ANZ J. Surg. 2007; **77**: 941–947 doi: 10.1111/j.1445-2197.2007.04287.x

CLINICAL REVIEW

OPTIMIZING THE APPROACH TO PATIENTS WITH POTENTIALLY RESECTABLE LIVER METASTASES FROM COLORECTAL CANCER

ELGENE LIM,* BENJAMIN N. J. THOMSON,‡ STEFAN HEINZE,§ MICHAEL CHAO,**
DISHAN GUNAWARDANA† AND PETER GIBBS¶

**The Walter & Eliza Hall Institute of Medical Research, ‡Department of Surgery, Royal Melbourne Hospital, §Department of Radiology, Royal Melbourne Hospital, **Department of Radiation Oncology, Western Health, †Department of Nuclear Medicine, Royal Melbourne Hospital, and ¶Department of Medical Oncology, Royal Melbourne Hospital, Ludwig Institute of Cancer Research Melbourne, Victoria, Australia*

Liver metastases are a common event in colorectal carcinoma. Significant advances have been made in managing these patients in the last decade, including improvements in staging and surgical techniques, an increasing armamentarium of chemotherapeutics and multiple local ablative techniques. While combination chemotherapy significantly improves median patient survival, surgical resection provides the only prospect of cure and is the focus of this review. Interpretation of published work in this field is challenging, particularly as there is no consensus to what is resectable disease. Of particular interest recently has been the use of neoadjuvant treatment for downstaging and downsizing disease in patients with initially unresectable liver metastases, in the hope of response leading to potentially curative surgery. This review summarizes the recent developments and consensus guidelines in the areas of staging, chemotherapy, local ablative techniques, radiation therapy and surgery, emphasizing the multidisciplinary approach to this disease and ongoing controversies in this field and examines the changing paradigms in the management of colorectal hepatic metastases.

Key words: colorectal cancer, liver metastasis, management, resection.

Abbreviations: 3-D-CRT, 3-D conformal radiotherapy; CEA, carcinoembryonic antigen; CT, computed tomography; HAI, hepatic arterial infusion; PET, positron emission tomography; RCT, randomized control trial; RFA, radiofrequency ablation; RT, radiotherapy; SIR, selective internal radiation; US, ultrasound.

INTRODUCTION

Colorectal cancer (CRC) is the second most commonly diagnosed cancer in Australia, with an annual incidence of more than 12 000 patients.[1] Hepatic metastases are very common and are an important cause of cancer-related death. The liver is the only site of disease in approximately one-third of patients dying from CRC. Metastases at this site are present in approximately 25% of patients at the time of primary diagnosis and overall, 50% of patients with CRC develop hepatic metastases within 5 years of diagnosis.[2]

Improved diagnostic methods have contributed to earlier detection and improved definition of metastases; however, surgical resection provides the only prospect of cure. Following surgery 5-year survival rates have increased from 31 to 40% over the last decade, with a significant proportion surviving 10 years and beyond.[3] Although only a small fraction of metastases are resectable at the time of presentation, an increasing number of patients can undergo surgery after systemic chemotherapy. While local ablative therapies, such as radiofrequency ablation (RFA), have increased the treatment options available to patients not fit for surgery, the role of these various therapies is yet to be defined.

This article reviews the recent developments and changing paradigms in the diagnoses and treatment of hepatic metastases, focusing on the timing of chemotherapy and surgery and the roles of local ablative therapies and radiation.

ASSESSMENT OF PATIENTS WITH HEPATIC METASTASIS

Computed tomography (CT) is the initial imaging method most commonly used in primary and repeat staging of patients with CRC. The reported sensitivity for detecting hepatic metastases with CT ranges from 36 to 94%; this is similar to 57–100% for ultrasound (US).[4,5] When the decision is made to carry out hepatic resection of lesions evaluated with CT alone, up to 40% of patients are found to have unresectable lesions at laparotomy; therefore more accurate staging is obviously desirable.[6]

Whole-body flouro-18-deoxyglucose (FDG) positron emission tomography (PET) assesses tumour metabolic activity, potentially complementing the anatomic information provided by CT. On a per-patient basis, PET appears to have superior sensitivity to CT or magnetic resonance imaging;[5] however, for lesions less than 1.5 cm in diameter, spiral CT appears to be more sensitive.[4,7]

E. Lim MB BS, FRACP; **B. N. J. Thomson** MB BS, FRACS; **S. Heinze** MB BS, FRANZCR; **M. Chao** MB BS, FRANZCR; **D. Gunawardana** MB BS, FRACP; **P. Gibbs** MB BS, FRACP, MD.

Correspondence: Dr Peter Gibbs, Department of Medical Oncology, Royal Melbourne Hospital, Parkville, Vic. 3050, Australia.
Email: peter.gibbs@mh.org.au

Accepted for publication 15 March 2007.

