Surgery for Colorectal Liver Metastases

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Abstract
Half of all patients with colorectal cancer develop metastatic disease. The liver is the principal site for metastases, and surgical resection is the only modality that offers the potential for long-term cure. Appropriate patient selection for surgery and improvements in perioperative care have resulted in low morbidity and mortality rates, resulting in this being the therapy of choice for suitable patients. Modern management of colorectal liver metastases is multimodal incorporating open and laparoscopic surgery, ablative therapies such as radiofrequency ablation or microwave ablation and (neo)adjuvant chemotherapy. The majority of patients with hepatic metastases should be considered for resectional surgery, if all disease can be resected, as this offers the only opportunity for prolonged survival.

Introduction
Colorectal cancer is the third most common cancer in the world and is increasing in incidence [1]. Half of all patients with colorectal cancer will develop metastatic disease, with the liver being the most common site. Historically the development of hepatic metastases had a poor prognosis with a median survival of approximately 5 months [2, 3]. Newer chemotherapy agents have improved the median survival to over 20 months [4]. However, long-term survival after systemic therapy alone is uncommon, and surgical resection is the only therapeutic modality that offers the potential for long-term cure, with 5-year survival rates of up to 58% [5–8].

Hepatic resection for colorectal liver metastases (CRLM) has developed over the past three decades. Appropriate patient selection and improvements in perioperative care have resulted in low morbidity and mortality rates, meaning that this is the therapy of choice in suitable patients [9, 10].

The indications for resectional surgery have evolved over time, and whilst the presence of multiple bilobar metastases was at one point a contraindication to surgery, this is no longer the case. Strategies for identifying those patients most likely to benefit from resection continue to evolve [11–13]. The current criteria for surgery revolve around the ability to achieve an R0 resection whilst leaving a sufficient residual volume of liver [14–16]. Many factors contribute to a successful outcome, and these include: accurate pre-operative staging; neoadjuvant and adjuvant chemotherapy; operative planning, and the use of combination treatments when appropriate [17].
Staging of Colorectal Liver Metastases

Staging consists of a clinical assessment, and radiological imaging. Clinical assessment should determine whether the patient would withstand major resectional surgery, and identify important cardiorespiratory comorbidities. Time should be taken during the initial consultation to assess the understanding patients have of their disease and the goals that they wish to achieve. Liver function tests including prothrombin time and albumin are essential to exclude underlying parenchymal disease, and baseline CEA may be useful for long-term follow-up [18]. There remains debate regarding the best functional measures of liver reserve, which is of particular importance in cirrhotic patients. Approaches including indocyanine green clearance, mebrofenin clearance and lidocaine metabolism (MEGX) have all been used successfully in certain centres, but these are not currently in general use [19–21]. Whilst they provide additional information, they also require additional equipment (indocyanine green clearance) or the use of radioisotopes (mebrofenin) and can be difficult to measure in standard laboratories (MEGX).

Cross-sectional imaging is essential to accurately locate all disease and to plan surgical strategy. The options include CT, CT-PET and MRI. The initial investigation of choice will depend on local expertise, but most centres use CT as the mainstay of investigation, with MRI reserved for selected cases. Modern multislice CT scanners provide high-resolution images which permit multiplanar reconstructions to facilitate operative planning. Most patients who are being staged for colorectal cancer will have a contrast-enhanced abdominal and pelvic CT undertaken during their workup. Arterial and portal venous phases are routinely used to aid identification and characterisation of liver lesions. It will also identify aberrant arterial or venous anatomy, and provides accurate volumetry data on the FLR.

MRI provides high-quality cross-sectional imaging of the liver and is now the imaging modality of choice in several centres [22, 23]. It has excellent discrimination for benign lesions such as fibronodular hyperplasia and hemangioma. MRI is superior to CT for detection of CRLM [24] and it has an important role in clarification of small lesions and for assessing liver lesions in patients with underlying liver disease [25]. There are a range of contrast agents and MRI sequences which can be performed to optimise the display of mass lesions, and the use of specific hepatobiliary and paramagnetic contrast agents improves lesion detection and discrimination [26].

