Colorectal liver metastases: alternatives to resection

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Surgical resection, in suitably selected patients, is the most effective treatment for colorectal liver metastases. In most series postoperative mortality is less than 4% and 5-year survival approaches 30%[1]. However, selection is of crucial importance and even on the most liberal criteria few patients' metastases are in fact suitable for surgical excision. By far the majority have disease which extends beyond surgical intervention or have comorbidity which makes the procedure untenable. The results of surgery depend upon an expert multidisciplinary team and surgical expertise, and survival rates will also depend greatly on the criteria for resection. This review article discusses novel concepts and techniques for dealing with unresectable colorectal liver metastases. It must be emphasized that optimum management requires input from many different specialties, with consideration of all options in the context of the patient's quality of life. The role of systemic chemotherapy is not specifically included in this review since the principle is established and patients are offered this treatment either as a solitary therapy or in combination with each of the three therapies discussed. Poon *et al.*[2] provide an up-to-date review of regimens for systemic chemotherapy in advanced disease[3].

NEOADJUVANT CHEMOTHERAPY

Attempts have been made to increase the resectability rate of patients with multiple or irresectable liver metastases. The hope is that, by downstaging of initially inoperable disease with chemotherapy, the patient becomes suitable for resection. There are no randomized trials of such an approach but several groups have reported evidence of survival improvement (Table 1). Other groups have utilized regional chemotherapy with the same objective and some of the results have been impressive (Table 2). Various chemotherapy regimens have been tried, and the combination of 5-fluorouracil (5-FU), folinic acid and oxaliplatin is particularly encouraging[6]; there is now a strong argument for testing of this regimen in a randomized trial.

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After downstaging by neoadjuvant therapy, surgery can be carried out with low morbidity and mortality, although the liver may be more than usually friable and haemorrhagic in these circumstances[6–10]. In the large study by Bismuth *et al.*[6], chemotherapy was achieved in an ambulatory setting with a time-dose programmed multichannel pump connected to a subcutaneously implanted venous port. The mean duration of chemotherapy before surgery was eight months. A further means to improve resectability rates is preoperative portal embolization. This technique is designed to induce a 40–60% increase in the volume of the non-embolized portion of the liver[11], so that a greater proportion of the diseased liver can be removed without critical loss of liver function. Portal vein embolization is performed by percutaneous ultrasound guided puncture of a portal vein radical.

INTRAHEPATIC ARTERIAL CHEMOTHERAPY

Colorectal liver metastases derive a substantial proportion of their blood supply from the hepatic artery, and appreciation of this fact has led to the evolution of hepatic arterial chemotherapy to target metastases. The high first-pass ratio of 5-FU and fluorodeoxyuridine through the liver leads to high hepatic drug concentrations with little systemic exposure[12]. Access to the hepatic circulation is gained via the gastroduodenal artery, through an incision similar to that for open cholecystectomy. (All patients require a preoperative angiogram to ensure that there are no vascular anomalies.) Prolonged infusions are used rather than bolus injection of drugs since 5-FU is cytotoxic in the S-phase of the cell cycle—thus long infusions 'catch' more susceptible cells.

Initial studies of this technique were hampered by technical difficulties related to hepatic arterial catheter placement and maintenance. With implantable pumps and subcutaneous ports many of these have been circumvented. Several research groups have reported response rates of over 50%, with improvement in overall survival. The few randomized trials also indicate improved locoregional response rates, though survival differences are more doubtful (Table 3). In a meta-analysis of the five studies comparing intra-arterial therapy with systemic therapy[18], the overall locoregional liver response rate was 41% versus 14% and median survival was 16 months versus 12.2

Table 1 **Neoadjuvant therapy—systemic chemotherapy**

Series	No.	Regimen	Outcome
Wadler *et al.* (Ref 3)	1	5-FU/interferon	Not given
Gayral *et al.* (Ref 4)	3	5-FU	Not given
Fowler *et al.* (Ref 5)	11	5-FU/leucovorin	3 disease free at 15, 18, 31 months
Bismuth *et al.* (Ref 6)	53	5-FU/leucovorin oxaliplatin	40% 5-year survival
Shankar *et al.* (Ref 7)	12	5-FU/leucovorin	53% 3-year survival

