Colorectal liver metastases

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Background: Despite major advances in therapies for liver metastases, colorectal cancer remains one of the commonest causes of cancer-related deaths in the UK.

Sources of data: The international literature on the management of colorectal liver metastases (CLM) was reviewed.

Areas of agreement: Due to a combination of highly active systemic agents and low perioperative mortality achieved by high-volume centres, a growing number of patients are being offered liver resection with curative intent. Patients with bilobar and/or extrahepatic disease who would previously have received palliative treatment only, are undergoing major surgery with good results. This review focuses on preoperative evaluation, surgical planning and the role of adjuvant therapies in the management of patients with CLM.

Areas of controversy: Can ablative therapies match the outcomes of surgical resection? How can even more patients be rendered resectable?

Growing points: The use of other therapies, such as radiofrequency ablation and selective internal radiation therapy.

Areas timely for developing research: New chemotherapy regimens for neo-adjuvant therapy and the development of new modalities of liver tumour ablation.

Keywords: colorectal liver metastases/surgery

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Introduction

Colorectal cancer is a major cause of mortality in the Western population and accounts for 10% of all cancer deaths in the UK. Colorectal liver metastases (CLM) are detected at the time of diagnosis of the bowel primary in 20–25% of cases. A further 40–45% of patients will subsequently develop metastases to the liver. Without treatment, the prognosis of these patients is poor, with a median survival of 1 year and few survivors beyond 3 years.\(^1\)\(^2\) Blood-borne metastases pass into the liver via the portal circulation, and it was apparent that a
significant proportion of patients were dying with liver-only disease. On that basis, surgical resection of liver metastases in patients without extrahepatic disease was attempted, and proved curative in some cases.\(^2\)

Since the initial reports of liver resection in patients with metastases, much progress has been made over the past 30 years, and according to a recent study, the number of liver resections performed in the UK more than doubled between 1998 and 2004.\(^3\) Indeed, there has been a paradigm shift in this field, from a nihilistic view that these patients are only eligible for palliative chemotherapy, to a very aggressive approach that offers patients substantial hope for long-term survival.\(^4\) This shift has occurred as a consequence of the improved safety and efficacy of surgery, novel strategies to treat bilobar disease and improved effectiveness of chemotherapy. Nonetheless, there can be no room for complacency, since liver resection is currently applicable to only a small proportion of patients with liver metastases, and even in patients who undergo successful surgery, disease recurrence remains a significant cause of death.

**Preoperative evaluation**

*Imaging*

All patients with colorectal cancer should be assessed for the presence of synchronous metastases by computed tomography (CT) scan, including thorax, abdomen and pelvis.\(^5\) However, for lesions that develop later (metachronous), it is not known whether intensive postoperative follow-up with imaging is associated with an improved resectability rate of metastases and/or better long-term survival compared with measurement of tumour markers alone. The Follow-up After Colorectal Surgery study has been designed to answer this particular question and the results of this trial are awaited.\(^6\) Although CT has become widely accepted as the gold standard for staging both hepatic and extrahepatic metastatic disease, other modalities such as magnetic resonance imaging (MRI) and positron emission tomography (PET) are often employed to corroborate CT findings. MRI is more sensitive than CT (83 vs. 61%),\(^7\) particularly for small lesions in fatty livers,\(^8\) and the addition of contrast agents (e.g. Tesla)\(^9\) and diffusion weighting\(^10\) may also enhance the sensitivity of MRI in comparison to CT. Lesions <1 cm are difficult to characterize with any imaging technique, and this limits the potential benefits of either MRI or PET in the decision-making process. Subcentimetre lesions should be re-imaged after an interval of 3–4 months and should be considered to be malignant if
there is either an increase in size, or if they shrink after chemotherapy. FDG-PET scan may identify occult extrahepatic disease and/or additional liver lesions in up to one-quarter of patients being considered for resection on the basis of CT, and the information derived from the PET scan may influence the surgical strategy or prevent futile surgery in a proportion of patients. In many liver surgery centres, PET is now part of the standard imaging protocol for assessment of CLM. However, in a study of 53 patients who underwent liver resection after both preoperative CT and PET, information from the PET scan would have changed the management in only 9% of patients. In addition, 6% of patients had lesions detected by PET that were found to be benign on postoperative histology (false positives), and may have incorrectly excluded these patients from surgical resection. It would therefore be reasonable to conclude that the precise role of PET in metastatic colorectal cancer has not been defined, but it may be useful for detecting extrahepatic disease in high-risk patients. PET-CT combines both modalities, and allows correlation between FDG avid lesions on PET and focal lesions detected by CT. However, in some cases interpretation of CT images on PET-CT may be compromised by a lack of contrast and/or suboptimal image quality.