For any patient who is being considered for operative intervention, exclusion of extrahepatic disease is essential. Previously this was achieved by CT encompassing the entire thorax, abdomen and pelvis. More recently, CT-PET is being used to assess for the presence of extrahepatic disease. FDG is used as a tracer and is sensitive in the identification of distant metastases, modifying the management in up to 20% of cases [27, 28]. As patients with distant non-pulmonary metastases are unsuitable for hepatic resection, this has become an important part of the pre-operative workup of patients with hepatic CRLM. It should be noted, however, that certain colorectal cancers have a low avidity for FDG, and so false negatives can occur, particularly in patients who have had chemotherapy, and a minimum 3-week interval following chemotherapy is recommended before performing PET-CT [29]. If pulmonary metastases are identified, this is only a contraindication for hepatic resection if the lung disease cannot also be resected [30].

Transabdominal ultrasound has largely been replaced by cross-sectional imaging for pre-operative staging, however in lesions which are difficult to assess it can provide complimentary information, particularly with the use of ultrasound contrast agents. Furthermore, it may be indicated if percutaneous ablative techniques are being utilised.

Role of Pre-Operative Biopsy

In the context of modern imaging techniques, histological confirmation of the diagnosis is not required. In the past, pathological confirmation was required before proceeding to liver resection [31]. However, in addition to the bleeding complications which can result [32], percutaneous biopsy can lead to tumour dissemination along the needle track, and has been shown to be associated with a poorer outcome [33]. With the support of tumour markers where appropriate, a confident pre-operative diagnosis can be made in the majority of cases. Hence the decision to perform a liver biopsy should only be taken following review by a specialist hepatobiliary multidisciplinary team [34].

Operative Planning

Following assessment of the patient and suitable staging, tailored operative planning is required to determine the most appropriate surgical strategy. The intention is to achieve an R0 resection at the end of treatment. Consideration must be given to: the anatomical distribution of
the disease; the residual functional volume of liver (future liver remnant, FLR); management of the primary disease (in the setting of synchronous CRLM); the timing and role of (neo)adjuvant chemotherapy, and whether all disease can be resected successfully at one sitting.

**Hepatic Anatomy**

An understanding of the anatomy of the liver is essential for hepatic surgery, and improvements in the knowledge of this anatomy were the key impetus for the development of hepatic surgery. Coinaud’s seminal anatomical studies described the segmental anatomy of the liver, making anatomical resection feasible [35]. This formed the basis for the Brisbane terminology to describe hepatic resection, based on the hepatic artery and bile duct divisions [36]. The liver has 8 segments. The right hemi-liver contains segments 5–8, and the left hemi-liver contains segments 2–4. Segment 1 is the posteriorly situated caudate lobe [36]. Minor anatomical hepatic resections are considered as 1–2 segments, and major resections as 3 or more segments. A standard right hepatectomy (segments 5–8) will remove approximately 60% of the liver volume, whilst an extended right hepatectomy (segments 4–8) will remove approximately 75% of liver volume. Maintenance of a suitable volume of FLR is critical to outcome, and a minimum of approximately 25% FLR in two contiguous segments of liver is required to minimise the risk of post-operative hepatic failure (40% in the presence of parenchymal disease, and 30% following chemotherapy) (fig. 1).

Standard anatomically-based segmental resections have traditionally been preferred to atypical resections as an atypical resection was felt to be associated with a higher risk of local recurrence [37, 38]. However, with the increasing need to retain as much functioning liver volume as possible, parenchymal-preserving resections are increasingly performed. Multiple series have demonstrated that atypical resections are not associated with increased local recurrence providing microscopic clearance has been achieved [39–41].

**Portal Vein Occlusion**

If initial assessment indicates that an extended hepatic resection may achieve cure, but is contraindicated due to a limited FLR, portal vein embolisation (PVE) can be undertaken to induce hypertrophy in the remnant liver. This procedure is premised on the observation that interrupting the flow of blood to one half of the liver increases the flow to the contralateral side, which undergoes compensatory hypertrophy. PVE is usually performed percutaneously under ultrasound guidance to access the portal vein and introduce embolisation coils. The liver is then re-imaged 4 weeks later to assess the degree of hypertrophy, and repeat CT volumetry is undertaken (fig. 2).