Table 2 **Neoadjuvant therapy—intra-arterial chemotherapy**

Series	No.	Regimen	Outcome
Maruo *et al.* (Ref 8)	3	5-FU/cisplatin, doxorubicin	
Elias *et al.* (Ref 9)	9	5-FU-mitomycin C or 5-FU pirubicin	6 disease-free at mean of 20 months
Link *et al.* (Ref 10)	50	5-FU/folic acid/ mitoxantrone, mitomycin C	Median survival 27.4 months

Table 3 **Intrahepatic arterial chemotherapy (randomized trials)**

		Liver response rate (%)		Median survival (months)	
Study	No.	HAI	Syst	HAI	Syst
Kemeny *et al.* (Ref 13)	99	52	20 *P*=0.001	17	12 NS
Hohn *et al.* (Ref 14)	117	42	10 *P*=0.001	17	16 NS
Cheng *et al.* (Ref 15)	50	62	17 *P*=0.003	22	12 NS
Martin *et al.* (Ref 16)	69	48	21 *P*=0.02	13	11 NS
Rougier *et al.* (Ref 17)	163	43	9 *P*=0.001	15	11 *P*=0.02

HAI=hepatic artery infusion; syst=systemic chemotherapy

months (not significant). The apparent absence of survival benefits may be attributable to study design and to the crossover between treatments in several of the studies. An MRC trial is currently comparing systemic 5-FU and folinic acid with intrahepatic high-dose 5-FU and systemic folinic acid.

Catheter-related difficulties still arise. Port sepsis and occlusion can develop early although the median time to occlusion is 9–12 months. Chemical hepatitis and liver failure have been reported but should be rare.

THERMAL ABLATION

Thermal ablation requires introduction of the heat source directly into the tumour and is usually performed percutaneously with image guidance—computed tomography, ultrasound or magnetic resonance singly or in combination. Some procedures have been performed laparoscopically or at open laparotomy.

Laser

It is nearly 10 years since the first reports of the use of laser energy to ablate liver metastases[19–21]. Both NdYAG and solid-state lasers are effective. Either bare tip laser fibres, which act as a point source producing a sphere of necrosis, or diffuser fibres are used[22,23]. Important developments in laser technology include internal cooling of the applicator to prevent charring (which impedes tissue heating) and an increase in power deposition[24].

Radiofrequency

Radiofrequency produces heating by ionic agitation. Initial electrodes were of low power (<50 W) and were not internally cooled. The new systems have cooled tip electrodes and high-power generators (<200W); arrays of electrodes can be activated simultaneously[25,26]. The two electrode designs now in use are a triple cluster (Radionics, Belgium), consisting of three parallel electrodes in triangular configuration with 5 mm between them, and an umbrella design which opens out after introduction (Radiotherapeutics, USA).

Radiofrequency or laser?

From surgical data we know that successful treatment of liver metastases demands resection with a 1 cm margin of normal-appearing tissue. Of the two techniques, laser has the advantage of being magnetic resonance compatible, permitting direct MR monitoring. However, extensive ablation, and in particular ablation of a margin of normal liver, is easier to achieve with radiofrequency[27] (Figure 1), and this advantage is likely to be reflected in rates of recurrence adjacent to areas of thermal ablation. Another development has been the adoption of thermal ablation as an adjunctive technique to hepatic resection or cryoablation[28].

Clinical results

The efficacy of radiofrequency has been validated in a small cohort of patients who subsequently underwent surgical resection: 8 of 9 showed complete ablation[29]. Curley *et al.*