PET has particular value in detecting extrahepatic lesions.[8] It upstages 9–29% of patients initially staged with CT who are being considered for hepatic resection by identifying additional hepatic lesions or occult extrahepatic metastases that renders the patient inoperable.[4,9–11] Conversely 2–7% of patients that are incorrectly upstaged and incorrectly deemed inoperable.[4,9–11] False-negative findings may occur during treatment with chemotherapy.[9,12] Pathological confirmation of extrahepatic lesions should be considered if this is the only factor excluding patients from potentially curative surgery. Dual-method CT–PET has shown improvements in staging accuracy over PET alone.[13]

Staging laparoscopy is neither routinely recommended nor carried out, as the overall yield is low, preventing non-therapeutic laparotomy in only 1 in 10 patients.[14,15] It is technically challenging following primary colon surgery with a risk of enteric perforation.

PATIENT SELECTION FOR SURGERY

Patient prognostic factors are listed in Table 1.[16–19] A minority of patients with poor prognostic indicators survive 5 years or more after hepatic resection and therefore each patient must be individually assessed.[17,20]

Guidelines for patient selection and contraindications for surgery are constantly changing with the increasingly aggressive approach to managing CRC liver metastases. Although the number of metastases has been shown to be a predictor of recurrence, recent reports show equivalent survival with four or more compared with fewer metastases, provided complete resection with a tumour-free margin can be achieved.[17,21] In addition, bilobar hepatic metastases do not appear to influence outcome, provided they are resectable.[17,18] Many would now argue that patients should be considered for resection irrespective of the number and size of hepatic metastases, as long as they can be completely removed and there is sufficient residual hepatic reserve. In a recent consensus statement, absolute contraindications to resection of liver metastases included unresectable extrahepatic metastases, >70% hepatic involvement, hepatic failure and being medically unfit for major surgery. The authors argued that patient age, primary tumour stage, timing of detection of metastases, prior hepatectomy and pre-resection carcinoembryonic antigen (CEA) levels, whereas all factors associated with prognosis should not independently define the treatment strategy. The consensus results have been incorporated into a computer program-based decision matrix, OncoSurge, to assist evaluation of individual patient resectability and optimal treatment approaches.[22]

Table 1. Prognostic factors for in colorectal cancer with liver metastases

Poor prognosis factors	Good prognosis factors
Large degree of hepatic involvement	Small degree of hepatic involvement
Positive surgical margin	Complete resection
Short disease-free interval from resection of primary tumour to detection of hepatic metastases	Hepatic metastases appearing more than 2 years after initial diagnosis of primary tumour
High preoperative carcinoembryonic antigen	Early stage of primary tumour

PREOPERATIVE TREATMENT

Modern chemotherapy regimens incorporating Oxaliplatin and Irinotecan in addition to 5-fluorouracil (5-FU) have produced impressive improvements in response rates in metastatic CRC, with significant reductions in disease bulk being seen in approximately 50% of patients, and median survivals approaching 2 years.[23] Without surgery, metastatic CRC remains incurable. There is some suggestion that for patients with liver-only metastases the combination of 5-FU and Oxaliplatin may lead to superior survival outcomes compared to 5-FU and Irinotecan.[24] Biological agents such as those targeting epithelial and vascular endothelial growth factor pathways have added to the array of treatment armamentarium with significant survival benefit in the metastatic setting.[25,26] However, there are little data in the preoperative setting and inclusion of these agents is currently not standard treatment.

The impressive response rates of combination chemotherapy in metastatic CRC have led to much enthusiasm for use before hepatic resection. This approach has the benefit of downsizing the tumour, potentially rendering a previously unresectable tumour resectable. Significantly this approach provides an opportunity to assess the tumour biology, particularly the responsiveness of the tumour to chemotherapy, with a recent study reporting that the initial response to chemotherapy is strongly predictive of long-term outcomes.[18] Five-year survival in patients who progressed on chemotherapy was 8% compared with 37% in responders and 30% in patients with stable disease, whereas 5-year survival was 3% compared with 21 and 20%, respectively. Based on these data patients that are initially borderline candidates for hepatic resection and progress through initial chemotherapy may be potentially spared unnecessary major surgery, but progression on chemotherapy alone may not be sufficient reason to not operate on an otherwise good surgical candidate. Finally, in addition to the prognostic information provided by preoperative chemotherapy, it is anticipated that the therapeutic response may be helpful when considering the use and choice of further chemotherapy postoperatively. One complication of chemotherapy in the preoperative setting is the risk of increased perioperative morbidity secondary to chemotherapy-associated steatohepatitis.[27] The presence of steatohepatitis has been shown to be associated with a significantly increased 90-day mortality.[27]

Approximately 12.5–16% of patients with initially unresectable disease may be rendered resectable following a response to combination chemotherapy, with surgery in this patient subgroup resulting in 5-year survival rates of 30–40% and 10-year survival rates of 23%, not dissimilar to outcomes in patients with de novo resectable disease.[18,28,29] Although 80% of patients ultimately developed recurrent disease further potentially curative surgery could be carried out in approximately half of these patients. The postoperative mortality rate was less than 1% and the morbidity considered acceptable.