**Patient fitness**

In addition to staging the disease, it is also necessary to assess the patient’s suitability for liver resection, in terms of both cardiorespiratory fitness and resectability. Significant cardiac or respiratory comorbidities are a contraindication to liver resection. However, in carefully selected low-risk patients, postoperative mortality after liver resection is as low as 1.5% in recent series from high-volume centres. Advanced age is not a contraindication to liver resection per se provided that the patient is fit and well and has a good exercise tolerance. Clinical evaluation by an experienced anaesthetist is an essential component of preoperative work-up, particularly in elderly patients, and when used in conjunction with objective tools (e.g. cardiopulmonary exercise testing), it is possible to stratify patients with respect to perioperative risk.

**Defining resectability**

There has been a shift in the concept of ‘resectability’ over the past two decades. Based on data from early series, patients were previously considered to have unresectable disease if any of the following criteria...
were met: (i) more than four metastatic deposits; (ii) resection margin <1 cm; (iii) bilobar disease; (iv) extrahepatic disease.\textsuperscript{16,17} Although these factors continue to convey a worse prognosis, they are no longer regarded as an absolute contraindication to liver resection, since a proportion of these patients can undergo successful tumour clearance and have long-term survival.\textsuperscript{4} Such an aggressive approach has been made possible by innovative strategies to enable complete tumour excision [e.g. portal vein embolization (PVE) and two-stage resection], and the availability of more effective chemotherapeutic agents (e.g. oxaliplatin, irinotecan). In the present era, resectable disease has been defined as an ability to achieve a negative margin, with preservation of at least two contiguous liver segments with an adequate vascular inflow and outflow, and an adequate liver volume.\textsuperscript{18} A margin of 1 cm is no longer considered necessary, and recent data suggest that 1 mm is sufficient, and that the presence of a negative margin is more important than the actual width of the margin.\textsuperscript{19,20} Good quality, up-to-date cross-sectional imaging is necessary to determine the location of all tumours, in particular to define their relationship to the hepatic veins and portal structures. If a major liver resection (hemihepatectomy or extended hemihepatectomy) is being considered, volumetric assessment of the future liver remnant may also be necessary.\textsuperscript{21} In a patient with normal background liver, up to 80\% of the liver may be safely resected.\textsuperscript{18} In patients with underlying liver disease, such as cirrhosis or chemotherapy-associated steatohepatitis, the future liver remnant must be significantly greater (>40 and >30\%, respectively).

\textit{Extrahepatic disease}

Although the presence of extrahepatic disease is no longer an absolute contraindication to liver resection, 5-year survival rates after resection are worse (26 vs. 58\%), and recurrence rates are significantly higher when compared with patients with liver-only disease.\textsuperscript{22} Multiple sites of extrahepatic disease and aortocaval disease appear to carry the worst prognosis (5-year survival of 14 and 7\%, respectively).\textsuperscript{22} Tumour involvement of portal lymph nodes was also associated with a poor outcome in historical series, and would have previously excluded patients from resection.\textsuperscript{23} More recent data suggest that coeliac or retroperitoneal nodal disease has more impact on survival than hilar lymph node disease,\textsuperscript{24,25} and that a subgroup of patients with hilar disease may be suitable candidates for liver surgery, provided that they are chemo-responsive. Histological examination of portal lymph nodes indicates that up to 15\% of patients who undergo liver resection for
colorectal metastases have microscopic lymph node metastases, although the evidence for routine lymphadenectomy in these patients is lacking.

The lung is the second commonest site of metastases in patients with colorectal cancer, and although lung metastases indicate the presence of systemic disease, sequential liver and lung resection has led to long-term survival in highly selected patients. Resection should be restricted to patients with solitary lung lesions that are stable after chemotherapy, with no other sites of disease. There have also been anecdotal reports of a survival benefit after resection of other sites of extrahepatic disease, including adrenal gland or peritoneum. However, the role of surgery in this group of patients is likely to be very limited, and the management of individual cases should be decided within a multidisciplinary team, with a particular focus on systemic chemotherapy in the first instance.

