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Treatment of colorectal liver metastases

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Background: Surgical resection is the only potentially curative treatment for colorectal liver metastases, with 5-year survival rates approaching 40 per cent. However, at present only 20–25 per cent of such lesions are deemed resectable. This review examines developments in neoadjuvant and adjuvant treatments of colorectal liver metastases that aim to improve the results of surgical management of this disease.

Methods: A literature review was undertaken based on a Medline search from 1970 to May 1998.

Results: Further evolution in surgical technique is unlikely to lead to a dramatic increase in the resectability rate of colorectal liver metastases. Recent developments in neoadjuvant and adjuvant chemotherapy schedules, together with a range of interventional radiological procedures and interstitial lytic techniques, show promise in terms of extending the limits of resectability and decreasing recurrence rates associated with these lesions. Using multimodality regimens 5-year survival rates of 40 per cent are now being reported for lesions that were initially considered irresectable.

Conclusion: Patients with colorectal liver metastases should be assessed in units that can offer all the specialist techniques necessary to deliver optimum care. Incorporation of newer neoadjuvant and adjuvant treatments into management strategies should occur in the setting of randomized trials.

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Colorectal cancer is one of the commonest solid tumours in humans and is responsible for approximately 10 per cent of cancer deaths in the Western world. The liver is the commonest site of distant metastasis in this disease and 50 per cent of all patients with colonic cancer ultimately develop liver involvement. Colonic cancer is unique among solid tumours in that surgical resection of distant metastatic (i.e. liver and lung) involvement can produce long-term survival and cure in selected patients[1]. Indeed, surgery is the only therapy that offers any possibility of cure in patients with hepatic metastatic disease, with 5-year survival rates after resection of all detectable disease of up to 40 per cent[2]. Unfortunately, only 20–25 per cent of patients with colorectal liver metastases are deemed suitable for hepatic resection; for the remaining patients treatment with standard systemic chemotherapy can be expected to produce only modest extensions to survival time[3].

Refinements in surgical technology have had a major impact on resectability rates and operative morbidity and mortality rates. Further significant improvements in resectability rates are unlikely to result from surgical ingenuity alone; they will require the combination of surgical resection with more effective neoadjuvant treatment strategies, designed to reduce tumour bulk or number sufficiently to allow complete surgical clearance. An additional problem is that, following apparently curative resection, recurrent tumour develops in 60 per cent of patients, indicating the need for some form of postoperative adjuvant therapy[4].

This review examines a range of chemotherapeutic, interventional radiological and interstitial lytic techniques that have been used, or deserve evaluation, as neoadjuvant and adjuvant treatments in association with surgery. A Medline search was performed for the period from January 1970 to May 1998 using a broad range of keywords individually and in combination. The terms that produced the highest yield of relevant material included liver, metastases, surgery, chemotherapy, intra-arterial, chemoembolization, immunotherapy and brachytherapy.

The target of resectability

Before assessing methods for increasing surgical resectability rates, it is worthwhile briefly considering the aim of these treatment strategies. Surgical resection of liver metastases is the only treatment that offers any chance of cure. The number of metastases is no longer considered to

be as important a predictor of long-term survival as previously. Indeed, complete excision of all demonstrable tumour with clear resection margins has been shown to be of much greater importance[2]. If this can be achieved, survival after resection of up to eight metastases is similar to that after resection of a solitary metastasis. If complete excision is not possible, surgical resection has no impact on the natural history of the disease and is nearly always pointless. Although a resection margin of 1 cm or more is desirable, occasionally this cannot be achieved for technical reasons[1]. Provided the margin is microsopically tumour-free, however, long-term survival and cure are possible[2] (although somewhat reduced) with margins of less than 1 cm. The presence of extrahepatic metastatic disease, including hilar lymph node metastases, should be considered a contraindication to resection with two important exceptions: locally invasive disease that can be removed *en bloc* with the metastatic liver disease (most commonly diaphragmatic involvement) and resectable pulmonary metastatic disease[1,5]. Insufficient information is available at present to determine whether there is an upper limit to the number of pulmonary metastases that should be considered for resection.

