operative staging and no neoadjuvant chemotherapy treatment options.[38] In turn, colorectal cancer presenting as an emergency has a more aggressive histopathologic profile and a more advanced stage.[39]

Traditionally, patients presenting with left-sided obstructing colorectal cancers required urgent surgery.[38] Urgent surgery in this setting can take the form of defunctioning stoma without resection of the primary.[40,41] In rectal cancers, urgent resection does not allow for prior neo-adjuvant chemoradiotherapy. However, the advent of colonic stenting has provided a non-surgical option for relief of intestinal obstruction in this setting.[42,43] If obstruction can be relieved by placement of a colonic stent, options for better staging and treatment can be evaluated.[43] The ongoing Cancer Research UK study CReST undertakes a randomized comparison of endoluminal stenting and emergency surgery for obstructing left-sided cancer.[44] The primary objective is a comparison of morbidity and mortality but secondary objectives include an assessment of overall survival.

Assessment and staging of liver metastases

i. Radiologic assessment and staging

Cross-sectional imaging by computed tomography (CT) or magnetic resonance (MR) is the mainstay for detection of colorectal hepatic metastases.[45] Current North American National Comprehensive Cancer Network (NCCN) guidelines for the initial staging of colorectal cancer suggest use of chest/abdomen/pelvis CT or MRI, with ^{18}FDG-PET CT reserved for surveillance or problem solving.[46] The value of comparing the diagnostic sensitivities and specificities of these various modalities is relatively limited as reports employ a range of different scanning protocols, utilise scanners with different image resolution properties and the 'gold-standard' comparator also varies[47,48,49,50]

Contrast CT is widely used as a first cross-sectional imaging test and should include views of the thorax and pelvis. Image acquisition should predate the use of any neo-adjuvant chemotherapy in order to obtain a pre-treatment baseline of the extent of disease distribution within the liver.

Technical advances in MR include the use of diffusion weighted imaging (which allows contrast diffusion through parenchyma and enhances the difference between normal liver and tumour tissue)[51] and liver-specific contrast such as gadolinium.[52] These liver specific contrast agents are taken up by hepatocytes but not by metastatic tissue. Liver MR provides an accurate 'road map' of the anatomical distribution of lesions, helps to distinguish metastases from benign lesions and also provides information relating to surrounding liver parenchyma (such as post-chemotherapy steatohepatosis).[45] MR machines are not suitable for patients who complain of claustrophobia, have implanted metal devices[45] or at potential risk of nephrogenic systemic fibrosis (NSF) associated with the use of gadolinium.[53]

^{18}FDG-PET has an important role in this diagnostic algorithm. Current evidence-based indications for the use of ^{18}FDG-PET in the United Kingdom recommend this test for the staging of patients with synchronous colorectal metastases at presentation prior to consideration of surgical resection.[54] The incorporation of ^{18}FDG-PET scanning into staging algorithms helps to detect extrahepatic disease and reduces the need for non-therapeutic laparotomy.[55,56]

False positives can be produced by uptake of ^{18}FDG in areas of increased metabolic activity due to inflammation (for example around recent intestinal anastomoses) and false negatives can be associated with mucinous primary colorectal adenocarcinoma and occasionally after prior chemotherapy.

The general availability of ultrasonography makes it a useful initial diagnostic test in an out-patient setting.[57] Contrast-enhanced ultrasound (CEUS) may be useful as an adjunctive test for characterisation of liver lesions.[58] In a detailed health technology assessment, the pooled estimate of sensitivity for any malignancy using CEUS was 95.1% and the corresponding specificity estimate was 93.8%.[58] CEUS is operator dependent and does not always provide the anatomical information of the relation between liver lesion and adjacent vascular structures that is necessary for liver resection planning.

Intra-operative ultrasonography (IOUS) is a standard component of liver surgery for colorectal hepatic metastases and a systematic protocol of scanning all liver segments prior to resection helps to confirm location of disease and correlate intra-operative findings with pre-operative imaging.[59] When used in a systematic intra-operative protocol, IOUS can also detect additional small volume lesions[60.]

ii. Biochemical assessment and staging

The complex glycoprotein carcinoembryonic antigen (CEA) is widely used in post-resection surveillance and current United Kingdom guidelines for the management of patients with colorectal hepatic metastases recommend that a baseline assay is undertaken at presentation in order to serve as a comparator for post-resection surveillance.[61] In addition, elevated pre-operative CEA has been demonstrated to be a good predictor of likely response to subsequent chemotherapy.[62]

iii. Staging laparoscopy

Staging laparoscopy is widely used in the pre-operative assessment of patients with upper abdominal malignancy as it complements CT by detection of small volume liver-surface or peritoneal metastatic disease.[63] In relation to gastric cancer, pre-operative staging laparoscopy is regarded as appropriate but of indeterminate necessity[64]. In contrast, in the assessment of patients with colorectal hepatic metastases it has relatively little additional value to cross-sectional imaging, creates a risk of procedure-related visceral injury in patients with previous colorectal cancer resection and is not routinely advocated.[65,66] Dunne and colleagues reported 12 non-

resectional laparotomies in a series of 274 patients undergoing open hepatectomy.[65] Unresectability was due to peritoneal carcinomatosis that could have been detected by laparoscopy in 5 (1.8%).[65]