There is no consensus as to the optimal timing and use of chemotherapy in patients with initially resectable hepatic metastases. Reasonable approaches include initial resection of the hepatic metastasis followed by consideration of adjuvant chemotherapy and as well as the use of preoperative therapy for the reasons mentioned. A potential concern in this setting is the risk of disease progression with delayed surgery, rendering an initially resectable lesion unresectable.[18]

Other than systemic chemotherapy, other forms of preoperative treatment include hepatic arterial infusion (HAI) and use of selective

internal radiation (SIR) spheres (Sirtex Medical, Sydney, Australia). HAI delivers chemotherapy directly into the hepatic artery, resulting in very high drug concentrations within the liver and reduced systemic exposure. A meta-analysis of six randomized control trials (RCT) published between 1988 and 1993 confirmed the significantly higher response rate (41% compared with 14%) for HAI compared with i.v. 5-FU-based chemotherapy and high response rates have been found with the addition of newer agents such as Oxaliplatin and Irinotecan.[30] Despite this, HAI is rarely used outside specialist treatment centres in Australia because of the limited availability of technical expertise, high cost of infusion pumps and ongoing concerns regarding the significant rate of catheter-related complications, in particular sclerosing cholangitis.[30,31]

Selective internal radiation spheres are ^{90}Y-containing microspheres introduced through the hepatic artery, leading to relatively selective delivery to the tumour as the portal circulation predominantly supplies the normal liver parenchyma. Data from several small RCT combining the use of SIR spheres with i.v. 5-FU and HAI chemotherapy have shown superior response rates over chemotherapy alone and suggested improved survival, but SIR spheres are not currently in routine use.[32,33] Data from patients with hepatocellular carcinoma treated with SIR spheres suggest that hepatic surgery after SIR treatment is not associated with excessive morbidity or mortality.[34] A large international RCT comparing SIR treatment, i.v. 5-FU and Oxaliplatin with the same chemotherapy alone has recently commenced and will more clearly define the role of this method in metastatic CRC.

INTRAOPERATIVE ASSESSMENT

Intraoperative evaluation of the liver and abdominal cavity is critical before proceeding with surgical resection, regardless of the findings of preoperative staging investigations. Intraoperative US has a reported sensitivity of up to 98% and may detect additional lesions in 10–50% of patients initially staged with CT and PET.[35,36] This is, however, not routinely carried out in Australia. Patients found to have peritoneal disease at laparotomy have traditionally not been candidates for hepatic resection as it was considered not to confer a survival advantage. However, this previous absolute contraindication to liver surgery is being challenged in highly selected groups of patients. Sugarbaker and co-workers reported a median survival of 20.4 months for patients who underwent complete cytoreductive surgery of the peritoneum as well as other metastatic sites in combination with aggressive systemic and i.p. chemotherapies.[37] Lasser and co-workers have reported similar findings in the treatment of synchronous peritoneal carcinomatosis and liver metastases with a 3-year overall and disease-free survival of 41.5 and 23.6%, respectively.[38] The presence of hilar lymph node metastases, however, is a poor prognostic factor associated with a 5-year survival of only 5–12%.[39,40] Although these reports challenge our current concepts of resectable hepatic disease few Australian centres will have the appropriate surgical and other expertise required to reproduce the results by Sugarbaker and Lasser and co-workers.[37,38]

LIVER RESECTION

Overall only 25% of patients with colorectal liver metastases will be suitable candidates for surgical resection; however, the definition of resectable disease is constantly changing because of the influence of preoperative chemotherapy, improved surgical techniques and a more aggressive surgical approach. Large series are consistently reporting 5-year survival rates of 30–40% in patients following resection of hepatic metastases and that surgery can be carried out with low morbidity and mortality.[18,19] Up to 75% of the functional hepatic volume in a patient with a healthy liver can be resected without a significant risk of hepatic failure.[41] The risk increases with existing hepatic disease such as hepatic fibrosis, cirrhosis or steatohepatitis. Risk factors for steatosis include alcohol, obesity and prior treatment with chemotherapy. Perioperative blood loss also increases the chance of hepatic failure and perioperative mortality.[42] Mortality from hepatic resection in most important hepatobiliary units in Australia is less than 2%. Hepatic resection may be carried out simultaneously with removal of the primary CRC, although it is more often carried out as a two-stage procedure.[43,44] There are several reports of repeat hepatic resection for recurrent colorectal hepatic metastases with results similar to those after initial resection and consideration of repeat resection is appropriate on a case-by-case basis.[18,20,45,46]

Improvements in surgical outcomes have been largely because of lower intraoperative blood loss, prevention of ischaemia to the remaining liver and preservation of hepatic volume. Vascular isolation techniques that minimize blood loss by controlling hepatic inflow include portal clamping (Pringle manoeuvre), hemihepatic clamping, portal dissection or bypass techniques. Bleeding from hepatic veins can be controlled with intraparenchymal ligation or with extrahepatic dissection and ligation before hepatic transaction. In addition, a central venous pressure of less than 4–5 cm H_2O during hepatic resection decreases blood loss and transfusion requirements following surgery.[47]