Surgical planning

There are several factors that should be considered when deciding on the most appropriate surgical strategy for an individual patient with resectable disease (Table 1). The traditional approach to synchronous, resectable liver metastases has been to resect the bowel primary first, followed by liver resection after an interval of 4–6 weeks. Although this approach allows assessment of tumour biology, borderline resectable liver lesions may become unresectable in the intervening period. For such borderline resectable liver lesions, one may consider performing the liver resection before the bowel resection, and the addition of neoadjuvant chemotherapy in such cases may also be beneficial (see below). The cumulative length of hospitalization and morbidity of two separate procedures may be greater than that of a single combined liver and bowel resection, and simultaneous resection has been

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<td>Bowel resection → liver resection</td>
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*Synchronous liver metastases.
advocated in selected patients. The risk of septic complications or liver failure after combined bowel/liver resection is related to the complexity of the bowel procedure (e.g. low anterior resection), the extent of liver resection, and the presence/extent of chemotherapy-induced liver damage (see below). Thus, minor liver resections (e.g. non-anatomical resection of small superficial lesions) may be safely performed at the same time as a colectomy, whereas a major hepatectomy should probably be performed on a separate occasion to a low anterior resection. Recent data suggest that for patients who require major liver resection, the optimal management may be neoadjuvant chemotherapy, followed by liver resection, and finally colorectal resection. In patients with bilobar liver disease, in whom a two-stage liver resection is being considered, it may be possible to perform the first-stage liver resection at the time of colectomy, followed by the second stage at a later date. It has been argued that a ‘liver-first’ approach may also be appropriate for patients with locally advanced rectal cancer and synchronous liver metastases. In such cases, chemotherapy prior to rectal surgery may increase the probability of an R0 resection of both primary and metastatic disease. Furthermore, by adopting a ‘liver-first’ approach for patients with borderline resectable disease, it may also be possible to identify unresectable liver metastases in some cases, and spare them from high-risk, futile rectal surgery. An approach to the management of CLM is suggested in the algorithm in Fig. 1.

As discussed previously, the objective of liver resection is to completely remove all viable disease with a negative margin, preserving sufficient liver volume to sustain liver function. In patients undergoing major liver resection, the volume of future liver remnant should be accurately measured by CT volumetry. If the predicted future liver remnant volume is suboptimal, PVE should be performed 4–6 weeks before surgery. After percutaneous cannulation of a major portal vein tributary, the vein supplying the lobe to be resected is occluded by injecting gelfoam particles or coils. This procedure induces hypertrophy of the contralateral lobe, and the future liver remnant volume can be re-assessed after 4 weeks, before proceeding to resection. In patients being considered for extended right hepatectomy, the segment IV branch should also be embolized. Preoperative PVE increases the volume of future liver remnant by 20–46%, and permits safe resection in the majority of patients with initially unresectable disease. There has been a concern that preoperative chemotherapy may reduce the efficacy of PVE in inducing liver regeneration, but recent data suggest that this may not be the case. Nonetheless, there is some evidence that regenerative capacity in patients with background hepatic steatosis is limited after PVE.
Large or deeply located liver metastases are typically treated by anatomical liver resection (hemihepatectomy). However, superficial liver lesions may be treatable by single or multiple non-anatomical resections (so-called parenchymal preserving liver resection). According to uncontrolled retrospective data, anatomical resections may be associated with greater blood loss than non-anatomical resections, but there does not appear to be a significant difference in cancer-related outcomes between the two groups.

Liver resection is traditionally performed using an open surgical technique via a long upper abdominal incision (e.g. reverse L, subcostal or Mercedes). In line with an increasing variety of other abdominal procedures, liver resection is now being undertaken laparoscopically in many centres. The technical challenges associated with laparoscopic liver surgery are gradually being overcome by advances in surgical technique, increasing experience and innovations in laparoscopic equipment. However, the laparoscopic approach is not yet universally
available in hepatobiliary units and many practicing surgeons are currently ascending the learning curve. At present, lesions in the left lateral segment or inferior aspects of the right lobe (IVb, V, VI) are readily amenable to laparoscopic resection, whilst laparoscopic major hepatectomy has only been performed by a few experienced surgeons. In carefully selected patients, laparoscopic resection can significantly shorten length of hospital stay, and based on increasing evidence predominantly from case-controlled studies, long-term cancer-related outcomes appear to be comparable between open and laparoscopic groups.