Surgical strategies

A number of technical, surgical advances have extended the boundaries of resectability for liver tumours over the past three decades. Recognition of the segmental basis of liver anatomy led to the evolution of segment-based resection. This has had a particular influence on surgery for colorectal metastases because it allows excison of bilateral or multiple liver lesions that might previously have been deemed irresectable[6]. Staged resection is another means by which a large amount of liver parenchyma may be resected without inducing hepatic insufficiency, and again may be useful for bulky bilateral lesions. A typical wedge resection is more likely to be associated with an inadequate excision margin than a segmental resection, and so the latter is preferred from an oncological standpoint[2,7].

Vascular occlusion techniques, particularly the Pringle manoeuvre, have had a major impact in reducing the morbidity associated with liver resection. Total vascular exclusion has become widely accepted as a means of minimizing blood loss when operating on difficult lesions. Belghiti and colleagues[8] reported a randomized comparison of portal occlusion *versus* total vascular exclusion in 52 non-cirrhotic patients undergoing major liver resection; blood loss was similar in the two groups. Caval clamping caused major haemodynamic disturbance in 14 per cent of patients. Although hospital stay was prolonged in patients who had total vascular exclusion, other measures of outcome were not significantly different between the groups. Although few surgeons use total vascular exclusion routinely, it is a technique that facilitates excision of lesions involving the vena cava or those lying near the junction of the hepatic veins and vena cava[8,9].

A greater willingness to resect and reconstruct segments of hepatic inflow or outflow vascular structures has meant that some lesions which would previously have been treated without operation can now be excised with clear resection margins[10]. In particular, replacement of hepatic vein and vena cava with autologous vein and prosthetic grafts respectively has been facilitated by the use of total vascular exclusion and by the adoption of a number of techniques, some of which owe their development to, or have been borrowed from, orthotopic liver transplantation[11]. The use of venovenous bypass in association with *in situ* hypothermic perfusion, and *ex situ* resection and autotransplantation, have both been important additions to the liver surgeon's armamentarium[12,13]. While these techniques are rarely required, there may be occasions when a centrally placed tumour cannot be excised safely without resorting to such methods[14]. The use of perfusion techniques extends the ischaemic time available to the surgeon, which may be particularly important if complex hepatic vein or vena cava reconstruction is required. While these surgical *tours de force* may be helpful in a limited number of cases, it seems clear that combinations of different treatment modalities will be required to produce a further substantial increase in the number of patients who can be offered the possibility of surgical cure.

Neoadjuvant chemotherapy

At present, by the time liver metastases are identified, only 20–25 per cent of patients are deemed to have resectable disease. This indicates a need for neoadjuvant treatment strategies to increase resectability rates. Reports on the use of fluoropyrimidine-based cytotoxic chemotherapy have focused mainly on the treatment of patients with advanced irresectable disease and as an adjuvant treatment following resection of the primary colonic tumour[15–19]. There are no randomized prospective studies of such therapy used specifically as part of a neoadjuvant programme before surgery. Given the proven benefits of surgery compared with standard cytotoxic regimens, it is hard at present to justify establishing a trial of neoadjuvant treatment with these agents in patients with resectable tumours. For primarily irresectable hepatic metastases there has been only a handful of non-randomized retrospective studies and case reports of individual patients that have described downstaging to resectability by chemotherapy (*Table 1*)[20–25].

Table 1 Studies reporting downstaging to resectability with chemotherapy in patients with colorectal liver metastases

Reference	No. of patients	Drugs given	Other preoperative treatment	Survival
Wadler *et al.*[22]	1	5-FU–α-interferon	None	Not specified
Gayral *et al.*[20]	3	5-FU	None	Not specified
Fowler *et al.*[21]	11	5-FU–leucovorin or PALA	None	Three patients disease-free at 15, 18 and 31 months; eight with recurrent disease
Maruo and Kosaka[23]	3	i.a. 5-FU–cisplatin–doxorubicin	None	Not specified
Elias *et al.*[24]	9	i.a. 5-FU–mitomycin C or 5-FU-pirubicin	Portal vein embolization (three patients)	Six patients disease-free at a mean of 20 months; three dead at 38 months
Bismuth *et al.*[25]	53	i.v. 5-FU–leucovorin–oxaliplatin	Portal vein embolization	40% 5-year survival rate

5-FU, 5-fluorouracil; PALA, *N*-(phosphonacetyl)-L-aspartate; i.a., intra-arterial; i.v., intravenous

