Recent Advances in

SURGERY
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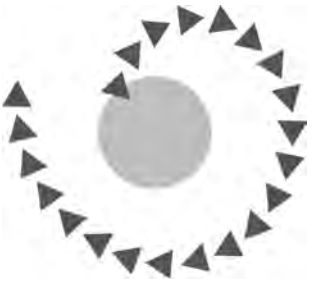

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SURGERY
37

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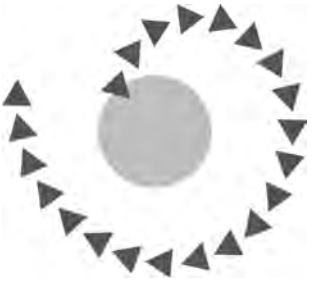

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Preface

In this volume of Recent Advances in Surgery, I have attempted to include topics in which there have been recent major changes involving patient care. Each subject has been written by experts in the field and provides an up-to-date review designed to be of value to surgeons taking professional examinations in General Surgery. I also hope that the issues covered will be of practical interest to all surgeons wishing to keep abreast of changes within the broad field of General Surgery.

The general themes include a review of modern day surgical training, the importance of confidential reporting systems in surgical practice, an update on the use of intravenous fluids and the important issue of the management of knife injuries.

Concepts relating to gastrointestinal surgery include the management of gastric cancer, gastroesophageal reflux, resectability in pancreatic cancer, management of synchronous colorectal liver metastases, enhanced recovery following colorectal resection, the use of robotics, and anal fistula management. Other specialist topics include modern prostate cancer management, phyllodes tumour of the breast, the management of varicose veins and superficial venous incompetence. The volume concludes with a review of recent randomised controlled trials in surgery.

I hope readers agree that this volume maintains the high standards of previous editions. I am most grateful to all our contributors for taking the time to provide comprehensive reviews of each topic.

Irving Taylor

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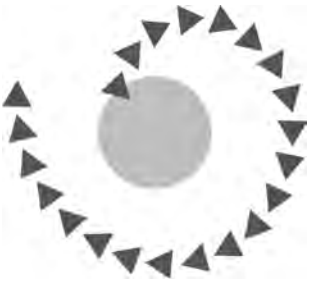

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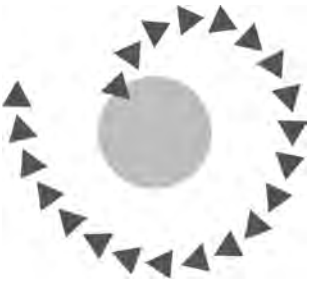

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13 Chapter

Management of Patients with Primary Colorectal Cancer and Synchronous Liver Metastasis

Alistair AP Slesser, Elizabeth Smyth, David Cunningham, Satvinder Mudan

INTRODUCTION

Approximately 40% of patients treated for colorectal cancer will develop liver metastases during their life time following treatment of the primary cancer, and these are defined as "metachronous" metastases. Approximately 15% of all patients diagnosed with colorectal cancer will have radiological evidence of liver metastases at the time of initial presentation,[1] and these are termed synchronous colorectal liver metastases (SCLM). It is the management of this group of patients which we will discuss. SCLM are accepted as indicative of a poor prognosis compared with metachronous lesions, consistently demonstrating more aggressive biological traits such as increased incidence of multiple, bilobar, large dimensional disease and thus irresectability.[2]

Colorectal liver metastases presenting within one year of the primary colorectal cancer are likely to behave biologically as those identified at the initial diagnosis, and this group of patients too will have an adverse biological behaviour from those who develop liver metastases several years later.[3]

Despite these apparent biological differences, the surgical management for both synchronous and metachronous liver metastases has, hitherto, been similar. The classical surgical strategy has been a sequential resection, whereby the primary tumour is resected first with subsequent adjuvant systemic chemotherapy followed by liver resection. Some centres are now undertaking a "reverse sequential" or "liver-first" approach, whereby the hepatic resection is performed first followed by the primary tumour resection for SCLM patients with rectal cancers on the postulate that in advanced rectal cancer the reverse strategy has a survival benefit, in sequential resections, by removing the main indicator of poor prognosis first thereby avoiding unnecessary rectal surgery in patients with incurable metastatic disease.[4,5] We consider the evidence supporting the different surgical approaches and impart our experience in managing this group of patients through the prism of a multidisciplinary team comprising academic surgeons, oncologists and radiologists in the institutional setting of an international comprehensive cancer centre.