Assessment of fitness for surgery

Oncological hepatic surgery for resection of colorectal liver metastases involves pre-operative assessment of the local extent of the disease and the confirmation of absence of extra-hepatic disease. An equally important aspect of staging is the assessment of patients' fitness for major liver surgery. In contrast to the relative sophistication of cancer staging, pre-operative assessment uses combinations of clinical assessment, risk scores and other tests such as pulmonary function[67], echocardiography[68] and cardiac perfusion scans[69]. Liver surgery is increasingly offered to older patients with co-existing co-morbidity. Further, the host (patient) ability to tolerate liver resection may be compromised by prior chemotherapy. In this setting cardiopulmonary exercise testing (CPET) provides a reliable, reproducible non-invasive test of dynamic cardiac and pulmonary function. Our group previously demonstrated that a low anaerobic threshold (AT) is a useful predictor of post-operative outcome.[70] An AT below 9.9 ml O_2 kg min^{-1} was associated with a 100% sensitivity and 76% specificity for prediction of in-hospital death with a positive predictive value of 19% and a negative predictive value of 100%.[70] No deaths occurred above this threshold in a cohort of 108 patients undergoing pre-operative CPET before liver resection.[70] Although CPET is increasingly used in pre-operative risk assessment, further independent validation of our findings in patients undergoing liver resection is required before more widespread adoption of this technique.

Management of colorectal cancer with "beyond-liver" systemic metastatic disease

Systemic chemotherapy is the mainstay of care for patients with advanced colorectal cancer (with a performance status sufficient to permit treatment).[8] Intervention to relieve intestinal obstruction may be required as a first step and for obstructing left-sided cancers, this may be achieved by endoscopic stent.[19] Liver lesions in this setting are typically asymptomatic. European Society of Medical Oncology (ESMO) guidelines consider systemic chemotherapy in this setting in two clinical scenarios: first, as neoadjuvant/palliative treatment in patients who

may become candidates for liver resection after downstaging chemotherapy and secondly as systemic treatment in patients who will never be candidates for surgery.[8] For patients with disease that will never be resectable a holistic approach based on palliation of symptoms and optimization of quality of life becomes important. Liver resection is not conventionally recommended in patients with unresectable, locally advanced primary tumours, [71] peritoneal metastatic disease,[72] nodal involvement of the liver hilus[73] or asymptomatic pulmonary metastatic disease[74] although these reports highlight selected scenarios where there may be clinical benefit. [71,72,73,74]

Management of colorectal cancer with liver and lung-limited systemic metastatic disease

Limmer and colleagues report a series of 1,497 patients with primary colorectal cancer undergoing surgical resection over an 18 year period.[75] Of these, 73 developed both hepatic and pulmonary metastases and 17 of these patients underwent synchronous liver and lung resection. Overall, 3-, 5- and 10- year survival after resection for patients with both hepatic and pulmonary metastases was 77%, 55% and 18% respectively (in a group of patients treated with adjuvant chemotherapy).[75] Clearly, these patients represent a highly selected series and resection of lung metastases from colorectal cancer remains controversial.

A national registry of lung resectional surgery for colorectal pulmonary metastases was established by the Grupo Español de Cirugía Metástasis Pulmonaires de Carcinoma Colo-rectal (GECMP-CCR) and reported outcome in 543 patients undergoing pulmonary metastasectomy (for one or more pulmonary nodules).[76] The majority 293 (55%) had a solitary metastasectomy and 155 (29%) had liver metastases at some point prior to pulmonary metastasectomy.[76] Seventy nine (15%) of these liver metastases were synchronous with the colorectal primary tumour and 45 (8%) were metachronous and detected at the time of pulmonary metastasectomy.[76] Survival data are awaited.

In particular, when presenting with synchronous colorectal liver metastases, current guidelines would categorise lung metastases as systemic disease and recommend systemic chemotherapy.[8,11]There is no randomized trial evidence to support the practice of lung resection in patients with colorectal cancer with synchronous hepatic metastatic disease although a recent survey of thoracic surgical practice in the United Kingdom (a questionnaire sent to members of the Society for Cardiothoracic Surgery in Gt. Britain and Ireland) revealed evidence of considerable variation in practice.[77] Specifically, although a solitary lung metastasis was the most frequent

indication for surgery, 59 (88%) of respondents did not consider lung lesions in the presence of liver metastases as contra-indications to surgery. To address this, PulMiCC a randomised trial of pulmonary metastasectomy in colorectal cancer is undertaking a feasibility study in 11 centres in the United Kingdom with a view to the conduct of a randomised trial.[78]

In summary, pulmonary metastasectomy must be considered with caution accepting the limited evidence base.