Bilobar liver metastases were previously considered to be a contraindication to liver resection. However, in patients with stable disease and favourable tumour biology, long-term survival may be possible in carefully selected patients. The principle of obtaining an R0 resection continues to be relevant in this subgroup, although it may not necessarily be achievable with a single procedure. The distribution of tumours and volume of the future liver remnant are key factors to be considered preoperatively. Bilobar disease may be treated either by a single procedure (e.g. multiple non-anatomical resections or major hepatectomy plus non-anatomical resection) or a two-stage procedure (e.g. non-anatomical resection of left lobe lesions, followed by right PVE, then right/extended right hepatectomy). Combining colonic resection with the first-stage liver resection, followed by a second-stage liver resection appears to be feasible. In a recent study, evaluating this approach in 33 patients, perioperative mortality was 3% and 5-year overall survival was 48%. However, the second-stage liver resection may not be possible in 20–25% of patients due to disease progression, death or poor performance after the first stage. Preoperative chemotherapy may be useful to identify patients with stable or responsive disease, or to downstage borderline tumours prior to resection. However, some patients may develop severe steatosis or steatohepatitis after chemotherapy, which may be disadvantageous, by preventing a subsequent R0 resection due to an inadequate functional liver reserve (see below). In order to prevent this complication, it may be more appropriate for some patients to receive adjuvant chemotherapy after two-stage liver resection.

Chemotherapy

The observed improvement in long-term survival after resection of CLM has been due in large part to the availability of highly active chemotherapeutic agents. Irinotecan is a topoisomerase I inhibitor and may be combined with 5-fluorouracil (5-FU) and leucovorin (LV) as...
the FOLFIRI regimen. Oxaliplatin is a platinum-based agent and is combined with 5-FU and LV as the FOLFOX regimen. These new regimens have achieved response rates of 33–62%, a significant improvement on the 20–30% observed with older regimens consisting of only 5-FU/LV. More recently, monoclonal antibodies that competitively inhibit growth factors or their receptors have been developed that further enhance the efficacy of existing chemotherapy regimens in patients with unresectable disease. Cetuximab is a monoclonal antibody against the epithelial growth factor receptor inhibitor. In a randomized trial comparing FOLFIRI with or without cetuximab in 1200 patients with metastatic colorectal cancer, the risk of progression was significantly reduced in the cetuximab arm (hazard ratio for progression-free survival of 0.85, 95% CI: 0.72–0.99, \( P = 0.048 \)).

It is important to note that 40–45% of CLM express mutations in the KRAS gene, and this subset does not respond to cetuximab. In a recent randomized study of 337 patients, in whom KRAS mutation status was available in 69%, the overall response rates in KRAS wild-type individuals were 61% for cetuximab plus FOLFOX and 37% for FOLFOX alone.

Bevacizumab is a humanized antibody against the vascular endothelial growth factor. The combination of bevacizumab and FOLFIRI significantly improved both response rate and median survival in a randomized study of 813 patients. The response rate in the bevacizumab/FOLFIRI group was 45% compared with 35% in the FOLFIRI group (\( P = 0.004 \)), and median survival was 20.3 and 15.6 months, respectively. Growth factor receptor inhibitors exert an anti-angiogenic rather than a cytotoxic effect, but importantly do not cause tumour shrinkage on CT. Rather, a therapeutic response is indicated by a change in tumour morphology, from a heterogeneous mass with an ill-defined margin to a homogeneous hypo-attenuating lesion with sharp borders. Despite some concern that biological agents may impede wound healing, data from a case-controlled study of 214 patients suggested that preoperative bevacizumab in combination with conventional agents does not significantly increase the morbidity of liver resection.

Chemotherapy is of proven benefit in patients with unresectable liver metastases, and up to 18% of patients in this group subsequently become resectable. In a series of more than 1000 patients with initially unresectable disease treated with an oxaliplatin-based regimen, 12.5% became resectable, and 10-year survival was 23%. In another study of initially unresectable patients, 101/620 patients (16%) proceeded to liver resection after two FOLFOX regimens. Of note, the majority (70%) of resections in this study were R0. The chemotherapy dosage and regimen used for patients with unresectable disease
differs according to whether it is given as downstaging treatment or with palliative intent. Downstaging chemotherapy is more toxic than palliative regimens, and it is therefore essential that the multidisciplinary team is explicit about the objective of treatment for each patient from the outset.