Theoretically PVE may induce accelerated growth in any disease present in the liver remnant. This remains a debateable phenomenon [42], and studies addressing this have small sample sizes. In a series of 18 patients undergoing PVE, Kokudo et al. [43] found that not only did tumour volume increase after PVE, but the proliferative index of the tumours appeared greater than seen in control patients. Hence if disease is present in the FLR, consideration should be given to removing this before PVE. Indeed, the portal vein branch may be ligated surgically at the time of the initial hepatic procedure. During either a percutaneous PVE or open portal vein ligation, biopsy of the proposed remnant can be useful to exclude paren-
chymal disease which may limit the hypertrophic response. Failure of the future remnant to adequately hypertrophy after PVE may indicate patients at high risk of post-operative morbidity and liver failure.

**Staged Hepatic Resections**

Staged hepatic resections can be performed to allow hypertrophy of residual liver tissue \[44\]. This approach can be used if it is not possible to resect all hepatic disease during a single procedure, as may occur in patients with multiple bilobar metastases (fig. 3). This can be successfully combined with synchronous resection of the primary tumour during the index procedure \[45\] or with PVE as required \[46\]. Staged resections are associated with 5-year survival rates of up to 42% but is only suitable for selected patients \[47\].

A recent development in marginally resectable patients has been operative portal vein ligation and in situ splitting, followed by hepatic resection 1–2 weeks post-portal vein ligation \[48, 49\]. This induces rapid growth of the FLR which is greater than that usually seen with PVE.

A recent study of 25 patients undergoing this procedure (of whom 14 had colorectal metastases) demonstrated a dramatic increase in the FLR volume even over a short interval (median 9 days) \[50\]. All patients were scheduled to undergo an extended right hepatectomy, and at the first procedure the right portal vein was ligated and the liver parenchyma split along the falciform ligament, but not resected. Whilst this does expose the patient to two laparotomies in a short period of time, this approach may have a role in permitting R0 resection in cases where the FLR is marginal. This is a technically complex procedure which has as yet only been performed in a few centres, and its place in the armamentarium of hepatic resection for CRLM remains to be determined.

Location of disease is a more important consideration than sheer volume. A 10-cm large tumour in segment 3 is technically easier to resect than a 5-cm tumour in segment 8. Indeed, involvement of the hepatic veins is an important factor in determining the resectability of metastatic disease, and may necessitate an extended resection for what may initially appear to be low-volume disease.
Resection of the hepatic vein confluence and IVC can be undertaken in selected patients with acceptable medium-term outcomes, but this remains a high-risk undertaking [51].

Synchronous Resection

In patients presenting with synchronous CRLM, it is possible to perform synchronous or sequential colonic and hepatic surgery. Theoretically, synchronous resection permits all disease to be dealt with at a single sitting, shortening the hospital stay and attendant costs, with acceptable morbidity in selected patients [52, 53]. However, no trial exists to provide definitive guidance and the decision to perform synchronous resection depends upon the magnitude of both procedures, as there is a synergistic effect on complication rates. The risks are lower with atypical or segmental hepatic resections than with major hemihepatectomy [54]. Similarly, the risks associated with right or extended right hemicolectomy are less than with left-sided colorectal resections. In most centres, synchronous resections are either limited to 4 or less hepatic segments in combination with right-sided colonic resections, or to atypical hepatic resections in combination with left-sided colonic procedures. Some centres report synchronous resection as feasible in 25% of patients [54].

Colon or Liver First Resection?

A ‘liver-first’ approach is advocated by some groups, whereby the liver resection is performed first, and the colonic surgery is performed only after the patient has recovered from their hepatic procedure [55]. The underlying rationale is to prevent progression of the CRLM which may otherwise occur whilst colonic surgery is undertaken, particularly if the anastomosis is high risk, as anastomotic breakdown may significantly increase the interval until they are sufficiently recovered for liver surgery. In patients who are asymptomatic from their primary cancer, and who will be receiving systemic therapy, this approach does not lead to significant colonic complications and indeed some groups would suggest that resection of an asymptomatic primary lesion is not always required in the age of modern chemotherapy [56].

Chemotherapy

The current mainstay of chemotherapy for metastatic colorectal cancer are regimens based on either oxaliplatin or irinotecan in combination with 5-FU and leucovorin (FOLFOX and FOLFIRI) [57–59]. Current Scottish guidelines suggest that patients with resectable diseases should be considered for perioperative chemotherapy prior to hepatic resection [60], and perioperative treatment does reduce recurrence rates, based on results from the EORTC Intergroup trial [61]. However, although progression-free survival was improved (the primary outcome of the study), there was no effect on overall survival and there was an increase in post-operative complications in those patients receiving chemotherapy. This lack of effect on overall survival is supported by a number of retrospective cohort studies and registry data [62], and a recent systematic review concluded that there was i-
sufficient evidence to support neoadjuvant therapy in patients with resectable disease [63].