Goals of management of colorectal cancer with liver-limited hepatic metastatic disease

Modern management of patients with colorectal cancer with liver-limited metastatic disease relies on optimal disease staging, awareness of the influence of the mode of presentation on available treatments and an integrated approach between oncology and surgery (including ablative treatments). In practical terms, treatment planning decisions should involve a multidisciplinary cancer care team (MDT). In the United Kingdom, current NICE recommendations are that all patients with liver-limited hepatic metastases of colorectal origin should have their care reviewed and an index treatment plan formulated at an appropriate regional Hepato-Pancreato-Biliary (liver) MDT.[11] Key members of such an MDT include medical and clinical oncologists, liver and colorectal surgeons, radiologists with expertise in cross-sectional imaging, nuclear medicine experts, histopathology and cancer nurse specialists. It is important that treatment planning decisions are communicated effectively and promptly to patients, that patients have the option of retaining a permanent record of consultation and are made aware of the range of treatment options and the evidence around these.[11]

i. Selection criteria for synchronous or sequential resection of colorectal cancer and liver metastases.

The synchronous approach can be utilised when a "standard" liver resection can be combined with a colon resection that does not involve extensive pelvic dissection.[79] Accepting the limited evidence, Poston's group suggest the following practical approach:[79]

a. Easy primary tumour resection and easy liver resection:synchronous resection
b. Easy primary tumour resection, borderline/unresectable liver tumours: chemotherapy, followed by hepatectomy, followed by primary resection
c. Difficult/unresectable primary tumour resection, easy liver resection: chemotherapy for primary tumour (chemoradiotherapy for rectal lesion), primary resection followed by a hepatectomy.

Limitations with this recommendation include the lack of definition of an "easy" liver resection, the relative lack of priority allocated to systemic chemotherapy and the lack of evidence base.

The synchronous approach may be considered in patients with rectal tumours who are candidates for short-course chemoradiotherapy. Patients who require long-course chemoradiotherapy may be better served by the liver-first approach.[16,17]

In planning for synchronous resection, siting of any future stoma should be given due consideration and a long midline incision with a right transverse extension may provide optimal access. Patients with left-sided liver tumours may be managed by a midline incision avoiding right transverse extension. The totally laparoscopic approach (laparoscopic colectomy plus laparoscopic hepatectomy) has been reported in small series of highly selected patients.[80]

ii. Neoadjuvant chemotherapy in colorectal cancer with surgically resectable liver-limited hepatic metastases

The European Organisation for Research and Treatment of Cancer intergroup trial 40983 undertook a randomised comparison of perioperative chemotherapy with FOLFOX 4 (administered as 6 cycles of chemotherapy prior to liver surgery and 6 cycles after) to liver resection alone in patients with up to 4 liver metastases.[81] Each cycle of chemotherapy lasted 14 days with the subsequent treatment cycle starting on day 15 giving a minimum period of 90 days of neoadjuvant chemotherapy. One hundred and twenty eight (35%) patients in this study had synchronous disease. Although outcome was not reported in relation to synchronous disease alone, the results showed that there was an absolute increase in the rate of progression-free survival at 3 years of 7.3% (from 28.1% [95.66 CI 21.3 to 35.5]) to 35.4% [28.1 – 42.7]; HR 0.79 [0.62 – 1.02]; P=0.058 in randomised patients and 9.2% from 33.2% (25.3 to 41.2) to 42.4% (34.0 to 50.5); HR 0.73 [0.55-0.97]; P=0.025

in patients undergoing resection.[81] This study established that perioperative chemotherapy with FOLFOX 4 was compatible with major liver surgery and at 3 years follow-up was associated with a better progression-free survival than resection alone. A subsequent retrospective analysis identified that the number of metastases (solitary metastasis compared to up to 4 lesions) had no influence on the benefit of perioperative chemotherapy.[62]

The absolute differences are small and the survival curves follow apparently convergent paths and thus it was perhaps to be expected that the longer-term follow up report of these data showed no difference in survival between groups due to insufficient numbers of patients (OS was not the primary endpoint).[62]

Nonetheless, this landmark study establishes two important points: first, up to 3 months of neoadjuvant chemotherapy is feasible in patients with synchronous colorectal cancer and liver metastases and second, major liver resection (86 [57%]) of patients in the chemotherapy arm had "plurisegmentectomy" – a liver resection incorporating multiple liver segments) is feasible in patients who have received systemic chemotherapy. Important lessons to be learnt from EORTC intergroup trial 40983 include the need for precise definition of the nature and extent of liver surgery – the term "plurisegmentectomy" is not a recognised term and could potentially encompass a series of small resections of non-adjacent segments or a single larger liver resection (see terminology below).