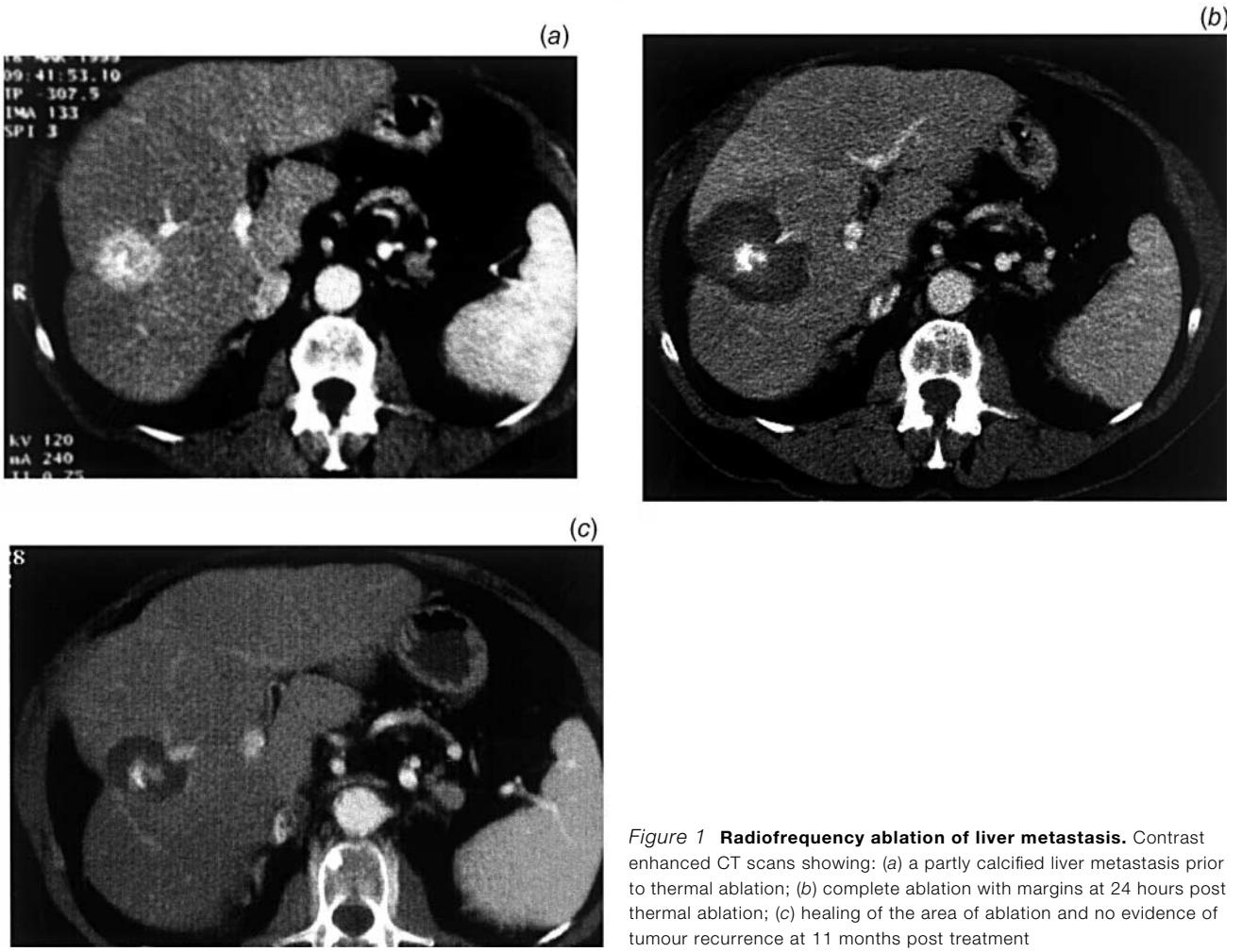

Figure 1 **Radiofrequency ablation of liver metastasis.** Contrast enhanced CT scans showing: (*a*) a partly calcified liver metastasis prior to thermal ablation; (*b*) complete ablation with margins at 24 hours post thermal ablation; (*c*) healing of the area of ablation and no evidence of tumour recurrence at 11 months post treatment

treated 75 patients with metastatic tumours and reported a recurrence rate of 1.8% at a median of 15 months and a complication rate of 2.4%[30]. The few complications include pneumothorax, pleural effusion, subcapsular haematoma and abscess formation. The worst morbidity has been associated with infection of necrotic ablated metastases, for which the main aetiological factor is biliary obstruction or a previous bilio-enteric anastomosis. Vogl *et al.* reported a mean survival of 35 months in a group of 88 patients with colorectal metastases treated with laser[31]. Our historical survival figures with laser showed a median survival of 33 months in patients with three or fewer metastases less than 5 cm in diameter[32]. Improvements in technology have permitted extension of the technique to patients with more widespread disease. More recent results show a median survival of 32 months and three-year survival of 39% in patients with fewer than five metastases smaller than 5 cm and no extrahepatic disease[33]. We currently use cooled electrodes, arrays for larger lesions and a high-power generator.

