

Are patients with multiple hepatic metastases from colorectal cancer candidates for surgery?

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Results from a retrospective review of data from patients who underwent resection for colorectal liver metastases indicate that partial hepatectomy for four or more hepatic colorectal cancer metastases is no longer contraindicated and is associated with a five-year survival rate of 28–51%.

Partial hepatectomy is the only therapy associated with long-term survival in patients with resectable hepatic colorectal cancer metastases, and is the therapy of choice for these individuals. Although many factors have been shown to adversely affect outcome after partial hepatectomy, most do not preclude long-term survival. Historically, the presence of four or more metastases has been a contraindication to hepatectomy because of dismal five-year survival prospects. Publications condemning hepatectomy for patients with four or more metastases must be interpreted cautiously, however, since they are from an era of ineffective chemotherapy, poor imaging and poor staging.

In accordance with other recently published papers,^{1–3} the report by Malik et

al. (see opposite) has shown that, in well-selected patients, long-term survival is possible after hepatectomy for four or more metastases. The other papers are all retrospective reviews and reflect the selection bias of the treating physicians, who are able to choose for surgery the patients most likely to do well. Nonetheless, with five-year actuarial survival rates ranging from 28% to 51%,^{1–3} surgery accomplishes an outcome that is probably not possible with chemotherapy alone. Malik et al. specifically analysed the number of tumours as a prognostic factor. Their major finding was that the presence of eight or more metastases was the only independent factor associated with poor survival. In fact, patients with four to seven metastases did no worse than those with fewer than four metastases. Patients

with more than eight metastases had a median survival time of 21 months, but a five-year survival rate of 24%.

The era of four or more metastases being a contraindication to hepatectomy for metastatic colorectal cancer is over. Enough series have now shown, in patients with multiple metastases, long-term survival rates that cannot be attributed merely to selection bias. Most importantly, however, we have to interpret the results of these series thoughtfully and honestly, assessing what we are accomplishing with surgery. The issues of disease-free survival and of 'cure' after resection of multiple metastases are raised by these findings. Every series assessing resection for four or more metastases has shown at least an 80% recurrence rate on the basis of incomplete long-term

follow-up.¹⁻³ Malik et al. reported an estimated five-year disease-free survival rate of 20% on the basis of a median follow-up of less than three years. My sense is that almost all the patients in this study will have recurrence of disease that would be observed if they were followed long enough, but only actual statistics after five years of follow-up will be able to definitively demonstrate this. Hepatectomy, therefore, seems to provide a chance of long-term survival, but rarely completely eliminates disease. We are probably not

'curing' patients with multiple liver metastases but, rather, prolonging survival by resetting their cancer timeline, altering disease patterns, or both. It is likely that chemotherapy, repeat surgery and ablation are also contributing considerably to long-term survival. Lastly, these resection outcomes have all been reported from tertiary referral hospitals with specialty hepatobiliary units, and the importance of evaluation and treatment at a specialty centre should be stressed.

It is an exciting time in which to treat

metastatic colorectal cancer. Modern surgery and chemotherapy provide us with effective tools with which to treat a population of patients whose prognosis, until recently, was felt to be hopeless. We must now study novel combinations of surgery and chemotherapy for patients with extensive disease, and Malik et al. have provided us with more stimulating data to encourage such trials.

Details of the references cited in this article can be accessed at www.cancerworld.org/magazine

Synopsis

HZ Malik, ZZR Hamady, R Adair et al. (2007) **Prognostic influence of multiple hepatic metastases from colorectal cancer.** *Eur J Surg Oncol* 33:468–473

Background. The method of management of patients with multiple liver metastases is controversial.

Objective. To review 10 years of experience gained in a tertiary referral hepatobiliary unit in managing multiple liver metastases from colorectal cancer.

Design and intervention. This was a retrospective review of a prospectively collected data set from patients who underwent resection for colorectal liver metastases at a single specialist centre in the UK from 1993 to 2003. No ablative therapy was performed. To be accepted for treatment, patients were required to be fit for major surgery, and lack disseminated or nonresectable extrahepatic disease according to CT and MRI scans. The extent of resection performed was decided on the basis of the location and number of metastases, because underlying chronic hepatic disease was not usually present. Patients were permitted adjuvant therapy with fluorouracil and calcium folinate, unless they had received adjuvant therapy within the year previous to surgery. Patients received a minimum of two years' follow-up at specialist clinics (range 2–12 years; median 33 months for survivors).

Outcome measures. The endpoints of the trial were overall and disease-free survival, morbidity and mortality, and length of postoperative hospital stay.

Results. In all, 484 patients were included in the analysis (mean age 62 years; range 23–84 years), and 225 had synchronous disease. The number of liver metastases per patient ranged from 1 to 21 (median 2). Multiple metastases (≥ 4) were present in 136 patients, of whom 36 had numerous metastases (≥ 8). Individual metastatic deposits ranged in size from 3 mm to 200 mm (median 40 mm). Complete resection was achieved in 67% of patients. Postoperative hospital stay ranged from 3 days to 139 days (median 8 days). The in-hospital mortality rate was 3%; all the deaths were in patients who had undergone major resection. There was a postoperative morbidity rate of 26%. For the whole group, five-year and 10-year survival rates were 41.7% and 28.6%, respectively. Median survival was 50 months for patients with fewer than four metastases, but was 32 months for patients with multiple metastases ($P=0.0072$). Survival differences between patients with fewer than four metastases and those with multiple metastases were not significant. Patients with multiple metastases had poorer disease-free survival than those with fewer than four metastases ($P=0.0142$). Patients with numerous metastases had the worst survival outcome (five-year survival rate 24.2%; median survival 21 months, 95% CI 15–27 months; $P=0.0245$ for ≥ 8 tumours in comparison with 4–7 tumours). On multivariate analysis, only the presence of numerous (≥ 8) metastases predicted for poorer overall ($P=0.047$) and disease-free ($P=0.015$) survival. There was also an association between increasing number of metastases and worsening intrahepatic recurrence, with 74% of patients with numerous metastases having intrahepatic disease ($P<0.001$ vs both patients with <4 metastases and those with 4–7 metastases).

Conclusion. Significant numbers of patients who receive surgery for multiple metastases survive for five years or longer; therefore, resection is recommended for such patients.

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