Key Points

- Approximately 15% of all patients presenting with colorectal cancer will have liver metastases at the time of initial diagnosis, and at least 40% of the remainder of patients will go on to develop liver metastases at some time later.
- Synchronous colorectal liver metastases are an indicator of poor prognosis when compared with metachronous colorectal liver metastases and so likely represent a different biological group.
- Patients developing liver metastases within one year of diagnosis also demonstrate an adverse tumour biology similar to that of SCLM patients.

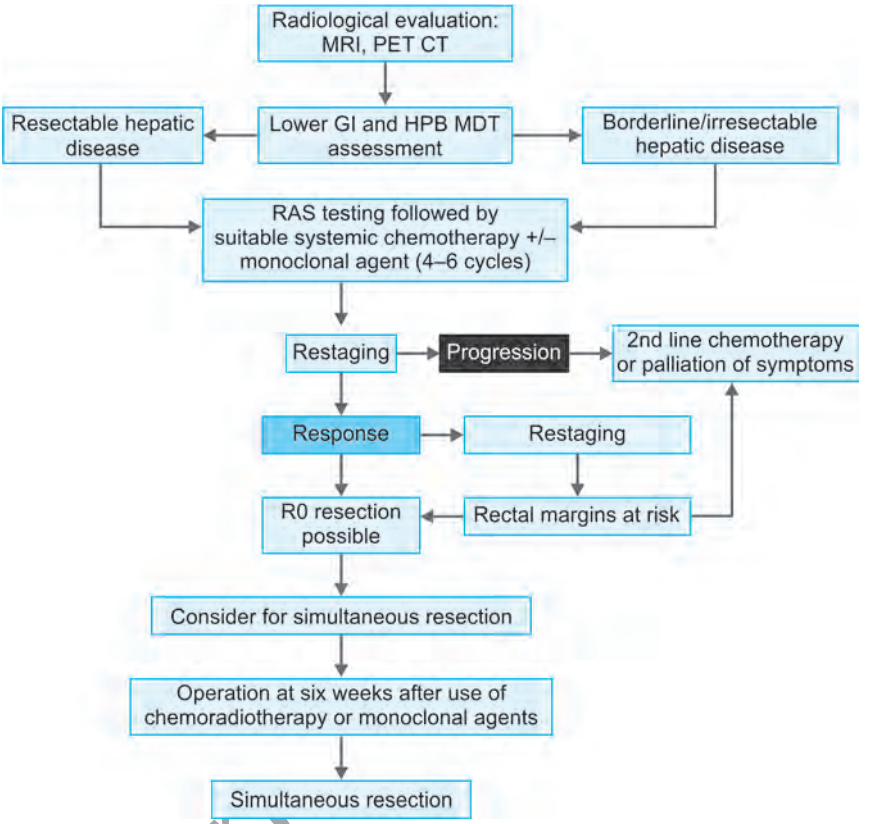
SELECTION FOR SURGERY

Full characterisation of the extent and distribution of disease is essential.[6,7] We recommend, all patients considered for radical treatment are evaluated by computed tomography (CT) of the chest, abdomen and pelvis, dedicated gadoxetic acid enhanced and diffusion-weighted magnetic resonance imaging (MRI) of the liver and 18F-FDG PET/CT to identify extra-hepatic metastases. Postchemotherapy morphological and functional metabolic response data[8-10] are used to aid in case selection. In the case of a rectal primary, pelvic MRI is performed.[11] All patients are discussed by the multidisciplinary team (MDT) in dedicated tumour-specific MDMs, where all relevant medical and ancillary disciplines are represented (Flowchart 13.1).