CONCLUSION

Both laser and radiofrequency are effective for ablation of liver metastases, and advances in both technologies mean that larger volumes of tissue can be ablated[34]. The next step will be controlled trials of thermal ablation versus liver resection in operable metastases and of chemotherapy and ablation versus chemotherapy alone.

REFERENCES

1 Georghegan JG, Scheele J. Treatment of colorectal liver metastases. *Br J Surg* 1999;**86**:158–69

2 Poon MA, O'Connell MJ, Wieand HS, *et al.* Biochemical modulation of fluorouracil with leucovorin: confirmatory evidence of improved therapeutic efficacy in advanced colorectal cancer. *J Clin Oncol* 1999;**9**:1967–71

3 Wadler S, Schwartz EL, Goldman M, *et al.* Fluorouracil and recombinant α-2a-interferon: an active regimen against advanced colorectal carcinoma. *J Clin Oncol* 1989;**7**:1769–75

4 Gayral F, Edouard D, Bedossa P, Dinh A, Paoli D, Larrieu H. Response to hepatic intra-arterial chemotherapy for metastatic colorectal cancer.

Anatomo-pathological evaluation apropos of three cases of secondary hepatic excision. *Gastroenterol Clin Biol* 1987;**11**:88–92

5 Fowler WC, Eisenberg BL, Hoffman JP. Hepatic resection following systemic chemotherapy for metastatic colorectal carcinoma. *J Surg Oncol* 1992;**51**:122–5

6 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

7 Shankar A, Renaut AJ, Ledermann J, Lees W, Gillams A, Taylor I. Neoadjuvant therapy improves resectability rates for colorectal cancer. *Br J Cancer* 1999;**80**:110

8 Maruo H, Kosaka A. Evaluation of cases of metastatic liver tumours resected following intra-arterial infusion chemotherapy. *Gan To Kagaku Tyobo* 1994;**21**:2143–6

9 Elias D, Lasser P, Rougier P, Ducreux M, Bognel C, Roche A. Frequency, technical aspects, results and indications of major hepatectomy after prolonged intra-arterial hepatic chemotherapy for initially unresectable hepatic tumours. *J Am Coll Surg* 1994;**180**:213–19

10 Link KH, Pillasch J, Formentini A, Sunelaitis E, *et al.* Downstaging by regional chemotherapy of non-resectable isolated colorectal liver metastases. *Eur J Surg Oncol* 1999;**25**:381–8

11 Kawasaki S, Makuuchi M, Kakazu T, *et al.* Resection for multiple metastatic tumours after portal embolisation. *Surgery* 1994;**115**:674–7

12 Einsminger WD, Rosowsky A, Raso V, *et al.* A clinical pharmacological evaluation of hepatic arterial infusions of 5-fluor-2-deoxyuridine and 5-fluorouracil. *Cancer Res* 1978;**38**:3784–92

13 Kemeney N, Daly J, Reichman B, Geller N, Botet J, Oderman P. Intrahepatic or systemic infusion or fluorodeoxyuridine in patients with liver metastases from colorectal cancer. *Ann Intern Med* 1987;**107**: 459–65

14 Hohn DC, Stagg RJ, Friedman MA, *et al.* A randomised trial of continuous intravenous versus hepatic intra-arterial floxuridine in patients with colorectal cancer metastatic to the liver: The Northern Californian Oncology Group Trial. *J Clin Oncol* 1989;**7**:1646–54

15 Chang AE, Schneider PD, Sugarbaker PH, *et al.* A prospective randomised trial of regional versus systemic continuous 5-fluorodeoxyuridine chemotherapy in the treatment of colorectal liver metastases. *Ann Surg* 1987;**206**:685–93