Chua's systematic review of 3,278 patients with colorectal hepatic metastases treated with neoadjuvant chemotherapy (in a range of trials and with a broad range of chemotherapy agents) reported that an objective (complete or partial) radiological response was observed in two thirds of patients. The median (range) disease-free survival was 21 (11-40) months and the overall survival (20-67) months.[82] This systematic review adds weight to the evidence for neo-adjuvant systemic chemotherapy in patients with colorectal cancer with synchronous liver metastases. The recently reported UK National Cancer research network portfolio study new-EPOC was an attempt to integrate treatment with biological agents into this neoadjuvant protocol.[83] Cetuximab is a chimeric monoclonal antibody to the epidermal growth factor receptor (EGFR).[84] The epidermal growth factor pathway is an important component of cell proliferation, apoptosis and tumour-induced neoangiogenesis.[85]

Activating mutations in KRAS which can result in EGFR-independent (and thus cetuximab resistant) constitutive activation of the RAS signalling pathway are found in 35-40% of patients with metastatic colorectal cancer.[85]

In patients with K ras wild type tumours, the addition of cetuximab to irinotecan-based chemotherapy resulted in a significant improvement in progression-free survival with the hazard ratio being 0.68 (95% CI, 0.50 to 0.94) in favor of the cetuximab–FOLFIRI group.[84] The results of new EPOC were presented at the American Society of Clinical Oncology and showed that contrary to expectation, the addition of cetuximab in a neoadjuvant setting was associated with a worse outcome than conventional oxaliplatin-fluopyrimidine chemotherapy.[83] The full implications of these findings have yet to be assessed.

To add to the current complexity around neoadjuvant chemotherapy the CELIM study, a randomised comparison of FOLFOX6 plus cetuximab to FOLFIRI plus cetuximab showed that the addition of the biological agent to chemotherapy increased resectability rates from 32 to 60% (with similar responses in both arms of the study).[86]

Thus a summary of current evidence would support systemic neoadjuvant chemotherapy prior to surgical intervention in patients with colorectal cancer with liver-limited hepatic metastases. This evidence can be integrated with ESMO guidance[8] to state that the current standard of care is that patients with resectable liver metastatic disease at presentation should receive perioperative treatment for 3 months followed by resection with 3 months postoperative adjuvant chemotherapy.

iii. Neo-adjuvant chemotherapy for downstaging in initially surgically unresectable liver metastases.

Patients with colorectal cancer with liver metastases may be unsuitable for surgery because of extra-hepatic disease. The extent and distribution of the disease burden within the liver may also render the liver metastases unresectable. In this regard, the Paul Brousse group reported outcome of a large single-centre series of patients with initially unresectable disease treated by systemic chemotherapy with "downstaging" intent.[87] From a consecutive series of 1439 patients with colorectal hepatic metastases managed in a single institution during an 11-year period (1988-1999), 1104 (77%) initially unresectable patients were treated by chemotherapy and 335 (23%) resectable were treated by primary liver resection. Chemotherapy mainly consisted of 5-fluorouracil and leucovorin combined with either oxaliplatin (70%), irinotecan (7%), or both (4%). Of the 1104 initially considered

unresectable, 138 (12.5%) underwent hepatic resection after an average of 10 courses of chemotherapy. After a mean follow-up of 48.7 months, 111 of the 138 patients (80%) developed tumor recurrence. Survival in this group was 33% and 23% at 5 and 10 years with a disease-free survival of 22% and 17%, respectively.[87]

In terms of choice of induction chemotherapy agent in patients with disease that may become resectable, a pooled analysis of 29 studies (8 randomized controlled trials, 1 phase IV trial, 2 phase II trials, 4 observational studies, 4 prospective nonrandomized cohort studies and 10 retrospective case series) evaluating 5-fluorouracil, folinic acid, irinotecan+bevacizumab (FOLFIRI-B) in a total of 3502 patients revealed an overall, pooled response rate of 51.4% with a Median PFS and OS 10.8 months (95% confidence interval [CI],

8.9-12.8) and 23.7 months (95% CI, 18.1-31.6), respectively.[71] The pooled rate of surgical resection of metastases was 9.3% (range, 3.6%-24%), and rate of liver resection was 18% (range 8%-25%).71 This study concludes that FOLFIRI-B remains the reference combination when bevacizumab is considered in neoadjuvant mode.[88]