Untreated, patients with SCLM have an overall five-year survival of 3%.[1] Only surgical intervention offers possibility of long-term cure, and survival for patients rendered free of all evaluable disease ranges from 37% to 58%.[12] Previously held criteria for inoperability with a curative intent such as more than three liver lesions, bilobar distribution or extra-hepatic disease are no longer considered contraindications to a hepatic resection, provided all sites of disease can be adequately treated. We acknowledge that there is a growing interest towards complete resection in the presence of controllable serosal disease, retroperitoneal nodal disease and even for maximally debulking operations, and that debulking operations and that by these criteria between 15–13% of patients with SCLM will be found to be eligible for resection with a curative intent.[13]

In an era of effective chemotherapy, we consider that patients in whom all sites of disease can be controlled are potentially operable and our criteria for resectability in the liver is the ability to gain negative resection margins whilst leaving sufficient residual functional liver volume with adequate inflow and outflow to support the patient in the postoperative phase. The use of portal venous embolisation, downsizing chemotherapy, radiofrequency ablation and two-stage hepatectomies has increased the proportion of eligible patients.[14]

Flowchart 13.1: Algorithm for management of colorectal cancer patient presenting with synchronous liver metastases.



As the majority of the patients will have significant medical comorbidities, which will impact on the decision, timing and strategy for operation, close cooperation between the colorectal, hepatobiliary, anaesthetic and postoperative care teams is essential.[15]

Key Points

- Liver metastases are best characterised by MRI and extra-hepatic disease identified with 18-FDG CT/PET.
- All patients should be discussed by colorectal and hepatobiliary MDTs, and close cooperation is essential.
- SCLM is a signal of poor tumour biology and prognosis and should be considered for neoadjuvant chemotherapy to assess response, demonstrate the tumour biology and treat occult micrometastatic disease.
- The response to neoadjuvant systemic chemotherapy is an indicator of long-term oncological outcome and can be demonstrated by morphologic and functional imaging.

- Complete elimination of all evaluable disease remains the only chance of cure.
- Only approximately 15% of patients with synchronous colorectal liver metastases will have resectable liver disease at presentation, but the use of techniques such as portal vein embolisation and multimodal liver-directed therapies such as RFA and conversion systemic or regional chemotherapy can enlarge the pool of resectable patients by approximately 10%.
- Main determinant of whether a patient is a surgical candidate is the ability to control all sites of intra- and extra-hepatic disease and retain sufficient functional liver volume, usually 25% in good quality liver and 40% in damaged liver.

ONCOLOGICAL MANAGEMENT

The adverse prognosis of patients with SCLM is understood. At diagnosis the patient may have upfront resectable disease or borderline/irresectable metastases. For patients with de novo resectable disease, the EORTC 40983 trial, which randomised 364 operable patients to 12 cycles of perioperative FOLFOX (oxaliplatin plus fluorouracil) chemotherapy or surgery alone, demonstrated a three-year progression-free survival (PFS) benefit of 8.1% in favour of chemotherapy Hazrd Ratio = 0.77, range 0.60–1.00; $p = 0.041$.[16] This trial was underpowered for overall survival (OS) and revealed a non-statistically significant six-year OS benefit of 4.1% for patients treated with perioperative chemotherapy. A small proportion of patients (7% in EORTC 40983) progressed during chemotherapy, and these patients demonstrated an aggressive disease biology unlikely to benefit from resection and we consider such patients as inoperable for treatment with curative intent.