One American series[21] described a group of 11 patients whose disease was sufficiently downstaged to undergo resection after a mean of 8 months' chemotherapy with 5-fluorouracil (5-FU) and leucovorin or *N*-(phosphonacetyl)-L-aspartate. All patients underwent resection with curative intent, but four were found to have histologically positive margins. Three of the 11 patients were disease-free at 15, 18 and 31 months after resection, with the remainder developing recurrent disease at a mean of 8 months after operation. Elias *et al.*[24] described 14 patients, nine of whom had colorectal metastases and who converted from being irresectable to resectable after 6 (mean 13, range 6–31) or more courses of intra-arterial chemotherapy with 5-FU combined with pirubicin or mitomycin C. As a consequence of the intra-arterial catheter, hepatic arterial thrombosis occurred in three cases, although this did not preclude subsequent surgery as adequate arterial collateralization was demonstrated by preoperative angiography. Three of these patients had portal vein embolization performed before operation to increase the volume of the future remnant liver and reduce the likelihood of postoperative hepatic insufficiency. Five of the nine patients were alive at 5 years. These 14 patients represented only 6 per cent of the total number of patients who had hepatic artery catheters inserted for treatment of irresectable liver tumours. Elias *et al.*[24] and other authors[20] have commented that hepatectomy is generally more difficult technically following arterial infusion therapy as the parenchyma tends to be more congested and friable. As well as morphological changes, persistent functional hepatic impairment may result from arterial chemotherapy. Elias and colleagues[24] recommend evaluation with iodocyanine green (ICG) retention as well as computed tomographic volumetry in these patients before resection. The results of the ICG retention test can be evaluated with Makuuchi *et al.*'s therapeutic protocol[26], which was originally designed as a guide in the selection of treatment for patients with hepatocellular carcinoma and cirrhosis *(Fig. 1)*.

Bismuth and colleagues[25] recently reported a series of 53 patients who underwent liver resection after neoadjuvant chemotherapy with systemic 5-FU, leucovorin and oxaliplatin. These 53 patients represented 16 per cent of the total number of patients with primarily irresectable colorectal metastatic disease seen at the authors' institution. The chemotherapy was administered in an ambulatory setting using a time–dose programmed multichannel pump connected to a subcutaneously implanted venous port[27]. The mean duration of chemotherapy before surgery was 8 months. A variety of additional techniques was used to increase resectability rates including preoperative portal vein embolization (five patients) and two-stage hepatectomy (five patients). Repeat hepatectomy in 15 patients and resection of pulmonary metastases in ten presumably also contributed to the excellent 5-year survival rate of 40 per cent in this group. While this series does not of itself prove the effectiveness of the specific cytotoxic regimen used, it is important because it demonstrates the benefit of an aggressive policy in which a multimodality regimen including neoadjuvant chemotherapy was used to achieve secondary hepatectomy. This experience illustrates the importance of regular review by a liver surgeon of patients with primarily irresectable liver metastases.

Adjuvant chemotherapy

Following resection of liver metastases, 60–70 per cent of patients will develop recurrent disease, most commonly in the liver, so effective postoperative adjuvant treatment is also required. However, the optimum regimen and route of delivery require clarification. Early trials of systemic or intraperitoneal chemotherapy after liver resection for colorectal metastases showed no benefit in terms of survival, an experience confirmed by more recent studies of systemic treatment[28–30]. In patients with irresectable