The broad aims of liver resection are to resect the tumour with a sufficient tumour-free margin while preserving as much normal liver parenchyma as possible. Surgical resection has traditionally been along the hepatic segmental anatomy. An alternative approach is a wedge or non-anatomical resection, removing a smaller volume of liver and with a potential benefit in reduced postoperative morbidity and mortality, but a higher risk of involved resection margins. The survival data regarding the optimal technique are conflicting.[48,49] In a recent series where 73% of wedge resections were carried out for single rather than multiple hepatic lesions, the incidence of positive resection margins was equivalent for both wedge resection and segmental resection (8.3%). Five-year survival was equivalent between both groups and an involved margin was associated with inferior survival.[49] Traditionally a resection margin of 1 cm was advised; however, recent data suggest that any margin greater than 1 mm is sufficient.[50] There are a variety of techniques used in hepatic transection, including the clamp crushing method, Cavitron Ultrasonic Surgical Aspirator (Tyco Healthcare, Mansfield, MA, USA), Hydrojet (Hydro-Jet, Erbe, Tubingen, Germany) and bipolar sealing devices. A recent RCT of these techniques concluded that the clamp crushing technique remains the most efficient in terms of reducing resection time, blood loss and cost.[51] Portal clamping, however, may lead to ischaemic injury to the remaining liver. Overall the availability of instruments and personal preferences dictate the hepatic transection technique used.

There is a significant risk of postoperative hepatic failure with extensive hepatic resection and options include reducing the hepatic volume to be resected or augmenting the surgical hepatic remnant. Preoperative chemotherapy can potentially decrease the volume of liver to be resected. Uncertainty remains in the treatment of tumours with a complete radiological response. A recent study reported 80% of such cases would still have viable tumour identified histologically

at operation supporting the approach of most surgeons who routinely resect the area in which the tumour had been positioned.[52] Preoperative embolization of the right or left portal vein branch can lead to significant augmentation of the contralateral liver allowing safer resection with a larger hepatic remnant. Although more commonly used for resection of hilar cholangiocarcinoma or hepatocellular carcinoma, this technique has also been described in the management of colorectal liver metastases.[53,54] Increasing the liver volume for patients with a predicted hepatic remnant of less than 25% with portal vein embolization appears to reduce the risk of postoperative liver dysfunction.[53]

A combined approach may be necessary for bilobar disease. Treatment options for the tumour in the remnant liver include wedge resection and RFA. *In situ* hypothermic and *ex vivo* surgery, where the liver is removed with back-table resection of metastases before re-implantation, has been adapted from liver transplantation.[55] It is associated with high perioperative mortality and data on long-term outcomes are not available. Another option is two-stage hepatectomy, which involves an initial resection followed by a recovery period allowing for hepatic regeneration, followed by second resection. A 3-year survival rate of 35% has been reported in a highly selected group of patients treated with chemotherapy and two-stage hepatectomy.[44] Liver transplantation has been abandoned as a treatment option because of poor results.[56] The rapid recurrences described are considered to be probably because of adverse initial disease staging and the effects of immunosuppression.

Several recent series have addressed the role of surgical resection for lung metastases, alone or in combination with hepatic resection in selected patients.[57–59] Operative mortality was low, with 5-year and 10-year survival rates in the order of 30–41% and 16–37%, respectively, in two reported series.[57,59] Patients should be considered for this approach on a case-by-case basis. Favourable prognostic factors include single-lung metastasis, a longer disease-free interval and normal preoperative CEA levels.[57] When feasible, reoperation is a safe with satisfactory long-term results.[57] As with hepatic metastases, the use of multimodality treatment, including chemotherapy, is required.

POSTOPERATIVE CHEMOTHERAPY

As an extension of the survival advantage seen in patients with stage III colorectal cancer, postoperative chemotherapy following complete resection of metastatic disease may lead to improved long-term outcomes. Although routinely practised, there remains a lack of robust data to mandate this as routine practice. Four recent RCT have attempted to define the benefit of adjuvant 5-FU chemotherapy, delivered through a hepatic artery catheter and/or i.v., following resection of hepatic metastases.[60–63] A consistent trend towards improved survival outcomes was shown in each of these underpowered studies, but in only one study did this reach statistical significance.[60] Although encouraging, these studies are largely redundant in an era of combination chemotherapy and the final results of the European Organization for Research and Treatment of Cancer study investigating the role of adjuvant 5-FU and Oxaliplatin are eagerly awaited.