For a patient with borderline/irresectable disease receiving preoperative chemotherapy, the speed and quality of response as measured by dimensional, morphological and functional changes bear strongly correlated to a probability of eventual resection and to both PFS and OS.[17-19] This implies that the most appropriate active regimen should be selected, with the caveat that for most patients this will be part of a continuum of care due to the metastatic nature of the cancer. Doublet or triplet chemotherapy using a fluoropyrimidine backbone with the addition of either or both of irinotecan and oxaliplatin has been examined for the purpose of "conversion" to resectability; triplet combinations are not only associated with increased response rates but also with increased toxicity.[19,20]

The use of anti-angiogenic and anti-EGFR monoclonal antibodies (bevacizumab and cetuximab or panitumumab, respectively) has led to significant improvements in survival for patients with stage IV irresectable colorectal cancer, and these drugs may also improve outcomes for patients with

resectable disease. However, it should be noted that most data are derived from trials that are not liver surgery specific, and consequently the absolute number of patients resected in any study is small, leading to significant inter-study heterogeneity and difficulty interpreting outcomes. Bevacizumab does not consistently increase response rates when added to cytotoxic chemotherapy, and this inconsistency is also reflected in liver resection rates in randomised trials. Although resection rates were increased from 6.4% to 8.1% in bevacizumab-treated patients in the NO16966 trial (Ox5FU ± bev), they were not significantly increased in other studies.[21,22] Despite these conflicting results, cytotoxic chemotherapy and bevacizumab for patients with RAS mutant SCLM remain a reasonable option as there is clear evidence that OS is improved.[23]

With respect to anti-EGFR therapy, extension of exon 2, 3 and 4 of *KRAS* and *NRAS* has aided in further refining the patient population who may benefit from these agents.[24] Retrospective analysis of chemotherapy plus cetuximab/panitumumab trials excluding patients with previously unexamined RAS mutations demonstrates that the addition of anti-EGFR therapy significantly increases response rates for these patients, independent of the chemotherapy companion arm.[24-26] For this reason, full RAS testing is recommended for all patients prior to initiation of anti-EGFR therapy. Increasingly, systemic therapy will become "personalised", maximising the therapeutic index and utilising cytotoxic and targeted biological agents.[27,28]

Key Points

- EORTC 40983 demonstrated that perioperative FOLFOX resulted in a three-year PFS benefit of 8.1% in patients with resectable disease.
- Patients may have "upfront" resectable metastases or borderline/irresectable disease. Response to preoperative chemotherapy correlates with conversion to resectability and also to OS.
- Although there is conflicting data, the use of bevacizumab is recommended in patients with RAS mutant as OS is shown to be improved.
- Extended RAS testing is necessary before considering anti-EGFR therapy.

OPERATIVE PLANNING

It is important to carefully consider both the effect of pre-existing liver damage, such as alcoholic or non-alcoholic steatohepatitis, and systemic chemotherapy on the functional and regenerative capacity of the remnant liver.[29] Most patients will have received at least doublet chemotherapy and likely, in addition, monoclonal agents such as bevacizumab. Irinotecan can induce steatohepatitis, fibrosis or even cirrhosis, and oxaliplatin may lead to

sinusoidal injury and intra-hepatic veno-occlusive disease.[29] Preoperative, percutaneous biopsy of the future remnant liver should be considered in cases of concern. We believe an interval of 4 weeks before operation to be safe in the absence of VEGF inhibitors and 6 weeks if the latter agents have been deployed.[23]

We routinely only perform hepatic resections for patients with SCLM with a curative intent and a simultaneous resection where possible. In simultaneous resections, it is our preference for the colorectal primary to be resected first, by open operation and laparoscopically for a rectal primary. It is important in simultaneous resections that the anaesthetic delivery, surgical techniques and postoperative care are carefully considered, and if there are concerns during the colorectal phase such as unexpected complexity, blood loss or physiological performance then dialogue between the surgical teams may lead to deferment of the liver phase.[15]

Laparoscopic liver resection is uncommonly feasible as most patients have extensive liver disease requiring major hepatectomies. Intraoperative ultrasound is routinely used to confirm the location, size and anatomic relationship of metastases. Where the surgical field cannot encompass all sites of disease, for example bilobar disease, preoperative, intraoperative or postoperative radiofrequency ablation can be considered but with awareness of the limitations of RFA determined by proximity to intra-hepatic vascular structures and tumour size resulting in higher local recurrence rates up to 50% for lesions > 3 cm.[30] The development of microwave ablation therapy should increase the range of lesions treatable by such in situ ablative techniques.[31]

To avoid ischaemia on the chemotherapy-exposed liver, we do not use inflow clamping (Pringle manoeuvre). The Aquamantys System (Medtronic; Minneapolis, MN) bipolar coagulator prior to division with a cavitation ultrasonic aspirator (Valley Boulder, CO) is preferred for parenchymal transaction.[32] To avoid imaging artefact on follow-up MRI, we do not use any metal clips on the resection surface.