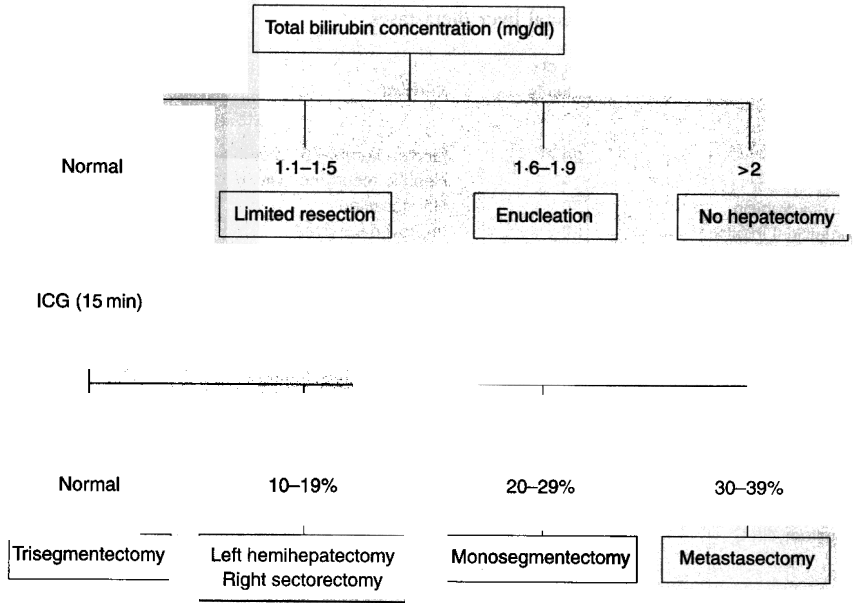

Fig. 1 Interpretation of iodocyanine green (ICG) retention test results in patients undergoing hepatectomy following neoadjuvant chemotherapy[26]. (The ICG test result indicates the percentage of the initial plasma concentration present 15 min after a bolus injection of ICG)

hepatic metastases, response rates may be improved by regional administration of cytotoxic agents through surgically implanted hepatic arterial ports[31–33]. However, intra-arterial chemotherapy has not been shown to improve survival compared with systemic administration of cytotoxics. In part this may be because problems in the design of the relevant studies have prevented satisfactory analysis of survival data[34]. A recent meta-analysis of the data from trials of intra-arterial infusion therapy for irresectable metastases detected no significant effect of this treatment compared with intravenous administration of 5-FU or 5-FUDR (5-fluoro-2-deoxyuridine)[35]. Despite this, hepatic artery infusion chemotherapy has been extensively evaluated as a means of delivering adjuvant chemotherapy following liver resection for colorectal liver metastases. There is a large number of anecdotal reports and non-randomized studies, and only a few randomized studies, examining the role of intra-arterial chemotherapy after liver resection; clear evidence of a survival benefit compared with systemic therapy has not emerged *(Table 2)*[30,36–49].

In one randomized study by Wagman *et al.*[47], the addition of hepatic artery infusion increased mean disease-free survival after resection of solitary liver metastases from 8·7 to 31·8 months, although the number of patients involved was small and this difference was not statistically significant. Lygidakis and colleagues[49] reported a randomized trial of 40 patients, half of whom were treated with liver resection alone and the other half received adjuvant regional immunochemotherapy. This comprised γ-interferon and aldesleukin (Proleukin; Chiron, Harefield, UK) emulsified in Lipiodol delivered through a splenic artery catheter, followed by a combination of Lipiodol, mitomycin C, epirubicin, carboplatin, 5-FU and leucovorin given through a hepatic artery catheter after liver resection[49]. A total of four cycles of this regimen was given during the first year after operation. Mean survival was increased from 11 months in the control group to 20 months ($P < 0{\cdot}001$) in patients who received adjuvant treatment following resection. Tsuji *et al.*[48] recently reported a small study comparing intra-arterial high-dose 5-FU with no adjuvant treatment following curative liver resection. Survival was significantly greater at 3 years in the group that received adjuvant treatment (eight of 12 patients) compared with the control group (four of 15).

All the remaining studies are non-randomized trials with historical (or no) control groups; as a result there is a paucity of useful information. Lorenz and co-workers[44] reported on 61 patients who received intra-arterial 5-FUDR following curative liver resection as part of a dose-finding study. Median survival was 36 months in the resected patients. No control group consisting of patients undergoing curative resection without additional treatment was included in the study. However, such a trial has since been initiated by this group and the results of this and a number of other similar randomized trials of intra-arterial chemotherapy after resection of colorectal liver metastases should eventually provide a clearer understanding of the benefit of this treatment. Comparison of intra-arterial with systemic chemotherapy is another important matter that has not been resolved adequately;

Table 2 Studies of intra-arterial chemotherapy following resection of colorectal liver metastases