NON-SURGICAL THERAPIES

Local ablative therapies and radiotherapy (RT) offer patients who may not be suitable for surgery, an alternative approach to the management of hepatic metastasis. They can be also be used in combination with surgery intraoperatively or postoperatively in the setting of close or involved margins.[64]

The most popular technique is RFA, whereby a metallic probe is introduced into a hepatic lesion under imaging guidance, either percutaneously or intraoperatively. Local ionic excitation results in the lesion being 'heated' to a level where cell death occurs. It has the advantage of low morbidity and multiple lesions may be targeted. There is no consensus as to the maximum size or number of metastasis potentially treatable with local ablative techniques. In a series of 117 patients with metachronous CRC and hepatic metastases, the size of the hepatic lesions treated with RFA ranged from 0.9 to 9.6 cm in diameter.[65] The 3-year survival was 46%; however, 39% of the patients developed local recurrence after treatment. In many instances retreatment was possible at recurrence. Recurrence and mortality rates were not significantly related to the number or size of metastases. There are no standardized eligibility criteria for RFA. In general, patients should only be considered if they are not surgical candidates (either because of anticipated technical resection difficulties or comorbidities), have five or fewer lesions, each less than 5 cm in diameter and are free of other distant metastases.[66] Lesion location may play a part in selection also; those close to, or abutting, the gall bladder, hepatic flexure of the colon, diaphragm and hepatic hilum require great care in treatment to avoid heat-related damage to adjacent structures and may result in patient exclusion.[66]

A single prospective RCT comparing RFA with surgery for solitary hepatic metastasis showed similar median and 3-year survival rates.[67] In another recent non-randomized single institution study, RFA was used when the resection would leave an inadequate liver remnant or if the comorbidity precluded safe surgery.[68] The 5-year overall survival rate was higher in the hepatic resection group (71 vs. 27%) and the local recurrence rate, higher in the RFA group (37 vs. 5%). Tumour size was found not to be a determinant of outcome. The Australian safety and efficacy register of new interventional procedures recently concluded that at present there is insufficient evidence to determine the safety or efficacy of RFA in the treatment of colorectal liver metastases.[69] Hepatic resection remains the preferred treatment option for solitary liver metastases, whereas RFA may be considered to improve the results of resections with involved margins.

The advent of 3-D conformal radiotherapy (3-D-CRT), which is associated with a reduced radiation dose to normal liver and a reduced risk of radiation-induced liver disease, has renewed interest in the use of external-beam RT as a potentially curative therapy for patients with medically or technically unresectable disease or as an alternative treatment in the palliative setting. 3-D-CRT allows for significantly higher radiation doses than those achievable by conventional means and for a quantitative understanding of the relationship between dose delivered, volume irradiated and the risk of complications.[70] Stereotactic RT may deliver an equivalent radiation dose to 3-D-CRT with conventional fractionation in a single-treatment or limited-treatment sessions.[71] Further studies will better define the emerging potential for RT in producing long-term disease control in patients with medically or technically unresectable hepatic lesions and limited or no extrahepatic disease.

FUTURE DIRECTIONS

A suggested assessment and treatment algorithm for CRC with hepatic metastases is illustrated in Figure 1. Surgery remains the

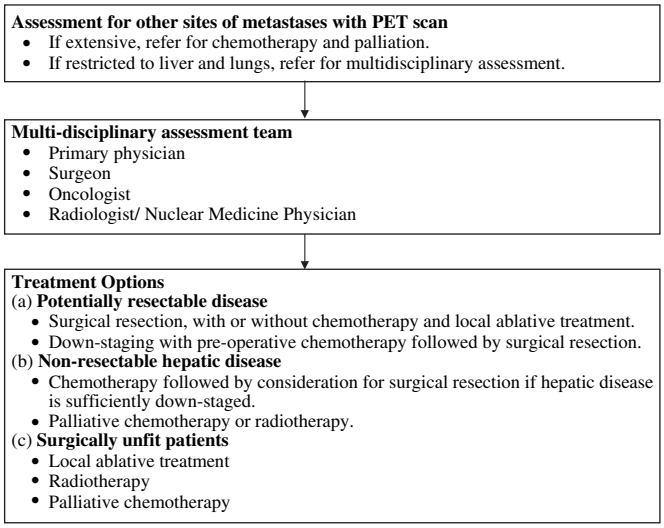

Fig. 1. Assessment and treatment algorithm following diagnosis of apparently isolated hepatic metastases on computed tomography imaging.

only treatment option with proven potential for long-term survival in patients with colorectal hepatic metastases. The indications for surgery continue to expand in parallel with significant advances in diagnostic imaging, surgery, chemotherapy, local ablative techniques and radiation therapy, resulting in constantly evolving treatment paradigms and improved patient outcomes. The advent of technology such as microarray analysis and gene profiling technology will probably lead to continued refinement of patient management. This review emphasizes the importance of a multidisciplinary approach for the optimal management of this disease.