The role of chemotherapy in patients with resectable liver metastases is less clear. In the EPOC trial, perioperative FOLFOX4 (six cycles oxaliplatin/5-FU/LV preoperatively + six cycles postoperatively) was associated with an improvement in 3-year progression-free survival from 33 to 42% ($P = 0.02$). Data from the New EPOC and EORTC trials, which compare the efficacy of FOLFOX combined with either cetuximab or bevacizumab respectively, will be available soon. Neoadjuvant chemotherapy has several potential benefits, including assessment of response (prognostic value), treatment of systemic microscopic disease and reduction of tumour volume. However, there are two main drawbacks to preoperative chemotherapy. First, irinotecan and oxaliplatin have both been associated with a significant incidence of liver damage, which in turn increases the risk of perioperative morbidity and mortality, particularly after major resections. Six cycles of chemotherapy is probably optimal, since the risk of liver damage after 12 cycles appears to be significant. Second, neoadjuvant chemotherapy may result in a complete radiological response in a small proportion of patients, and this may potentially lead to difficulty in locating the lesions intraoperatively. In those patients with a complete radiological response, there is some evidence that viable tumour cells persist, and that liver resection is probably still necessary in these cases. The type of resection should be determined by pre-treatment imaging in these patients, but in order to ensure a tumour-free margin, a larger resection may be necessary.

Adjuvant chemotherapy after liver resection would seem to be a logical alternative to neoadjuvant treatment, and would avoid the risks of operating on patients with steatohepatitis. However, for patients who develop postoperative complications and have a prolonged recovery, they may miss the therapeutic window for clinical benefit. A randomized multicentre trial that evaluated adjuvant 5-FU/LV in 173 patients demonstrated an improvement in 5-year disease-free survival (33.5 vs. 26.7%, $P = 0.028$) in the treatment arm. However, there is currently no available data evaluating the role of oxaliplatin-based regimens or biological agents in the adjuvant setting.
Radiofrequency thermal ablation

Several techniques are available which allow local ablation of liver tumours, such as CLM. However, the precise indications for each technique have not been clearly defined, and in the absence of prospective randomized studies, there is currently insufficient data to support their routine use ahead of liver resection in surgically fit patients. In unfit patients, the choice of technique employed has been based primarily on local availability and expertise. Worldwide experience with radiofrequency ablation (RFA) of liver tumours far exceeds that of the other commonly used techniques, cryotherapy and microwave ablation. Cryotherapy was previously advocated as a useful tool for treating unresectable disease, but has been superseded by RFA in most centres. Cryotherapy was previously advocated as a useful tool for treating unresectable disease, but has been superseded by RFA in most centres. Microwave ablation has been introduced more recently and initial results are promising. Although long-term survival data are not yet available, microwave ablation may be superior to RFA for the treatment of larger tumours (>3 cm), and does not appear to be affected by the ‘heat-sink’ effect (see below) in experimental models.

RFA works by generating an alternating electric current within tumour tissue, which produces high temperatures (over 50°C) and results in coagulative necrosis. Single deployment of the RF instrument can cause complete ablation of tumours <3 cm in diameter, although larger lesions may be treatable by overlapping burns. RFA may be performed either percutaneously or intraoperatively (e.g. combined resection and RFA of bilobar disease), using either ultrasound or CT guidance under sedation or general anaesthesia. Minor complications such as fever, pain, leukocytosis and minor elevation of liver enzymes are common after the procedure, whilst major complications, such as liver abscess and bile leaks are rare. Needle track tumour seeding has also been described, although the risk appears to be very low (<2%). Complete tumour ablation is dependent on several factors, such as tumour location, operator experience and accurate positioning of the electrode tip. It is difficult to completely ablate tumours that are adjacent to large veins, due to the ‘heat-sink’ phenomenon, since it is not possible to achieve the high temperatures necessary for effective destruction in the ablation zone due to the flow of blood past the lesion. Local tumour recurrence is more likely for ablated lesions that are adjacent to veins >3 mm in diameter (27 vs. 6%).