Reference	Drugs given	No. of patients	Survival
Non-randomized studies			
Patt *et al.*[36]	FUDR–mitomycin C	20	Median survival 51 months
Kawano *et al.*[37]	5-FU, mitomycin C	14	Hepatic recurrence within 12 months 36%
Yasui *et al.*[38]	5-FU, mitomycin C, doxorubicin	76	Not specified*
Isshiki *et al.*[39]	Mitomycin C–doxorubicin–Lipiodol	22	Improved survival*
Moriya *et al.*[40]	5-FU, mitomycin C and oral HCFU	16	Hepatic recurrence 31%
Takahashi *et al.*[41]	5-FU	22	Lower local recurrence rate*
Lorenz *et al.*[42]	FUDR *versus* FUDR–leucovorin	90	Disease-free survival 19 *versus* 12 months (control), $p < 0{\cdot}05$; survival not significantly improved
Curley *et al.*[43]	5-FU for 6 months	20	50% disease-free survival rate at 3 years better than that in historical controls
Kemeny *et al.*[32]	i.a. FUDR with i.v. 5-FU–leucovorin	8	Mean disease-free survival 23 months
Lorenz *et al.*[44]	FUDR *versus* 5-FU–leucovorin	61	Median survival 36 months
Donato *et al.*[30]	5-FU	102	3-year survival rate: surgery only 44% *versus* surgery with chemotherapy 47%
Shimada *et al.*[45]	5-FU–epirubicin	28	3-year survival rate 53·9%
Hanada *et al.*[46]	5-FU–doxorubicin–mitomycin C	55	Improved survival*
Randomized studies			
Wagman *et al.*[47]	FUDR, continuous infusion	35	3-year survival rate: solitary metastasis – control 50% *versus* FUDR 60%; multiple metastases–control 40% *versus* FUDR 14%
Tsuji *et al.*[48]	5-FU	27	3-year survival rate: treated 69% *versus* resection only 25%
Lygidakis *et al.*[49]	γ-Interferon–aldesleukin–Lipiodol, then mitomycin C–carboplatin-epirubicin–5-FU–leucovorin	40	Mean survival: treated 20 months *versus* control 11 months, $P < 0{\cdot}001$

*Result available in abstract form only. FUDR, 5-fluoro-2-deoxyuridine; 5-FU, 5-fluorouracil; HCFU, hexylcarbamoyl-5-fluorouracil; i.a., intra-arterial; i.v., intravenous

some of the ongoing trials have systemic treatment arms to address this issue.

Hepatic artery infusion chemotherapy is associated with certain technical difficulties and morbidity. The Meta-Analysis Group in Cancer has recently stressed the importance of including consideration of toxicity, quality of life and cost issues in any assessment of hepatic artery infusion chemotherapy[34]. Attention to detail in catheter insertion and aftercare is crucial if morbidity is to be minimized and a real therapeutic benefit achieved. The main toxicity is biliary sclerosis, which in earlier studies was reported to occur in up to 25 per cent of patients. Corticosteroid treatment is effective in reducing the incidence of this complication[50,51]. The incidence of duodenal ulceration secondary to hepatic arterial infusion therapy can be minimized by careful decollateralization at the time of port implantation[52]. The most important limiting factor is the development of extrahepatic metastases, which occur in 40–70 per cent of patients. It seems logical that, to be useful, intra-arterial chemotherapy must be combined with systemic therapy. However, in the study conducted by Lorenz and colleagues[44] the administration of systemic treatment in addition to intra-arterial 5-FUDR did not affect the time to development of extrahepatic disease.

Portal vein infusion is an alternative route for regional delivery of cytotoxic agents to the liver. Early experience with this technique examined its efficacy as adjuvant treatment following excision of the primary colonic tumour. The initial study by Taylor and colleagues[53] found a beneficial effect and, while several susequent studies were unable to confirm this improvement, two recent reports, one from Switzerland[54] and the other from the USA[55], describe a survival benefit associated with this treatment. In both of these studies improved survival was due to a reduction of recurrences at all sites, not just the liver, and it was concluded that the impact on survival was due largely to the systemic effects of 5-FU. Intraportal chemotherapy after liver resection has been reported in at least five non-randomized trials, each with small numbers of patients (*Table 3*)[56–60]. Preliminary work established the feasibility and safety of intraportal chemotherapy with 5-FU after liver resection, but subsequent efforts have not demonstrated a survival benefit[56,57]. Takano *et al.*[59] were unable to detect any difference in recurrence of hepatic colorectal metastases after liver resection between groups treated with systemic, intra-arterial or intraportal chemotherapy. Another Japanese study found that intraportal chemotherapy with 5-FU and Lipiodol–aclarubicin after liver

Table 3 Studies of intraportal chemotherapy following resection of colorectal liver metastases

Reference	Drugs given	No. of patients	Survival
Elias *et al.*[56]	5-FU for 14 days	12	Not specified
Seitz *et al.*[57]	5-FU for 7 days	6	Not specified
Tsujitani *et al.*[58]	Mitomycin–5-FU for 40 days	5	No difference in median survival
Takano *et al.*[59]	Mitomycin for 960 days	5	No difference compared with systemic or intra-arterial treatment
Ambiru *et al.*[60]	5-FU– Lipiodol–aclarubicin for 14 days	28	Improved median survival at 1 year (89 versus 63 per cent for untreated controls); no difference at 2 and 3 years

5-FU, 5-fluorouracil

resection improved survival at 1 year, but not at 2 or 3 years after liver resection[60]. There was no difference in the incidence of intrahepatic recurrence, suggesting that the limited benefit demonstrated in this trial was due to the systemic effect of 5-FU rather than any specific advantage of the intraportal route.