The optimal duration of neoadjuvant chemotherapy is currently unclear. Although the Paul Brousse group used up to 10 cycles in neoadjuvant downstaging mode[87], Kishi and collleagues report that neoadjuvant treatment of ≥ 9 cycles was associated with greater hepatotoxicity without a corresponding increase in oncologic response.[89]

In summary, although the goal of surgery after downstaging is the removal of all areas of the liver which carried liver metastases, this may not be technically feasible in patients with multi-segment involvement and such patients may be better regarded as “never resectable”. In practice, all such decisions including the assessment of response to chemotherapy given with downstaging intent require input from an experienced multidisciplinary team.[11]

iv. Current definitions of resectability in relation to colorectal hepatic metastases

Extent of liver resection

Up to 70% of the normal adult human liver can be resected. The amount of parenchyma that can be safely resected is compromised by host factors such as age and co-existent disease (fatty liver disease) and also by the late effects of systemic chemotherapy. Oxaliplatin is associated with sinusoidal obstruction producing a "blue tinge" to the post-chemotherapy liver[90] while irinotecan is associated with steatohepatitis.[91] In contemporary liver surgical practice, important criteria in defining resectability are that hepatic portal and arterial inflow (together with biliary drainage) to the neo-remnant liver together with hepatic venous drainage must be preserved (figure 1).[92]

Liver resection nomenclature

Part of the difficulties around understanding the extent of liver resection relate to the use of non-standard terminology. Increasing acceptance of the terminology proposed at the Brisbane 2000 consensus conference (see figure 2) helps to standardise description of liver resection across reports.[93] Sections of the liver are anatomically discrete with their own hepatic arterial/portal inflow and biliary drainage. The Right hemi-liver has an anterior section (segments V and VIII) and a posterior section (segments VI and VII) (figure 1) separated by the right hepatic vein. The left hemi-liver has a lateral section (segments II and III) and a medial section (segment IV). In terms of anatomical liver resection, the classical operation of right hemi-hepatectomy (removal of the right anterior and posterior section) is a right bi-sectionectomy. Although perhaps slightly cumbersome in use, the terms are clear, anatomically accurate and most importantly, permit comparison across reports.

Non-anatomical resection vs anatomical resection

For resection of colorectal hepatic metastases, the principal operative goal is to achieve a complete (R0 – no residual disease) resection. The importance of the resection margin is debated – although a 1cm resection margin has been the conventional surgical goal, lesser distances between tumour and resection margin are also associated with low local recurrence rates[94] In a clinical cohort study of 2715 patients undergoing liver resection for colorectal hepatic metastases a 1-mm cancer-free resection margin was sufficient to achieve 33% 5-year overall disease-free survival. Additional width in terms of resection margin did not aid disease-free survival

advantage (P > 0.05). There was no significant difference in disease-free survival between patients with negative narrow and wider margin clearance [hazard ratio (HR) 1.0; 95% (confidence interval) CI: 0.9-1.2; P = 0.579 at 5-mm cut-off and HR 1.1; 95% CI: 0.96-1.3; P = 0.149 at 10-mm cut-off].

Hepatic surgery for colorectal liver metastases can take the form of metastasectomy (resection of the metastasis – with a clear surrounding margin of normal liver parenchyma). This type of "non-anatomical" resection is not associated with a higher recurrence than formal hepatectomy.[95] Parenchymal-preserving liver surgery has the advantage of preserving liver substance to allow for repeat hepatectomy at a future date.[96] The question of whether more radical index resection prevents or reduces the need for future liver surgery is currently unanswered.

v. Modification of the future remnant liver to achieve hepatic resection

For more complex and major liver resections, formal assessment of likely adequacy of residual liver volume can been utilised. In particular, this may of value in older patients with co-morbidity and chemotherapy-induced changes to liver parenchyma. Functional assessment of liver volume can be undertaken by indocyanine green clearance.[97] Topographical, anatomical assessment can be undertaken by CT volumetry.[98] If the future remnant liver after resection is thought to be inadequate, this can be modified by the technique of percutaneous portal vein embolization (PVE).[99] In this technique, ultrasound guidance is used to place either foam or coils into the portal vein to either the right or left hemi-livers to cause occlusion leading the embolised side to atrophy and the contralateral side to hypertrophy.[100] The rate of hypertrophy (kinetic growth rate) of the future remnant liver after PVE is a good predictor of post-resection outcome.[101] It should be noted that there are reports which suggest that PVE is associated with increased tumour growth rate in the remnant liver.[102]

Modification of the future remnant liver can also be carried out operatively. Ligation of the right portal vein and *in situ* splitting of the liver facilitates rapid hypertrophy of a (previously inadequate sized) left lobe.[103] This technique, known as ALPPS (Associated ligation and portal partition) is new and the indications and the risk:benefit ratio remains undefined. At the present time it would be prudent to regard this as a procedure requiring more formal evaluation, in particular to define indications, safety profile and outcome.

