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Colorectal liver metastases: is 'no treatment' still best?

Approximately 6000 patients aged less than 70 years die each year in England and Wales from colorectal cancer[1]. Hepatic metastases are found at autopsy in 80% of cases of disseminated colorectal carcinoma[2], and in 20% these appear to be limited to the liver[3,4]. It is probable that in some cases dissemination to other organs is by secondary metastasis from the liver[5]. It is clear that attempts to improve the outlook for patients with colorectal carcinoma must address the problem of hepatic metastases.

In the UK, traditional management of patients with colorectal hepatic metastases emphasizes the maintenance of quality of life. It is usual for no treatment to be given prior to development of symptoms and thereafter for any potentially symptom-relieving treatment, for example systemic 5FU, steroids or analgesics, to be given a trial. This approach is based on the view that since available treatments have virtually no effect on survival and hepatic metastases may be asymptomatic and slow growing[6], it is preferable to avoid subjecting the patient to treatment-induced morbidity for no proven benefit. There is a danger that this view could become self-fulfilling if, as a result, few patients with hepatic metastases are entered into suitably designed trials evaluating the effect of treatments which are potentially beneficial to survival and quality of life.

Experience from a non-randomized personal series[7,8] suggests that resection is the most effective treatment for established hepatic metastases - achieving long-term (>5 year) survival for 20-25% of patients whose metastases are resected. Although only 10% of patients with colorectal hepatic metastases are thought to be suitable for metastasis resection[9], only a minority of the 600 patients who might be suitable each year in England and Wales actually undergo resection[10]. It is to be regretted that there are no randomized trials in the UK assessing the value of hepatic resection.

The majority of patients with colorectal liver metastases cannot be helped by resection. Results of systemic chemotherapy for disseminated colorectal carcinoma are disappointing, with partial response rates of roughly 20%[11-13] and minimal prolongation of survival in responders[14]. Studies administering FUDR (a 5FU analogue which has similar cytotoxic properties) via the hepatic artery[15] indicate that a 10-fold increase in tumour FUDR concentration can be achieved with reduced systemic toxicity, compared to systemic administration. In vitro and clinical studies[16,17] suggest that the cytotoxic effect of 5FU is enhanced by higher tumour concentration and time of exposure, so this approach may be more effective than systemic administration. This is also suggested by experience of adjuvant 5FU liver perfusion via the portal vein at the time of primary tumour resection. Survival - presumably in patients with occult hepatic metastases - is improved over that of prospectively randomized control patients not receiving adjuvant 5FU liver perfusion[18]. Initial experience of continuous hepatic artery perfusion for established hepatic metastases suggested a partial response rate of greater than 50%[19,20] but the drawback was that the continuous hepatic perfusion required for established metastases involved an external catheter and pump which was unpleasant for the patient and prone to complication[21].

The development of a totally implantable pump which is filled every 2 weeks via needle puncture of the overlying skin has reduced pump and catheter-related morbidity to less than 5%[22], and allows the patient to undertake virtually all normal activities. Similar partial response rates (30-88%) to those with the external system have been obtained[23-25], but the absence in these studies of a prospectively randomized, symptomatically-palliated control group has meant that the more crucial questions - does the treatment prolong survival or sustain quality of life - cannot be answered.

Liver perfusion with FUDR is not without complication - in particular, a significant but variable (8-56%) incidence[13,26] of biliary sclerosis which is dose limiting. Nor does it provide a cure - the majority of patients eventually succumb to extrahepatic, particularly pulmonary, metastases[13]. Despite this, the technique has been adopted in the United States where over 8000 pumps have been inserted for colorectal liver metastases, many in patients not included in clinical trials. More recently the technique has been taken up in western Europe.

The uncritical adoption of such an unproven treatment is hardly surprising since there is no remedy for established colorectal liver metastases which is of proven value and many patients will settle

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for anything which might help without waiting for the results of a perfectly designed trial. However, it is irresponsible to advocate potentially expensive treatments for advanced cancer in the absence of a clear appreciation of the size of the benefit[27]. It is the responsibility of those who look after these patients to assess treatments which show promise, so that desperate patients can avoid those which are useless or harmful, and be recommended to try those where there is evidence of some benefit.

Trials of these treatments should have a randomized control group receiving 'conventional' palliation, and should measure quality of life as well as survival. A multicentre trial of this design, has been set up under the auspices of the CRC Clinical Trials Centre (trial tel. number 01-748-5620). The aim is to compare survival and quality of life in patients with unresectable hepatic metastases treated by implanted pump with that in patients receiving conventional palliation. Costs of the trial have been met by a consortium of charities and industry. However, the study also requires support from colorectal surgeons and oncologists who should consider including patients with colorectal liver metastases in this trial. With this support, the question posed in the title can be answered within 5 years.

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