The majority of patients currently undergoing liver resection will previously have been treated with 5-FU combined with leucovorin or levamisole. Tumour resistance to repeated use of the same cytotoxic agents is a factor that needs to be considered in the selection of adjuvant chemotherapy for colorectal liver metastases as response rates can be markedly reduced in previously treated patients. A number of options is available, although the drugs and dose regimens selected will need to have low toxicity profiles if they are to be acceptable as adjuvant or prophylactic treatments after R_0 resection. For recurrent colonic cancer the use of high-dose 5-FU is associated with an increased response rate in patients who have previously failed standard 5-FU-based treatment[61]. Delivery of cytotoxic drugs by prolonged infusion can reduce toxicity and these agents may be given as an ambulatory treatment using an implantable pump. These modifications may have significant benefits in terms of quality of life compared with standard regimens. There are a number of newer agents, currently being assessed as adjuvant treatments for primary colonic cancer, that could be evaluated as adjuvant treatments following resection of metastatic liver lesions[62,63].

Immunotherapy

Early attempts at tumour-specific immunotherapy in metastatic liver tumours have not been particularly rewarding and have mainly addressed the problem of advanced disease that has failed to respond to conventional therapy. The effectiveness of 5-FU with levamisole, a non-specific immune stimulant, in adjunctive treatment serves as a paradigm for combination of cytotoxics with immune modulators; further exploration of different combinations of this type may provide new neoadjuvant regimens[64,65]. In an animal model of liver metastases, modulation of 5-FU activity by interferon is effective as a neoadjuvant treatment[66]. Further animal studies are required to allow rational selection of agents for use in clinical trials. Elias and colleagues[67] have recently reported a phase I–II study of neoadjuvant immunotherapy with interleukin 2 before hepatectomy for colorectal metastases in 19 patients. Treatment was associated with acceptable toxicity and did not delay surgery in any instance. Pretreatment with interleukin 2 prevented the postoperative immunodepression seen in control patients, although this made no difference to early clinical outcome. Longer follow-up data are awaited to determine whether prevention of perioperative immunodepression can reduce the potential for perioperative tumour cell dissemination and metastasis implantation, leading to improved long-term survival.

Clinical trials have shown that the monoclonal antibody 17-1A is effective in increasing survival following resection of Dukes C primary colorectal tumours[62,68]. Further studies of this and other monoclonal antibodies in patients with colonic cancer are continuing. As an extension of this, evaluation of these agents as adjuvant treatments before or after liver resection for colorectal metastases seems worthwhile.

Hepatic artery chemoembolization

Hepatic artery chemoembolization (HACE) was developed as a treatment for irresectable non-disseminated liver tumours. It increases the response rate compared with systemic administration of cytotoxic agents, although it has not been shown to prolong survival. HACE has been studied most extensively in the treatment of hepatocellular carcinoma, but has also been used in patients with metastatic colorectal cancer[69–72]. Preoperative chemoembolization has been proposed as a possible means of

decreasing perioperative tumour dissemination, although this concept has not been subjected to a randomized trial nor has it been evaluated systematically in large numbers of patients. Sasaki and colleagues[72] performed preoperative HACE in ten of 30 patients undergoing resection of colorectal liver metastases. There was no significant difference in 3-year survival between the two groups, although the criteria by which patients were selected for preoperative chemoembolization were not clearly stated. Routine preoperative HACE for hepatocellular carcinoma has been abandoned by most centres with large series of patients because of the significant associated morbidity and lack of evidence that it produces any survival benefit[73]. There are anecdotal reports of patients with borderline resectable tumours (including colorectal metastases) in whom HACE caused sufficient tumour shrinkage to allow resection, and it is worth considering in this situation. Nevertheless, it seems unlikely that HACE will have a major impact in altering resectability rates for colorectal metastases and its main use is in the palliative treatment of localized but irresectable lesions.