vi. Two-stage hepatectomy for colorectal cancer with synchronous liver metastases

In patients with bi-lobar, liver-limited hepatic metastases (with or without hypertrophy after PVE) sequential two-stage hepatic resection is an option for removal of the liver disease.[104,105] Typically, a unilateral hepatectomy is undertaken. The recovery period from this operation allows for liver regeneration to take place. The disease in the remnant liver is resected as a second operative procedure at a later stage. Although the indications for this option and the criteria for patient selection tend to be highly individualised, a general overview would be that this is an option where unilateral hepatectomy has to be combined with either an anatomical segmental resection of the contralateral hemi-liver or several metastasectomies. It is likely that there is an appreciable clinical overlap between these patients and those regarded as having "unresectable" liver metastases.

In the setting of colorectal cancer with synchronous liver metastases, one option may be to combine the index liver resection with resection of the primary tumour or alternatively to undertake a major hepatectomy as the first step (liver-first) and to undertake the remnant hepatectomy (second-stage liver resection) with the colorectal tumour resection.

vii. Ablative (non-resectional) treatments with or without hepatectomy for colorectal cancer with synchronous liver metastases

Colorectal liver metastases can be treated by ablation instead of resection. Radiofrequency ablation (RFA) was the first liver tumour ablative technique to be widely utilised[ref Decadt and Siriwardena Lancet Oncology]. Although much of the experience relating to the use of RFA derives from case series, the CLOCC study undertook a randomised evaluation of RFA compared to systemic chemotherapy. It is difficult to extrapolate from the findings of CLOCC to the settings of patients with synchronous colorectal hepatic metastases. In practice, RFA is often used as an adjunct to surgery – for example, unilateral hemi-hepatectomy with ablation of lesions in the contralateral liver. When used intra-operatively, the effectiveness of RFA is critically dependent on precise localisation of the tumour by intra-operative ultrasound. RFA is not effective for larger liver lesions (> 5cm) and in tumour deposits adjacent to large vessels loss of thermal energy by conductive loss produces a heatsink effect which compromises ablative efficacy.

Microwave ablation is an alternative technique using a different thermal source. Microwave ablation is quicker and can be used for larger liver lesions. It too is influenced by the heat sink phenomenon of proximity to larger vessels. Microwave ablators also manufacture a roller ball device which can be used to ablate resection surfaces in an attempt to reduce local tumour recurrence.Evidence for this?

viii. Hepatic arterial infusion chemotherapy (HAI)

HAI delivers chemotherapy directly to the liver via an infusion catheter placed in the common hepatic artery. Colorectal hepatic metastases receive a predominantly arterial neovascular supply and thus HAI preferentially targets the liver lesions. HAI has been used a primary treatment for colorectal hepatic metastastases, as a means of downstaging disease to permit surgical resection and as an adjunct to surgery. Procedure-specific risks of the technique include catheter-induced thrombosis of the common hepatic artery and dislodgement of the catheter and potential intra-abdominal haemorrhage evidence.

Outcomes of surgical intervention for colorectal cancer with synchronous liver metastases

Developing techniques

Technologically driven developments for the treatment of colorectal hepatic metastases include the use of drug-eluting beads to deliver intra-tumour irinotecan (DEBIRI) together with systemic irinotecan. Selective internal radiotherapy (SIRT) delivers radioactive beads to liver tumours. The newest technique is chemosaturation. This involves highly sophisticated interventional radiology approaches to isolate the hepatic venous outflow; catheter-directed saturation of the hepatic artery with very high doses of melphalan, embolizing branches of the artery to prevent chemotherapy from leaking into arteries that supply other organs; and haemofiltration of blood to reduce the toxicity of chemotherapy. The technique has undergone phase 1 and phase 2 testing and is currently being studied in a phase 3 trial in patients with liver metastases, ocular melanoma, or neuroendocrine tumors (J Clin Oncol. 2005;23:3465-3471).

Summary

The management of colorectal cancer with synchronous liver metastases is a common clinical problem. This article has highlighted the need for careful use of terminology in relation to synchronous and metachronous disease and options for assessment and management. The lack of adequately powered randomised trial evidence matched by the constant emergence of new technologically sophisticated treatments creates an environment where selection of the optimal care package for any given individual is complex. In turn, this highlights the need for multidisciplinary treatment planning and the need to give due consideration to patient preferences.

FIGURE 1: FLOW CHART FOR MANAGEMENT OF COLORECTAL CANCER WITH SYNCHRONOUS LIVER METASTASES (MODIFIED FROM ESMO GUIDELINES).

FIGURE 2: SEGMENTS OF THE HUMAN LIVER

AND CURRENT SURGICAL NOMENCLATURE OF LIVER SECTIONS.