Key Points

- Low threshold to exclude chemotherapy-induced hepatic damage before proceeding with surgery.
- Primary tumour should be resected first during a simultaneous resection to allow the hepatic resection to be postponed if there are concerns regarding duration of surgery or blood loss.
- Anaesthetic techniques including low central venous pressure and oesophageal Doppler should be used to minimise the risks of surgery.
- Avoid metal clips to prevent future imaging artefact during follow-up.

DISCUSSION

The standard surgical treatment for patients with SCLM has been a sequential resection. Recently, however, there has been a growing trend to favour simultaneous resections in many centres.[33] There remain concerns about the safety and the long-term outcomes of simultaneous resections. This has led to most surgical units undertaking "simultaneous" resections in only a highly selected group of patients and restricted to straightforward colonic and hepatic resections.[33] Moreover, sequential resections tend to be favoured in patients considered to be high risk, that is the elderly, or patients with chemotherapy-induced hepatic damage requiring a substantial liver resection.[34] In a recent meta-analysis, we demonstrated that most centres had elected to perform sequential resections in patients with more extensive metastatic disease.[35] Where the patient's performance status is the source of concern, simultaneous resections may be inappropriate. We have demonstrated that, where the appropriate expertise exists, neither the extent of the metastatic burden nor the stage or location of the primary tumour should necessarily preclude simultaneous resections.[34]

Whether simultaneous resections for patients with SCLM have an oncological benefit when compared with sequential resections remains unclear, and the heterogeneity of disease burdens when comparing the two surgical strategies make reported data difficult to interpret.[35] Supporters of sequential resections feel that an interval prior to the hepatic resection permits progressive metastatic disease to declare itself and excludes such patients from further surgery and have concerns that simultaneous resections may leave behind occult micro-metastases in the remnant liver.[29,36] Analysis of our series of patients with SCLM undergoing simultaneous resections demonstrated that when stratified for extent of metastatic disease, those patients undergoing synchronous resections attained similar three-year overall and disease-free survivals to those treated by sequential resection.[34] In addition, it is thought that a better oncological result can be achieved with simultaneous resections by avoidance of the postoperative suppression of cell-mediated and humoral immunity and induction of pro-inflammatory and coagulopathic cascades as a consequence of firstly operation to resect the primary,[37-39] and then again at liver resection and moreover by avoiding the inevitably longer delay in the commencement of adjuvant chemotherapy associated with sequential resections.[40] A clear benefit of simultaneous resection is a reduction in the length of hospital stay by obviating the need for two admissions.[34,35]

The majority of studies comparing sequential versus simultaneous resections have a higher proportion of colonic primaries in the simultaneous resection group.[33,41] Rectal cancer resections and major hepatectomies dominate in our cohort of simultaneous resection for SCLM, and we have shown good postoperative and oncological outcomes.[34] Patient safety is key

to selection regarding whether patients should undergo a sequential or a simultaneous resection. It is clear that a sequential approach will remain an important tool in the surgeon's armamentarium, particularly in patients where there are concerns regarding age or fitness or when an emergency primary tumour resection is required. Simultaneous resections are extensive and complex operations that should only be undertaken in centres where these procedures are routine. Moreover, it is essential that there is a close cooperation with all members of the multidisciplinary team, in particular a close association between the colorectal and liver surgical teams.[15]

Key Points

- Simultaneous resections are an emerging strategy for patients with SCLM.
- Sequential resections have a role when there are concerns regarding patient fitness, age or in an emergency presentation.
- Simultaneous resections prevent a delay in systemic chemotherapy and avoid the effect of postoperative immunosuppression associated with a sequential approach.
- Where the appropriate expertise exists, simultaneous resections are safe even for patients with rectal cancer or need for major liver resections.
- Simultaneous resections should only be undertaken in centres where they are routinely performed.