REFERENCES

1. Australian Institute of Health and Welfare (AIHW) 2007. ACIM (Australian Cancer Incidence and Mortality) Books. AIHW: Canberra.
2. Millikan KW, Staren ED, Doolas A. Invasive therapy of metastatic colorectal cancer to the liver. *Surg. Clin. North Am*. 1997; **77**: 27–8.
3. Choti MA, Sitzmann JV, Tiburi MF *et al*. Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann. Surg*. 2002; **235**: 759–66.
4. Ruers TJ, Langenhoff BS, Neeleman N *et al*. Value of positron emission tomography with [F-18] fluorodeoxyglucose in patients with colorectal liver metastases: a prospective study. *J. Clin. Oncol*. 2002; **20**: 388–95.
5. Bipat S, van Leeuwen MS, Comans EF *et al*. Colorectal liver metastases: CT, MR imaging, and PET for diagnosis – meta-analysis. *Radiology* 2005; **237**: 123–31.
6. Jarnagin WR, Fong Y, Ky A *et al*. Liver resection for metastatic colorectal cancer: assessing the risk of occult irresectable disease. *J. Am. Coll. Surg*. 1999; **188**: 33–42.
7. Wiering B, Krabbe PF, Jager GJ, Oyen WJ, Ruers TJ. The impact of fluor-18-deoxyglucose-positron emission tomography in the management of colorectal liver metastases. *Cancer* 2005; **104**: 2658–70.
8. Fong Y, Saldinger PF, Akhurst T *et al*. Utility of 18F-FDG positron emission tomography scanning on selection of patients for resection of hepatic colorectal metastases. *Am. J. Surg*. 1999; **178**: 282–7.
9. Topal B, Flamen P, Aerts R *et al*. Clinical value of whole-body emission tomography in potentially curable colorectal liver metastases. *Eur. J. Surg. Oncol*. 2001; **7**: 175–9.
10. Truant S, Huglo D, Hebbar M, Ernst O, Steinling M, Pruvot FR. Prospective evaluation of the impact of (18F)fluro-2-deoxy-D-glucose positron emission tomography of resectable colorectal liver metastases. *Br. J. Surg*. 2005; **92**: 362–9.
11. Flamen P, Stroobants S, Van Cutsem E *et al*. Additional value of whole-body positron emission tomography with fluorine-18-2-fluoro-2-deoxy-D-glucose in recurrent colorectal cancer. *J. Clin. Oncol*. 1999; **17**: 894–901.
12. Akhurst T, Kates TJ, Mazumdar M *et al*. Recent chemotherapy reduces the sensitivity of [18F] fluorodeoxyglucose positron emission tomography in the detection of colorectal metastases. *J. Clin. Oncol*. 2005; **23**: 8713–16.
13. Cohade C, Osman M, Leal J *et al*. Direct comparison of 18F-FDG PET and PET/CT in patients with colorectal carcinoma. *J. Nucl. Med*. 2003; **44**: 1797–803.
14. Jarnagin WR, Conlon K, Bodniewicz J *et al*. A clinical scoring system predicts the yield of diagnostic laparoscopy in patients with potentially resectable hepatic colorectal metastases. *Cancer* 2001; **15**: 1121–8.
15. Grobmyer SR, Fong Y, D'Angelica M, Dematteo RP, Blumgart LH, Jarnagin WR. Diagnostic laparoscopy prior to planned hepatic resection for colorectal metastases. *Arch. Surg*. 2004; **139**: 1326–30.
16. Ekberg H, Tranberg KG, Andersson R *et al*. Determinants of survival in liver resection for colorectal secondaries. *Br. J. Surg*. 1986; **73**: 727–31.
17. Registry of hepatic metastases. Resection of the liver for colorectal carcinoma metastases. A multi-institutional study of indicators for resection. *Surgery* 1988; **103**: 278–88.
18. Adam R, Pascal G, Castaing D *et al*. Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases? *Ann. Surg*. 2004; **240**: 1052–61; discussion 1061–4.
19. Malafosse R, Penna C, Sa Cunha A, Nordlinger B. Surgical management of hepatic metastases from colorectal malignancies. *Ann. Oncol*. 2001; **12**: 887–94.
20. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann. Surg*. 1999; **230**: 309–18; discussion 318–21.
21. Fong Y, Blumgart LH, Cohen AM. Surgical treatment of colorectal metastases to the liver. *CA Cancer J. Clin*. 1995; **45**: 50–62.
22. Poston GJ, Adam R, Alberts S *et al*. OncoSurge: a strategy for improving resectability with curative intent in metastatic colorectal cancer. *J. Clin. Oncol*. 2005; **23**: 7125–34.
23. Goldberg RM. Advances in the treatment of metastatic colorectal cancer. *Oncologist* 2005; **10** (Suppl. 3): 40–48.
24. Giacchetti S, Perpoint B, Zidani R *et al*. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J. Clin. Oncol*. 2000; **18**: 136–47.
25. Hurwitz H, Fehrenbacher L, Novotony W *et al*. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N. Engl. J. Med*. 2004; **350**: 2335–42.
26. Tabernero JM, Van Cutsem E, Sastre J *et al*. An international phase II study of cetuximab in combination with oxaliplatin/5-fluorouracil (5-FU)/folinic acid (FA) (FOLFOX-4) in the first-line treatment of patients with metastatic colorectal cancer (CRC) expressing Epidermal Growth Factor Receptor (EGFR). Preliminary results. *Proc Am Soc Clin Oncol* 2004: **22**: 14S: 3512.
27. Vauthey JN, Pawlik TM, Ribero D *et al*. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J. Clin. Oncol*. 2006; **24**: 2065–72.