Portal vein embolization

Preoperative portal vein embolization can decrease the likelihood of liver insufficiency occurring after extensive liver resection by inducing hypertrophy in the future remnant liver[74]. Most experience with this technique has been in patients with hilar cholangiocarcinoma[75]; however, it has also been used for metastatic colorectal tumours. Kawasaki *et al.*[76] described five patients with between three and 12 colorectal metastatic lesions who underwent preoperative right portal vein embolization to allow extended right-sided liver resection in combination with wedge excision of lesions in the left lateral segment. Portal vein embolization was performed 9 days to 8 months before surgical resection and mean survival was 47 months. In patients with non-cirrhotic livers, preoperative portal vein embolization can be expected to induce a 40–60 per cent increase in the size of the non-embolized portion[76]; a similar degree of compensatory hypertrophy is not seen after arterial embolization. Portal vein embolization may be performed either by percutaneous ultrasonographically guided puncture of a portal vein radicle (through tumour-free liver) or by operative exposure of an ileocolic vein to allow portal access. Although embolization of the right portal vein has been reported most commonly, left portal vein embolization is also possible for patients requiring an extended left hepatectomy[77]. The material used for embolization is usually a mixture of Lipiodol and enbucrilate (Histoacryl; Sherwood, Davis and Geck, Gosport, UK) or Gelfoam (Pharmacia and Upjohn, Kalamazoo, Michigan, USA)[76,78]. Portal vein embolization is usually well tolerated and produces a less severe systemic reaction than intra-arterial chemoembolization. Another additional benefit of portal vein embolization may relate to the fact that the periphery of many larger tumours receives some blood supply from the portal system, so that in addition to inducing hypertrophy of the future remnant liver it may also have a role in 'sterilizing' the tumour before surgical manipulation[79].

As mentioned previously, portal vein embolization is most likely to be useful as part of a multimodality treatment strategy including neoadjuvant chemotherapy. The studies of Elias *et al.*[24] and Bismuth *et al.*[25], although focusing primarily on the downstaging of metastatic liver disease to resectability with chemotherapy, both included patients who in addition to chemotherapy underwent portal vein embolization to increase the size of the future remnant liver. The combined use of preoperative hepatic artery chemoembolization and portal vein embolization has been reported for hepatocellular carcinoma and background cirrhosis, although not for colorectal liver metastases[80]. There may be occasional patients with bulky solitary metastases in whom the combination of arterial and portal vein embolization is considered worthwhile to reduce tumour bulk and induce hypertrophy of the future remnant liver. Based on the available experience with the combination of these two techniques in the treatment of hepatocellular carcinoma, the two embolization procedures should be separated by an interval of 4–6 weeks[80].

Brachytherapy

Neoadjuvant treatment protocols using combined radiochemotherapy have shown great promise, particularly in the treatment of oesophageal and rectal carcinomas. Unfortunately, such combined treatment modalities are not applicable to colorectal liver metastases because of the sensitivity of normal liver to external-beam irradiation. As an alternative to external-beam radiotherapy, brachytherapy with yttrium-90 microspheres or iodine-125 seeds has been used with favourable responses following non-curative resection and in patients with irresectable colorectal metastases[81–83]. Armstrong and colleagues[83] reported a series of 12 patients in whom iodine-125 implants were placed at laparotomy as adjunctive treatment for either microscopically positive margins after resection or grossly irresectable liver colorectal metastases. Overall median survival was 18·2 months, and five of the 12 patients survived for more than 2 years. Extrahepatic metastases occurred in ten patients and local

recurrence at the implant site developed in five. Thomas *et al.*[84] described 22 patients who received intraoperative iridium-192 irradiation for irresectable metastases; in two, subsequent biopsy at the tumour site demonstrated total eradication. Local control was achieved in 76 per cent of patients at 6 months, but intrahepatic recurrence at non-irradiated sites occurred in 15 patients, underlining the need for additional systemic therapy. As an alternative to direct surgical implantation, radioactive material may be applied in a relatively selective fashion by combining the radioisotope with Lipiodol, with delivery by radiological embolization[85]. These techniques are unlikely to be applicable as neoadjuvant treatments but may be helpful in decreasing recurrence in selected patients after surgical resection.

