

Colorectal cancer with synchronous liver metastases

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At the time of diagnosis, 15–20 per cent of patients with colorectal cancer have synchronous liver metastases. Synchronous metastases may confer a poorer prognosis than metachronous metastases but this is uncertain¹. In any event, effective treatment requires an overall strategy that addresses both the primary and the metastatic disease, paying attention to optimal timing between surgical and medical interventions. Modern chemotherapy and stents for sub-occlusive tumours add further complexity. Strategy is generally influenced by two criteria: the symptom pattern of the primary tumour and the potential resectability of the liver metastases. Certain clinical presentations are clear indications for immediate surgical treatment of the primary tumour – notably occlusion, perforation, bleeding and locally advanced disease. Patients are usually elderly and ill, and the increased operative risks render a major one-stage procedure (resection of both primary and hepatic lesions) unwise. This contrasts with an asymptomatic primary tumour when management depends on the resectability of the liver metastases.

In the asymptomatic setting, resection of synchronous liver metastases along with the primary lesion is warranted simply because this is the sole strategy with curative potential – a 5-year survival of 25 to 38 per cent^{2–4}. But should patients be treated initially by operation or by neoadjuvant chemotherapy? No randomized trial is yet available to answer this question directly, but a retrospective study examining outcomes in patients with

more than four liver metastases suggests that neoadjuvant chemotherapy plus surgery offers a better survival than immediate operation⁵. A similar trend occurs in the LiverMetSurvey analysis of an international registry of patients operated for hepatic colorectal metastases. This shows that, while neoadjuvant chemotherapy does not improve outcome after resection of a single liver metastasis, it is associated with improved survival when more than four metastases are removed. While it seems logical that multinodular disease is likely to respond well to neoadjuvant chemotherapy because of a greater probability of undetected small metastases, this hypothesis deserves further scrutiny. In current practice, immediate surgery is the standard treatment for patients with few metastases, but neoadjuvant chemotherapy followed by surgery may be appropriate for those with multinodular disease.

Combining hepatic with colorectal resection has the appeal of a single operation, which may be beneficial in terms of quality of life and cost. Contraindications are based on the risk of morbidity and mortality, and include emergency indication for operation on the primary tumour, a locally advanced colorectal tumour, and the need for a major hepatectomy (involving three or more segments). Otherwise, combined resections seem appropriate^{2–4}. An alternative is colorectal resection with hepatic resection delayed for 2–3 months, with chemotherapy in between. It has been argued that combined resection may decrease the risk of metastatic spread by avoiding

the repetitive immunosuppression of major surgery and by facilitating the efficacy of chemotherapy⁶. Delayed hepatic resection, however, is the preferred approach of those who believe that a period of observation allows better selection of those likely to benefit from liver surgery⁷. The choice may depend on the experience of the surgical team.

Any decision must also consider the extent of the hepatectomy. Although there is no increase in operative mortality for one-stage procedures involving limited hepatectomies (one or two segments), a large study suggests this may not be so when a hepatectomy of three or more segments is required¹. Consistent with these data, most initial work with one-stage procedures has restricted this strategy to patients with right colon cancer and a limited number of liver metastases^{2–4}. Unfortunately, such restriction allows less than half of the eligible patients with synchronous metastases to be treated with a single operation. Such a narrow policy has recently been challenged – experienced groups are now reporting similar mortalities with one-stage and two-stage strategies that include major hepatectomies⁸. These reports also indicate that the one-stage approach has the benefit of a shorter hospital stay⁹.

Long-term survival must also be considered. Most advocates of a one-stage approach report survival results similar to those obtained with delayed hepatectomy^{2,3}. However, as one-stage procedures have usually been offered only to patients with limited metastatic disease, true equivalency

of survival is moot, and others have reported worse survival rates for one-stage procedures⁷. It seems that, although experienced teams can perform one-stage procedures with morbidity and mortality as low as those for delayed operations, the advantage of the one-stage approach is far from proven.

Turning now to unresectable liver metastases, should operation or chemotherapy be offered first? Conventional wisdom has been to resect the primary tumour and then employ chemotherapy as palliation. The rationale is to avoid the risk of local complications, such as pain, occlusion, bleeding and perforation. This attitude, however, may be challenged for patients without gastrointestinal symptoms for whom outcome is related more to the progression of hepatic tumour burden than to local complications from the primary lesion. Starting with medical therapy avoids the progression of a disseminated disease during recovery from an operation directed solely at a local problem. Endoscopic deployment of a trans-tumoural stent to prevent occlusion is a useful non-surgical treatment in this context. Another factor favouring the chemotherapy-first approach is that the new anti-neoplastic agents (oxaliplatin and irinotecan) induce response rates in over 50 per cent, with median survival times of over 20 months. Indeed, this has been amplified by biotherapies (cetuximab and bevacizumab), which may increase the response rate to over 80 per cent. Accordingly, the strategy for patients with unresectable liver metastases has become less 'surgical'.

Retrospective studies employing initial chemotherapy suggest that only between 9 and 22 per cent of patients develop progression of colorectal disease that requires either an operation or stenting. Median survival appears

similar to that expected with conventional treatment but with a reduction in hospital stay, morbidity and mortality^{10,11}. In addition, patients with initially unresectable metastases may experience tumour downsizing with chemotherapy to such an extent that they become suitable for resection of both primary and metastases¹². Although initial surgery does not deny this last advantage, early initiation of chemotherapy may be critical in converting patients with advanced metastatic disease to a resectable situation. It is possible to reverse unresectability of hepatic metastases in about 15 per cent of patients, allowing 'rescue' liver surgery with a survival of 33 per cent at 5 years¹². Furthermore, downsizing also applies to the primary tumour; for rectal primaries this may facilitate sphincter-saving procedures.

Should surgery of the primary lesion take precedence over resection of the metastases? For patients who respond to systemic therapy, the conventional view has been to resect first the primary and then the metastases. This has recently been challenged by Mentha *et al.*, who advocate resection of advanced synchronous liver metastases before the primary¹³. The rationale is that this allows better selection of those patients who will benefit from surgery (those responding to chemotherapy), focuses on the more important tumour site, and may reduce the disease recurrence in the liver and at distant sites that might occur while treating the primary tumor. These authors found that resectability and survival rate (median of 46 months) were better than expected from published outcomes for patients with disease of similar severity. Further experience with this approach should determine its role in the treatment of synchronous disease.

The management of synchronous liver metastases is changing. While the strategy for resectable lesions is something of an open question, for irresectable lesions there is a trend to initial treatment with systemic chemotherapy. Still, there are as yet no clear data on which strict treatment recommendations can be made. Controlled trials are needed to elucidate the best approach for each clinical scenario but, given that there are few ongoing studies, evidence-based answers to the clinical questions raised in this article seem unlikely to be available any time soon.

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