16 Martin JK Jr, O'Connell MJ, Wieand HS, *et al.* Intra-arterial floxuridine vs systemic fluorouracil for hepatic metastases from colorectal cancer. A randomised trial. *Arch Surg* 1990;**125**:1022–7

17 Rougier P, Laplanche A, Huguier M, *et al.* Hepatic arterial infusion of floxuridine in patients with liver metastases from colorectal carcinoma: long term results of a prospective randomised trial. *J Clin Oncol* 1992;**10**:1112–18

18 Meta-Analysis Group in Cancer. Reappraisal of hepatic arterial infusion in the treatment of nonresectable liver metastases from colorectal cancer. *J Natl Cancer Inst* 1996;**88**:252–8

19 Masters A, Steger AC, Lees WR, Walksley KM, Bown SG. Interstitial laser hyperthermia: a new approach for treating liver metastases. *Br J Cancer* 1992;**66**:518–22

20 Nolsoe CP, Torp-Pederson S, Burcharth F, *et al.* Interstitial hyperthermia of colorectal liver metastases with a US-guided Nd-YAG laser with a diffuser tip: a pilot clinical study. *Radiology* 1993;**187**:333–7

21 Schroder T, Castren-Persons M, Lehtinen A, Taavitsainen M. Percutaneous interstitial laser hyperthermia in clinical use. *Am Chir Gynecol* 1994;**83**:286–90

22 van Hillergsberg R, van Staveren HJ, Kort WJ, Zondervan PE, Terpstra OT. Interstitial Nd-YAG laser coagulation with a cylindrical diffusing fiber tip in experimental liver metastases. *Lasers Surg Med* 1994;**14**:124–8

23 Amin Z, Donald JJ, Masters A, *et al.* Hepatic metastases: interstitial laser photocoagulation with real-time US monitoring and dynamic CT evaluation of treatment. *Radiology* 1993;**18**:339–47

24 Vogl TJ, Mack MG, Roggan A, *et al.* Internally cooled power laser for MR-guided interstitial laser-induced thermotherapy of liver lesions: initial clinical results. *Radiology* 1998;**209**:381–5

25 Lorentzen T. A cooled needle electrode for radiofrequency tissue ablation: thermodynamic aspects of improved performance compared with conventional needle design. *Acad Radiol* 1996;**3**:556–63

26 Goldberg SN, Gazelle GS, Dawson SL, Rittman WJ, Mueller PR, Rosenthal DI. Tissue ablation with radiofrequency using multiprobe arrays. *Acad Radiol* 1995;**2**:670–4

27 Lees WR, Gillams A. Comparison of the effectiveness of cooled tip radiofrequency and interstitial laser photocoagulation in liver tumour ablation. *Radiology* 1999;**213**:122

28 Bilchik AJ, Rose DM, Allegra DP, Bostick PJ, Hsueh E, Morton DL. Radiofrequency ablation: a minimally invasive technique with multiple applications. *Cancer J Sci Am* 1999;**5**:356–61

29 Scudamore CH, Lee SI, Patterson EJ, *et al.* Radiofrequency ablation followed by resection of malignant liver tumours. *Am J Surg* 1999;**1777**:411–17

30 Curley SA, Izzo F, Delrio P, *et al.* Radiofrequency ablation of unresectable primary and metastatic hepatic malignancies: results in 123 patients. *Ann Surg* 1999;**230**:1–8

31 Vogl TJ, Mack MG, Straub R, Roggan A, Felix R. Magnetic resonance imaging-guided abdominal interventional radiology: laser-induced thermotherapy of liver metastases. *Endoscopy* 1997;**29**:577–8

32 Gillams A, Lees WR. Survival after percutaneous image guided thermal ablation of hepatic metastases from colorectal cancer. *Dis Colon Rectum* 2000;**43**:656–61

33 Gillams A, Lees WR. Image guided ablation of colorectal liver metastases: time for a randomised controlled trial versus hepatic resection. *Radiology* 1999;**213**:212

34 Dodd GD, Soulen MC, Kane RA, *et al.* Minimally invasive treatment of malignant hepatic tumours: at the threshold of a major breakthrough. *Radiographics* 2000;**20**:185–94