Cryotherapy and other interstitial therapies

Although not established as a curative treatment for colorectal liver metastases, cryotherapy may play a role in managing residual inaccessible lesions in conjunction with liver resection[86,87]. In Bismuth *et al.*'s series of 53 patients who underwent secondary hepatectomy after chemotherapy[25], cryotherapy was used in four patients to treat residual tumour nodules or to freeze the resection surface when only a narrow resection margin (less than 1 cm) could be achieved. Alcohol injection was also used in this series in two patients with disease that was found to be irresectable at initial laparotomy, but who subsequently underwent resection after chemotherapy. Adam *et al.*[87] subsequently described 25 patients with colorectal liver metastases from the same centre who were treated with cryotherapy. Tumour recurrence had occurred in 11 patients at a mean of 16 months. Most of these recurrences were local, suggesting that some viable malignant cells survived despite ultrasonographic documentation that the iceball formed during cryotherapy extended beyond the margins of the tumour. Preketes and colleagues[88] in Sydney examined the efficacy of combining cryotherapy with hepatic artery chemotherapy in 38 patients. In this retrospective study, the 2-year survival rate was prolonged from 12·5 per cent in the group treated with cryotherapy alone to 21 per cent in those who also received intra-arterial chemotherapy, although this difference was not significant. This study provides further encouraging evidence of the potential benefits to be gained through multimodality treatment strategies, although confirmation is required from properly structured randomized trials.

The reported experience with interstitial laser hyperthermia has been limited largely to patients with irresectable metastases, most of whom have been treated percutaneously[89–91]. Preliminary data suggest that this treatment is capable of producing prolonged regression of tumour. Vogl and colleagues[92] reported their experience with 20 patients with 33 colorectal metastases treated by magnetic resonance image-guided laser hyperthermia. For lesions less than 2 cm in diameter local control was obtained in 23 cases at 6 months and in 15 at 12 months. Local control was less satisfactory for larger lesions. Longer follow-up is required to allow definitive assessment of the role of interstitial laser hyperthermia in this disease. Alcohol injection tends not to be as satisfactory in colorectal metastatic disease as in hepatocellular carcinoma because the firmer tumour tissue texture associated with the former limits even diffusion of the agent[25,89]. No specific data are available on the long-term effectiveness of alcohol injection in colorectal metastases. Lesion size is, not surprisingly, a critical determinant of the effectiveness of all these interstitial lytic therapies. As a response to this, newer multitipped laser probes have been developed which offer the possibility of treating larger lesions.

Any of the local interstitial therapies may be used as adjuncts to incomplete surgical resection and, as such, they may help extend the boundaries of resectability. No information is available about the maximum number of lesions that can successfully be treated in conjunction with surgical resection. None the less their use in this situation provides the best opportunity for assessing their potential role as curative therapies. Certainly, at present, the application of these modalities as primary treatment for patients with resectable tumours does not seem justified.

One of the advantages of interstitial laser hyperthermia and alcohol injection is that both may be used percutaneously in patients with irresectable tumours[88], although the risk of tumour needle-track contamination may prejudice future attempts at liver resection should the tumour be downstaged by chemotherapy. Percutaneous techniques should not be considered as part of a neoadjuvant programme.

Conclusion

Surgery remains the only treatment that can cure patients with colorectal hepatic metastatic disease. Regular postoperative surveillance ultrasonography and measurement of tumour markers should be performed in an effort to detect hepatic metastatic disease at an early stage since this has a major impact on resectability rates. Five-year survival rates approaching 40 per cent can be achieved in patients undergoing primary resection of hepatic colorectal metastases. In certain groups previously considered irresectable, similar survival rates can be attained with the aggressive use of combined modality treatment. Further

combinations of chemotherapeutic regimens with surgical resection and interstitial lytic therapies should continue to increase the numbers of patients who can be offered curative treatment for this disease. The limits of resectability have been expanded to the point where every patient with colorectal liver metastases, even those with apparently irresectable disease, should be assessed by a liver surgeon. Patients with primarily irresectable disease who are treated with chemotherapy should remain under surgical review so that the possibility of secondary hepatectomy is considered regularly.

One of the greatest challenges facing liver surgeons is how best to evaluate these new therapies in combination with resectional surgery. At a time when the value of much surgical research has been called into question, it is imperative that liver surgeons maintain the intellectual rigour to design and enter patients into appropriate randomized trials to evaluate the effectiveness of these new treatment modalities[93,94]. These trials will need to be multi-institutional if they are to recruit sufficient numbers to provide useful information.

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