IRRESECTABLE SYNCHRONOUS COLORECTAL LIVER METASTASES

The majority of patients presenting with colorectal liver metastases will be initially found to have irresectable disease.[29] It is currently advised that all patients should receive neoadjuvant systemic chemotherapy.[29] Moreover, this strategy, if downsizing is sufficient, can render the metastatic disease resectable in between 12% and 40% of patients with initially irresectable disease,[42] and the use of monoclonal agents has been shown to increase this percentage.[21-27,43] With this approach, 5-year OS rates of 33% have been reported, almost replicating the OS rates of patients with initially resectable colorectal liver metastases.[42,43]

There is no consensus regarding the optimal management of the primary tumour in patients with irresectable liver disease. Management of the primary tumour should take into consideration the nature and severity of symptoms from the primary tumour and patient's wishes and comorbidities.[44,45] The treatment should aim to maintain or improve the patient's quality of life, control symptoms and prolong OS.[44,45] Patients with rectal cancer and who are capable of tolerating a major surgical intervention should be considered for chemoradiation when there is a high risk of obstruction or

likelihood of developing debilitating pelvic symptoms. Otherwise, the following options should be considered: defunctioning colostomy, primary tumour resection, stenting, chemotherapy/chemoradiation or laser recanalisation to achieve effective palliation and equivalent survival.[46]

ADJUNCTIVE TREATMENTS

There is evidence to suggest that hepatic arterial infusion with chemotherapy combined with systemic chemotherapy, or intra-arterial infusion of yttrium-90 microspheres combined with systemic chemotherapy, show good response rates in patients with irresectable liver disease. However, despite improvements in time to progression, it remains unclear whether there is a translation into improved OS.[14,47]

The development of stereotactic body radiotherapy (SBRT) has been shown to have a low toxicity and can prevent progression in patients with limited hepatic disease and is now thought that SBRT will be a useful adjunct in the presence of limited irresectable disease.[14,47,48]

Key Points

- Majority of patients with SCLM will have irresectable disease on presentation.
- 12–40% of patients with intially irresectable disease can be converted to resectable disease with systemic chemotherapy.
- All patients with irresectable disease who can tolerate systemic chemotherapy should be so treated.
- Management of the colorectal primary should be according to whether it is symptomatic or asymptomatic. There are no clear guidelines on management, and it should be dictated by the patient's prognosis and wishes.
- Adjunctive therapies such as RFA and microwave ablation have a role to play particularly in irresectable disease. The use of RFA can increase the proportion of curative resections. SBRT is emerging as a useful adjunct in patients with irresectable limited hepatic disease.

EXTRA-HEPATIC METASTASES

Patients presenting with colorectal liver metastases and synchronous extra-hepatic disease pose a dilemma to both surgeons and oncologists. Until recently, the presence of extra-hepatic disease was considered an absolute contraindication to surgery. However, good five-year survival data of 28–40% are reported in patients, where the extra-hepatic disease is controlled by systemic or surgical treatment.[49]

Key Point

- The presence of extra-hepatic metastases is no longer an absolute contraindication to potentially curative liver resection in a highly selected group of patients.

FOLLOW-UP

Despite the many oncological and surgical advances in the management of patients with SCLM, the majority of patients will develop hepatic recurrence within two years following surgery with a curative intent. Close surveillance of patient's postcurative resection is essential as a significant proportion of patients who develop a hepatic recurrence will be amenable for further surgery.[29,50]

Key Point

- Close follow-up following curative hepatic resections is essential as the majority of patients will develop a recurrence, which will be amenable to further surgery.

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