It is difficult to interpret the available data regarding the therapeutic efficacy of RFA in the treatment of CLM, since many studies have included mixed tumour types, and have combined data from different ablation techniques. For example, a retrospective review compared the outcome of RFA and resection in over 350 consecutive patients, and
found that overall (84 vs. 52%), liver-only (44 vs. 11%, \( P < 0.001 \)) and local recurrence rates (9 vs. 2%, \( P = 0.02 \)) were higher after RFA and that 4-year overall survival was significantly better after resection (65 vs. 22%, \( P < 0.0001 \)). However, the retrospective nature of this and other studies introduces significant selection bias, as patients in the RFA group had been considered surgically unresectable, and therefore more likely to have more advanced disease. Moreover, tumours that were deemed unresectable due to proximity to vascular structures were treated by RFA, and these lesions were probably incompletely ablated due to the heat-sink effect.

Three-year survival rates of 37–50% have been reported after RFA of unresectable colorectal metastases. RFA may also be suitable for solitary, small liver metastases, and data from small retrospective case-controlled studies indicates that median survival may be comparable to liver resection. However, long-term survival data for this subgroup is not available, and there are no published randomized trials comparing ablation with surgical resection.

**Selective internal radiation therapy**

Liver parenchyma is prone to radiation-induced injury, and this has limited the application of external beam radiotherapy for the treatment of primary and secondary liver tumours. Selective internal radiation therapy (SIRT) circumvents this problem by infusing radiolabelled microspheres directly into a tumour via the hepatic artery. Liver tumours receive their blood supply predominantly from the hepatic artery, in contrast to normal liver, which derives its blood supply mainly from the portal vein. Thus, radioembolization of the hepatic artery delivers effective radiation doses without inducing significant injury to normal liver tissue. SIRT spheres are composed of Yttrium-90 (beta-emitting radioisotope) incorporated into resin or glass microspheres (SIRTex Medical, Syndey, Australia), and received FDA approval for the treatment of unresectable CLM in 2002. Prior to infusion, it is necessary to exclude a significant shunt (>20%) between the liver and lung or gastrointestinal tract, in order to avoid the risk of radiation pneumonitis and/or gastritis, respectively. More common side effects after SIRT include abdominal pain, fever and transient elevation in liver enzymes. The addition of SIRT to chemotherapy increased the median progression-free survival from 4.6 to 11.5 months \( (P = 0.004) \) in a randomized study of 21 patients. However, this study was performed in the pre-oxaliplatin era, and it is therefore not possible to extrapolate their results to the modern regimens. At the present time, due to insufficient evidence of an improvement in survival
and/or quality of life, SIRT can only be recommended within the constraints of a clinical trial (e.g. FOXFIRE trial).

**Postoperative tumour recurrence**

The risk factors for recurrence after liver resection for colorectal metastases relate to the biological features of the colorectal primary, the burden of metastatic disease (liver and extrahepatic) and surgical factors, such as resection margin positivity and postoperative morbidity (see Table 2). The majority of cases of recurrence occur within 1 year after liver resection, and these patients are also more likely to have unresectable liver disease and/or extrahepatic disease compared with patients presenting later. Patients who are diagnosed with tumour recurrence should be investigated thoroughly to determine the site and extent of disease. A small proportion of patients with liver-only recurrence may be candidates for repeat liver resection, provided that the same principles of resection are applied as for the initial resection, such as an ability to achieve a negative resection margin, and preservation of an adequate liver remnant. Indeed, in carefully selected patients, repeat resection of recurrent disease has been associated with survival rates similar to initial liver resection.

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<th>Table 2 Risk factors for recurrence after initial and repeat liver resection.</th>
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<td>Colorectal primary</td>
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<td>Liver disease burden</td>
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<td>Postoperative morbidity</td>
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Conclusions

The outlook for patients with metastatic liver disease from colorectal cancer has improved significantly over the past two decades, due principally to major advances in surgical techniques and the availability of more effective systemic therapies. Although response rates for chemotherapy regimens have improved, the prognosis for a large number of patients with chemo-resistant unresectable disease remains dismal. Similarly, postoperative tumour recurrence is a common event and is a reflection of unfavourable tumour biology. Recent results with monoclonal antibody therapy should stimulate further research into the molecular biological properties of colorectal metastases, an understanding of which is likely to be a critical step towards developing more effective systemic treatments in the future.

References

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