28. Adam R, Avisar E, Ariche A *et al*. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal cancer. *Ann. Surg. Oncol*. 2001; **8**: 347–53.
29. Leonard GD, Brenner B, Kemeny NE. Neoadjuvant chemotherapy before liver resection for patients with unresectable liver metastases from colorectal carcinoma. *J. Clin. Oncol*. 2005; **23**: 2038–48.
30. Kelly RJ, Kemeny NE, Leonard GD. Current strategies using hepatic arterial infusion chemotherapy for the treatment of colorectal cancer. *Clin. Colorectal Cancer* 2005; **5**: 166–74.
31. Vauthey JN, Marsh Rde W, Cendan JC, Chu NM, Copeland EM. Arterial therapy of hepatic colorectal metastases. *Br. J. Surg*. 1996; **83**: 447–55.
32. Gray BN, Anderson JE, Burton MA *et al*. Regression of liver metastases following treatment with yttrium-90 microspheres. *Aust. N. Z. J. Surg*. 1992; **62**: 105–10.
33. Gray BN, Van Hazel G, Hope M *et al*. Randomised trial of SIR-Spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastase from primary large bowel cancer. *Ann. Oncol*. 2001; **12**: 1711–20.
34. Lau WY, Ho SKW, Yu SCH, Lai CM, Leung TWT. Salvage surgery following downstaging of unresectable hepatocellular carcinoma. *Ann. Surg*. 2004; **240**: 299–305.
35. Khatri VP, Petrelli NJ, Belghiti J. Extending the frontiers of surgical therapy for hepatic colorectal metastases: is there a limit? *J. Clin. Oncol*. 2005; **23**: 1–11.
36. Conlon R, Jacobs M, Dasgupta D, Lodge JP. The value of intraoperative ultrasound during hepatic resection compared with improved preoperative magnetic resonance imaging. *Eur. J. Ultrasound* 2003; **16**: 211–16.
37. Carmignani CP, Ortega-Perez G, Sugarbaker PH. The management of synchronous peritoneal carcinomatosis and hematogenous metastasis from colorectal cancer. *Eur. J. Surg. Oncol*. 2004; **30**: 391–8.
38. Elias DM, Benizri E, Pocard M, Ducreux M, Boige V, Lasser P. Treatment of synchronous peritoneal carcinomatosis and liver metastases from colorectal cancer. *Eur. J. Surg. Oncol*. 2006; **32**: 632–6.
39. Laurent C, Sa Cunha A, Rullier E, Smith D, Rullier A, Saric J. Impact of microscopic hepatic lymph node involvement on survival after resection of colorectal liver metastasis. *J. Am. Coll. Surg*. 2004; **198**: 884–91.
40. Elias DM, Ouellet JF. Incidence, distribution, and significance of hilar lymph node metastases in hepatic colorectal metastases. *Surg. Oncol. Clin. N. Am*. 2003; **12**: 221–9.
41. Shoup M, Gonen M, D'Angelica M *et al*. Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. *J. Gastrointest. Surg*. 2003; **7**: 325–30.
42. Melendez J, Ferri E, Zwillman M *et al*. Extended hepatic resection: a 6-year retrospective study of risk factors for perioperative mortality. *J. Am. Coll. Surg*. 2001; **192**: 47–53.
43. Martin R, Paty P, Fong Y *et al*. Simultaneous liver and colorectal resections are safe for synchronous colorectal metastasis. *J. Am. Coll. Surg*. 2003; **197**: 233–41; discussion 241–2.
44. Adam R, Laurent A, Azoulay D, Castaing D, Bismuth H. Two-stage hepatectomy: a planned strategy to treat irresectable liver tumors. *Ann. Surg*. 2000; **232**: 777–85.
45. Bismuth H, Adam R, Levi F *et al*. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann. Surg*. 1996; **224**: 509–22; discussion 520–22.
46. Adam R, Bismuth H, Castaing D *et al*. Repeat hepatectomy for colorectal liver metastases. *Ann. Surg*. 1997; **225**: 52–62; discussion 60–62.
47. Wang WD, Liang LJ, Huang XQ, Yin XY. Low central venous pressure reduces blood loss in hepatectomy. *World J. Gastroenterol*. 2006; **12**: 935–9.
48. DeMatteo RP, Palese C, Jarnagin WR, Sun RL, Blumgart LH, Fong Y. Anatomic segmental hepatic resection is superior to wedge resection as an oncologic operation for colorectal liver metastases. *J. Gastrointest. Surg*. 2000; **4**: 178–84.
49. Zorzi D, Mullen JT, Abdalla EK *et al*. Comparison between hepatic wedge resection and anatomic resection for colorectal liver metastases. *J. Gastrointest. Surg*. 2006; **10**: 86–94.
50. Hamady ZZ, Cameron IC, Wyatt J, Prasad RK, Toogood GJ, Lodge JP. Resection margin in patients undergoing hepatectomy for colorectal liver metastasis: a critical appraisal of the 1 cm rule. *Eur. J. Surg. Oncol*. 2006; **32**: 557–63.
51. Lesurtel M, Selzner M, Petrowsky H, McCormack L, Clavien PA. How should transaction of the liver be performed? a prospective randomized study in 100 consecutive patients: comparing four different transaction strategies. *Ann. Surg*. 2005; **242**: 814–22; discussion 822–3.
52. Benoist S, Brouquet A, Penna C *et al*. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? *J. Clin. Oncol*. 2006; **24**: 3939–45.
53. Hemming AW, Reed AI, Howard RJ *et al*. Preoperative portal vein embolization for extended hepatectomy. *Ann. Surg*. 2003; **237**: 686–91; discussion 691–3.
54. Selzner N, Pestalozzi BC, Kadry Z, Selzner M, Wildermuth S, Clavien PA. Downstaging colorectal liver metastases by concomitant unilateral portal vein ligation and selective intra-arterial chemotherapy. *Br. J. Surg*. 2006; **93**: 587–92.
55. Lodge JP, Ammori BJ, Prasad KR, Bellamy MC. Ex vivo and in situ resection of inferior vena cava with hepatectomy for colorectal liver metastases. *Ann. Surg*. 2000; **231**: 471–9.
56. Kappel S, Kandioler D, Steininger R *et al*. Genetic detection of lymph node micrometastases: a selection criterion for liver transplantation in patients with liver metastases after colorectal cancer. *Transplantation* 2006; **81**: 64–70.
57. Rena O, Casadio C, Viano F *et al*. Pulmonary resection for metastases from colorectal cancer: factors influencing prognosis. Twenty-year experience. *Eur. J. Cardiothorac. Surg*. 2002; **21**: 906–12.
58. Ike H, Shimada H, Togo S, Yamaguchi S, Ichikawa Y, Tanaka K. Sequential resection of lung metastasis following partial hepatectomy for colorectal cancer. *Br. J. Surg*. 2002; **89**: 1164–8.
59. Saito Y, Omiya H, Kohno K *et al*. Pulmonary metastasectomy for 165 patients with colorectal carcinoma: a prognostic assessment. *J. Thorac. Cardiovasc. Surg*. 2002; **124**: 1007–13.
60. Kemeny N, Huang Y, Cohen AM *et al*. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N. Engl. J. Med*. 1999; **341**: 2039–48.
61. Kemeny MM, Adak S, Gray B *et al*. Combined-modality treatment for resectable metastatic colorectal carcinoma to the liver: surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy – an intergroup study. *J. Clin. Oncol*. 2002; **20**: 1499–505.
62. Portier G, Rougier P, Milan C *et al*. Adjuvant systemic chemotherapy (CT) using 5-fluorouracil (FU) and folinic acid (FA) after resection of liver metastases (LM) from colorectal (CRC) origin. Results of an intergroup phase III study (trial FFCD - ACHBTH - AURC 9002). *Proc Am Soc Clin Oncol* 2002: **21**: 528.
63. Langer B, Bleiberg H, Labianca R *et al*. Fluorouracil (FU) plus l-leucovorin (l-LV) versus observation after potentially curative resection of liver or lung metastases from colorectal cancer (CRC): results of the ENG (EORTC/NCIC CTG/GIVIO) randomized trial. *Proc Am Soc Clin Oncol* 2002: **21**: 592.
64. Elias D, Debaere T, Muttillo I, Cavalcanti A, Coyle C, Roche A. Intraoperative use of radiofrequency treatment allows an increase in the rate of curative liver resection. *J. Surg. Oncol*. 1998; **67**: 190–91.
65. Solbiati L, Livraghi T, Goldberg SN *et al*. Percutaneous radiofrequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients. *Radiology* 2001; **221**: 159–66.