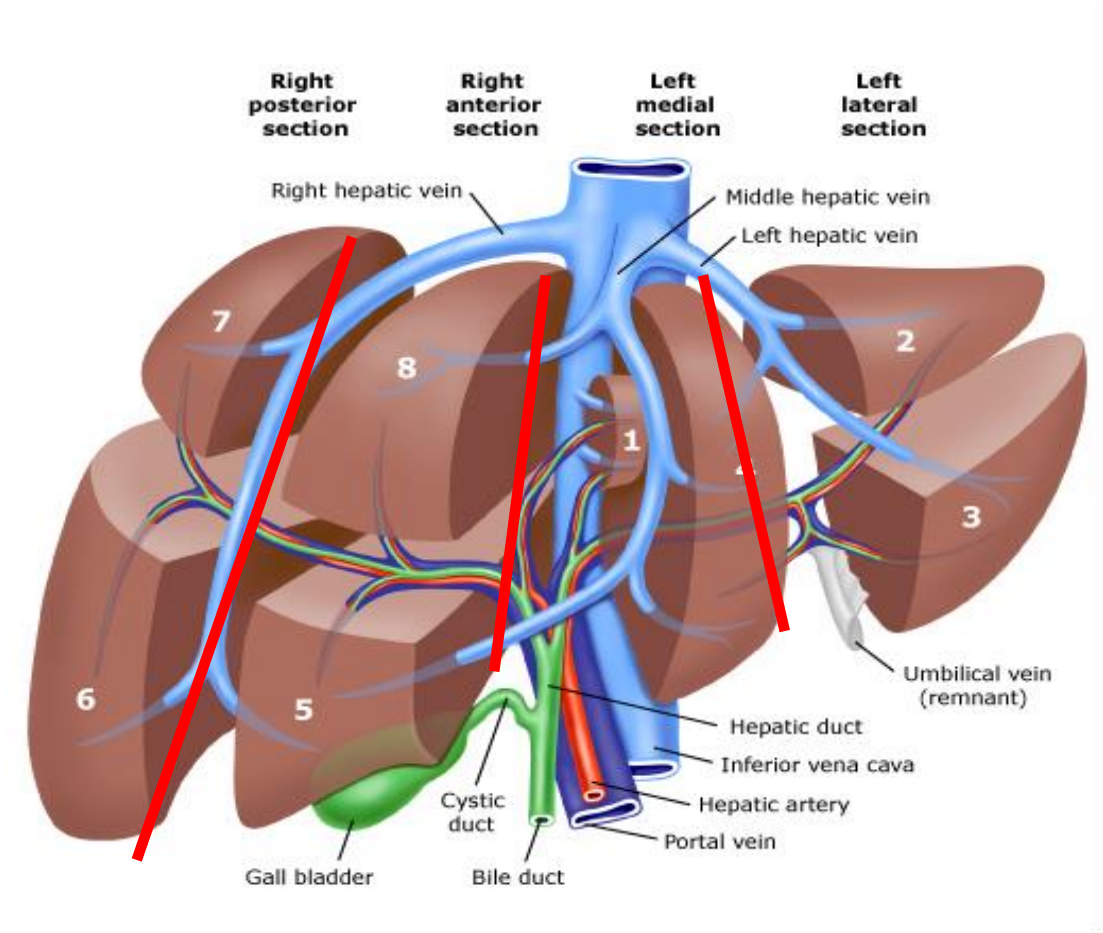
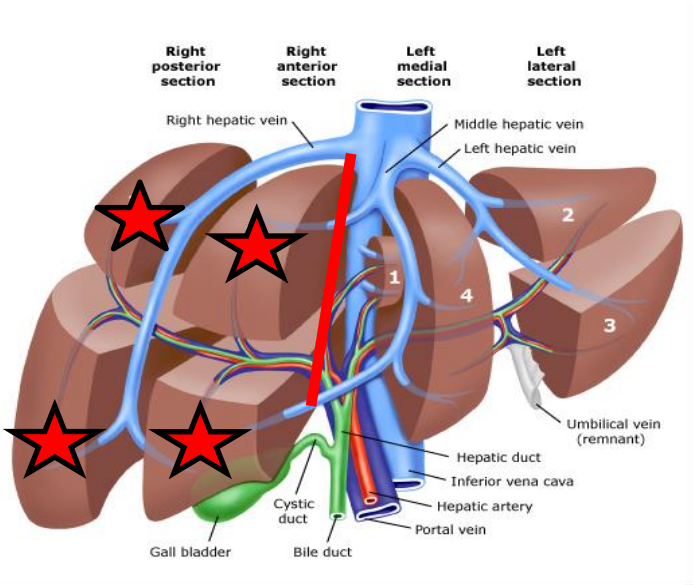
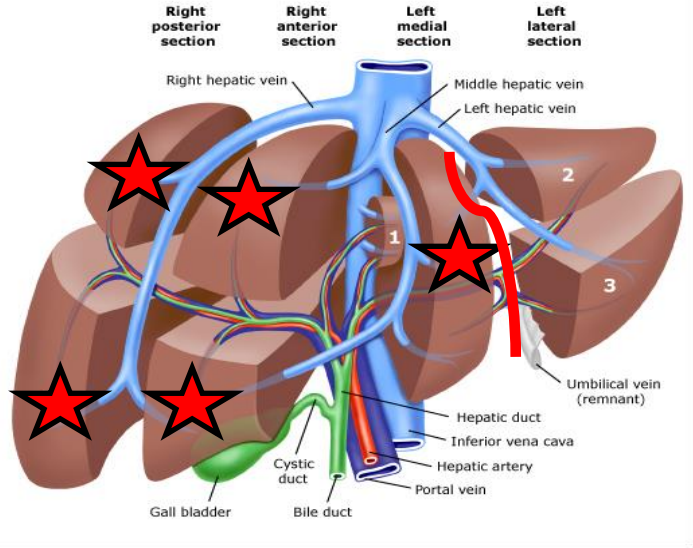