Pre-operative chemotherapy has a deleterious effect on hepatic function. Platinum-based therapies are associated with sinusoidal obstruction syndrome, characterised by sinusoidal thrombi, whilst irinotecan-based regimens are associated with an acute steatohepatitis. Both of these responses impair the function of the residual liver and increase post-hepatectomy complication rates [64]. The risk is reduced with shorter pre-operative courses of treatment, and by allowing a window of 4–6 weeks for recovery of liver function between cessation of chemotherapy and subsequent surgical resection. Occasionally a complete radiological response can be seen following chemotherapy. However, the affected area of liver is likely to still contain viable tumour cells [65] and, in most circumstances, resection of the tumour-bearing liver, utilising the pre-treatment imaging, would still be indicated. Disease progression during chemotherapy denotes an aggressive tumour and whilst it is not an absolute contraindication to resection, it may necessitate the use of additional adjuvant therapies in order to achieve satisfactory results [66, 67].

Beyond neoadjuvant treatment, chemotherapy may be used to downsize or downstage the disease, allowing resection to be undertaken [66]. Such downsizing can be achieved with FOLFOX (and to a lesser extent with FOLFIRI), but novel biological agents offer the hope of greater response rates. In the UK, cetuximab is currently licenced specifically for the downsizing of CRLM in patients with K-ras wild-type disease, based on the results of two clinical trials [68–70]. However, the more recent MRC COIN trial [71] failed to confirm an additional effect of cetuximab, and subsequent studies are awaited.

Hepatic artery infusion (HAI) has been used to deliver local chemotherapy to CRLM. It has been used in neoadjuvant, adjuvant and palliative settings and it can be delivered through a surgically-placed catheter introduced to the hepatic artery via the GDA, or through percutaneous techniques. HAI provides a high concentration of chemotherapy in the liver, whilst minimising systemic toxicity. Delivery through the arterial supply improves the tumour specificity, as the metastases preferentially use arterial blood. However it can be associated with biliary toxicity and gastric ulcers [72]. Studies have shown that HAI results in higher response rates than that seen with systemic chemotherapy. However they have failed to consistently demonstrate a survival benefit [73]. Most studies performed on HAI were performed prior to 2,000 and have utilised chemotherapy regimens which would currently be considered suboptimal [74]. There is a need to perform studies using HAI and modern chemotherapy regimens. Operative Approach

The majority of hepatic resections are currently performed using open surgery. A rooftop or hockey stick incision in the right upper quadrant is used, commonly with a table-mounted retraction system. An initial laparotomy excludes occult disease, and allows intraoperative ultrasound to confirm the pre-operative imaging findings and to confirm the planned resection. Use of intraoperative ultrasound allows the identification of occult disease which may have been missed on previous imaging studies, and also confirms the location of the hepatic veins in relation to the proposed resection. Following mobilisation of the liver from its attachments, parenchymal transection can be performed using a variety of techniques including crush-clamping and ultrasonic aspirator devices such as CUSA. Portal dissection and selective vessel ligation is not required for atypical resections. Portal clamping (Pringle manoeuvre) can be used during transection to minimise blood loss.

Management of Lymph Node Metastases

Whilst the presence of regional lymph node involvement influences survival [75, 76] and portal lymphadenectomy may improve staging accuracy [77, 78], there is no evidence that routine portal lymphadenectomy improves oncological outcomes [79, 80].