66. McGhana JP, Dodd GD 3rd. Radiofrequency ablation of the liver: current status. *AJR Am. J. Roentgenol*. 2001; **176**: 3–16.
67. Oshowo A, Gillams A, Harrison E, Lees WR, Taylor I. Comparison of resection and radiofrequency ablation for treatment of solitary colorectal liver metastases. *Br. J. Surg*. 2003; **90**: 1240–43.
68. Aloia TA, Vauthey JN, Loyer EM *et al*. Solitary colorectal liver - metastasis: resection determines outcome. *Arch. Surg*. 2006; **141**: 466–7.
69. Sutherland LM, Williams JA, Padbury RT, Gotley DC, Stokes B, Maddern GJ. Radiofrequency ablation of liver tumours: a systematic review. *Arch. Surg*. 2006; **141**: 181–90.
70. Robertson JM, Lawrence TS, Walker S, Kessler ML, Andrews JC, Ensminger WD. The treatment of colorectal liver metastases with conformal radiation therapy and regional chemotherapy. *Int. J. Radiat. Oncol. Biol. Phys*. 1995; **32**: 445–50.
71. Herfarth KK, Debus J, Lohr F *et al*. Stereotactic single-dose radiation therapy of liver tumors: results of a phase I/II trial. *J. Clin. Oncol*. 2001; **19**: 164–70.