FIGURE 3: CURRENT TERMINOLOGY FOR MAJOR LIVER RESECTIONS ILLUSTRATING SECTIONS AND SEGMENTS REMOVED AT EACH PROCEDURE.



Segments removed in formal right hepatectomy (V, VI, VII, VIII) designated by star.

Right anterior and posterior sections resected = Right bi-sectionectomy.

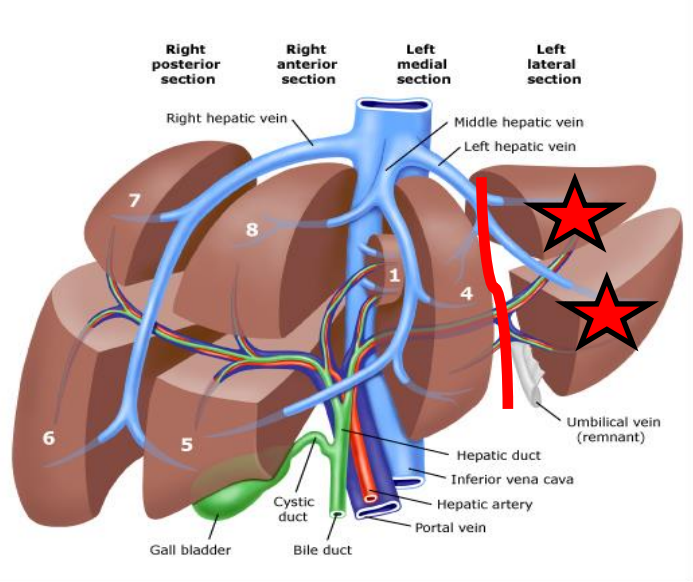


Segments removed in extended right resection (IV,V, VI, VII and VIII) designated by star.

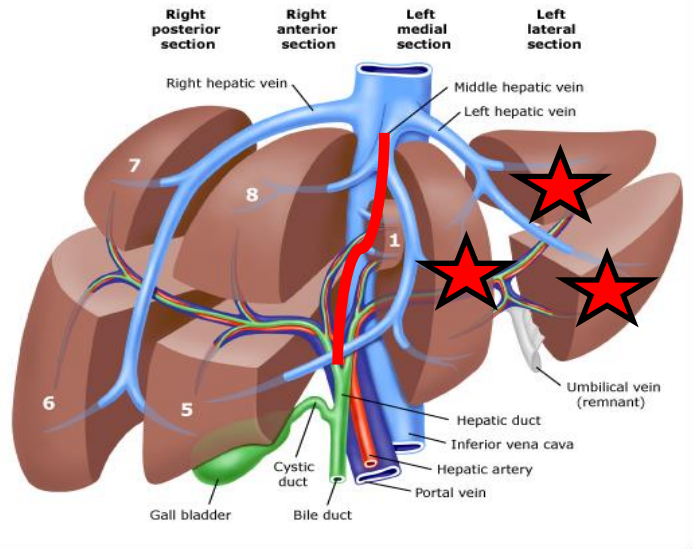
Right anterior and posterior sections resected plus left medial section = Right trisectionectomy.

Note: the arterial and portal inflow to the left lateral section is preserved in right trisectionectomy.

FIGURE 3 (continued): CURRENT TERMINOLOGY FOR MAJOR LIVER RESECTIONS ILLUSTRATING SECTIONS AND SEGMENTS REMOVED AT EACH PROCEDURE.



Segments removed in left lateral sectionectomy (II and III)



Segments removed in left hepatectomy (II, III and IV).

Left bi-sectionectomy.

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