Laparoscopic Hepatic Resection

Laparoscopic resections can be performed with satisfactory oncological outcomes [81]. Major anatomical resections are technically demanding but atypical superficial resections or resection of the left lateral segment is increasingly undertaken and is standard practice in certain units [82]. There is a significant learning curve and advanced laparoscopic skills are required [83, 84]. Published series have demonstrated reduced blood loss and conversion rates with the accumulation of experience [85]. The role of laparoscopic major hepatectomy is currently evolving. All forms of major resection can be undertaken laparoscopically [86] and it has the potential to speed post-operative recovery. However, it has not yet achieved the widespread uptake seen in colorectal surgery.
Adjuncts to Surgery

Ablative therapies have gained a role in the management of patients with complex disease [87, 88]. If the full extent of disease is not resectable in a single sitting due to anatomical constraints or a threat to the FLR, then ablation in combination with resection may be utilised. Radiofrequency ablation (RFA) consists of inserting an electrode into the lesion (under ultrasound guidance) and generating an alternating current which passes to a distant ground plate. This results in generation of heat locally within the liver. Current devices provide a 4-cm³ burn area, meaning that they can be used to target lesions up to 3 cm³, with a 1-cm margin. Limitations relate to a heat sink effect seen in lesions adjacent to the major veins, and the risk of thermal injury to major biliary structures. In contrast to when it is performed percutaneously, the risk of inadvertent burns to bowel or diaphragm and pleura is reduced when RFA is used intraoperatively. Data from institutional series have shown that it is effective for unresectable disease. However, in the presence of resectable disease, its high local recurrence rate compares unfavourably with surgery [89–91]. This data is obtained from case series, and the poorer outcomes may be explained in part by differences in baseline disease pattern and tumour biology which led to these patients being considered for ablative therapy [92, 93]. Currently, RFA is used as an adjunct to chemotherapy or resection, but it has not yet been able to replace resection [94]. Microwave ablation (MWA) is also utilised to generate thermal ablation. New devices have a greater burn area with a more consistent penumbra when compared to RFA [95, 96]. These treatments are likely to have an evolving role in the future either in combination with resection or in isolation [97].

The first randomised controlled trial of RFA for CRLM has recently reported [98]. This study randomised 119 patients with unresectable hepatic disease to chemotherapy alone or chemotherapy plus RFA. This demonstrated an improvement in progression-free survival of 7 months with the addition of RFA. This was initially intended as a phase III trial but suffered from slow recruitment leading to its re-design as a phase II trial. It was not powered to detect differences in overall survival, and so firm conclusions cannot be drawn. Further trials in this area are needed, but in light of the difficulties in recruitment experienced, the authors question whether an adequately powered trial could be successfully completed.

Specific Considerations

Re-Resection in Face of Recurrent Disease

As the indications for hepatic resection expand, more patients are presenting with recurrent disease. Further resections in this setting should be carefully considered. The principle of resection remains as for primary hepatic surgery, namely that all recurrent disease can be resected and that sufficient liver volume will be preserved following resection. As a result, re-resection can only be offered in a limited proportion of patients. Those individuals with limited tumour load are best suited to repeat procedures [99]. Furthermore, there is a greater need for parenchymal-sparing rather than anatomical resections, as second and third procedures can be considered [100]. If the disease cannot be resected surgically, then these patients may be considered for percutaneous ablation with RFA or MWA, which will result in the greatest preservation of hepatic parenchyma.

Resection in Setting of Pulmonary Metastases

The presence of pulmonary metastases does not preclude hepatic resection, and 5-year survival rates of over 50% can be achieved following pulmonary metastasectomy [101, 102]. If the lung disease can be resected or ablated, then the patient may be considered for hepatic resection [103, 104]. Analogous to synchronous metastases, in the presence of pulmonary and hepatic disease, consideration can be given to either a lung-first or a liver-first resection. Options for dealing with the lung disease may include open or video-assisted resection, or percutaneous RFA [105, 106]. Video-assisted procedures are most suited to smaller, peripheral lesions <15 mm which do not require major lobectomy. Synchronous resection of hepatic and pulmonary metastases is clearly possible, but magnifies the perioperative risk. Repeated resections can be performed if there is late recurrence [107]. The presence of extrahepatic disease is associated with a poorer survival, and careful patient selection is required as the risk of recurrence is high [108, 109]. Nevertheless, if the patient is counselled appropriately, combined liver and lung resection should be considered.

Conclusion

Hepatic resection for colorectal metastases is an important option in the armamentarium of clinicians dealing with colorectal cancer. Long-term survival rates
have continued to improve after liver resection. Such surgery can now be carried out with an acceptable perioperative risk, and the increasing use of parenchymal-sparing resections and the use of ablative therapies such as RFA and MWA mean that this is now a viable option for most patients. All patients with colorectal cancer who develop or present with liver metastases should be considered for hepatic surgery, as this offers the potential for long-term cure in appropriately selected patients.

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