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Review

Liver metastases from colorectal cancer: lessons from past and present clinical studies

I. TAYLOR

Department of Surgery, UCL Medical School, Charles Bell House, 67–73 Riding House Street, London W1P 7LP, UK
Correspondence to: Professor I. Taylor

In patients with primary colorectal cancer the development of liver metastases has traditionally been equated with imminent demise. This metastatic event is remarkably common; indeed, liver metastases are present in some 25 per cent of patients at the time of initial colorectal resection and over 50 per cent of patients will eventually develop them. Some 90 per cent of patients who die from colorectal cancer have liver metastases. There are few cancers in which the metastatic pattern has such a high degree of predictability. Information from past and present clinical studies should, therefore, provide a basis for logical approaches to prevention and treatment.

More than 50 per cent of patients with primary colorectal cancer develop liver metastases[1]. Spread of malignant cells from primary colorectal cancer to the liver occurs via portal venous drainage. Subsequent growth and nutrition is dependent upon an arterial blood supply[2]. The mechanism by which cancer cells reach the liver is complicated. Initially they must detach themselves from the primary colorectal cancer, migrate through the basement membranes and extracellular matrix, travel unhindered within the portal venous circulation, reach the liver in an active and unharmed state, and reattach themselves to liver parenchyma[3,4]. If they are to grow and develop they must take on the characteristics of a micrometastasis and hence stimulate the development of a neovascular blood supply (angiogenesis)[5]. This is a sophisticated process and much can go wrong. It is inconceivable that every malignant cell entering the portal circulation will successfully develop into a micrometastasis. Indeed, in animal models utilizing portal vein injection of malignant cells, the liver is demonstrated to be a very effective 'trapper' of malignant cells as 'the organ of first encounter' but is comparatively inhospitable to subsequent metastatic development[6,7]. Animal liver metastases will only develop if more than 10^6 malignant cells are injected into the portal venous system. Once trapped, however, the malignant cells fail to recirculate and subsequent metastases (e.g. to the lungs) only develop from liver metastases[8]. In other words, it is likely that extrahepatic metastases arise from liver metastases. This pattern is recognized in the clinical situation where extrahepatic metastases are rare in the absence of synchronous liver metastases. In animal models any form of trauma to the liver, either before or soon after tumour cell injection, increases the incidence of liver metastasis both at the site of injury and in lobes distant from the site of local trauma[9].

There is much evidence to suggest that in most, if not all, patients with primary colorectal cancer, micrometastases exist in the liver in a dormant state[10,11]. It is probable that only a very small proportion of micrometastases develop into clinically overt disease; although trapped in the liver they are presumably prevented from growing owing to failure of mechanisms that determine metastatic growth. In this regard it is the development of a neovascular circulation that appears to be of major importance[12]. The change from portal venous to hepatic arterial perfusion is responsible for changes in hepatic haemodynamics which are becoming increasingly recognized. Blood vessels in established liver metastases have abnormalities in neuropeptide innervation and an incomplete, or indeed absent, smooth muscle coat[13]. This explains why the introduction of vasoconstrictor drugs, such as angiotensin II, into the hepatic artery reduces blood flow to normal liver by vasoconstriction and so diverts flow to tumours whose blood vessels are unable to constrict[14]. Recent studies have also suggested that negative regulators of angiogenesis, possibly arising from the primary tumour itself, determine whether metastases have the ability to grow[5].

Clinical studies have also revealed a change in distribution between arterial and portal venous flow, recognized by hepatic flow scintigraphy with sulphur colloid. A hepatic perfusion index is derived which correlates with the subsequent development of liver metastases[15]. More recently duplex ultrasonography has been used to measure hepatic arterial and portal venous flow in patients with colorectal cancer[16]. The Doppler perfusion index (DPI) is higher in patients with liver metastases present at the time of colorectal resection or in those who develop them during the following year[17,18]. The sensitivity of DPI for liver metastases is 100 per cent with a predictive accuracy of 86 per cent, providing further evidence for occult liver metastases influencing long-term prognosis[18]. Studies using other complex hepatic imaging techniques, such as sequential computed tomography[19] and technetium-99m macroaggregated albumin injections[20], have provided additional confirmatory evidence for the existence and prognostic significance of occult liver metastases.

Attempts have been made to use simpler clinical parameters to predict which patients will subsequently develop liver metastases. For example, in one prospective study patients without detectable colorectal liver metastases (either clinically or by imaging) were followed for up to 10 years and regular scanning of the liver

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performed. A clinical prognostic index was derived to determine which factors correlated with the subsequent development of liver metastases. The most sensitive parameters were Dukes C disease and a change in serum alkaline phosphatase at the time of initial colorectal resection[21].

Patients with Dukes C disease have metastases in adjacent lymph nodes and, therefore, have clones of malignant cells with the ability to spread via the lymphatic system into adjacent lymph nodes and grow. It would seem reasonable that these same tumours have malignant cells which are more likely to enter and grow in the liver and develop into overt metastases. Lymph node metastases may well represent a marker of malignant potential indicating a greater likelihood for development of overt hepatic metastases.

Hypothesis

The following hypothesis is proposed. In all patients with primary colorectal cancer malignant cells enter the portal venous system and are trapped within the liver. Although the liver is an effective trapper, it is relatively refractory to metastatic growth; however, some micrometastases eventually develop into overt metastases. Although multiple factors determine which malignant cells grow, the development of a neovasculature is important. However, it is likely that specific characteristics of the malignant cells themselves will determine their propensity to develop into metastases. If it were possible to recognize which patients possess potentially malignant micrometastases, this would influence the decision with regard to adjuvant therapy. If this hypothesis is valid for determining a therapeutic strategy then confirmatory evidence should be available from existing clinical studies.

Evidence from clinical studies

Adjuvant chemotherapy

Let us first consider the available data from randomized prospective trials on adjuvant systemic chemotherapy in patients with primary colorectal cancer. Since the liver is considered to contain occult metastases that are more likely to become overt in patients with Dukes C disease than in those with Dukes B lesions, any benefits for systemic chemotherapy following 'curative' resection of colorectal cancer should be greater for Dukes C disease, with minimum advantage for Dukes B disease. In addition, any survival benefit should correspond with a reduced incidence of metachronous liver metastases. Is this so? Undoubtedly yes.

In 1988[22] a meta-analysis of randomized adjuvant studies using systemic 5-fluorouracil (5-FU) for up to 1 year demonstrated a marginal overall reduction in the odds ratio of death of approximately 17 per cent ($P = 0{\cdot}03$) and an absolute 5-year survival benefit of 3·4 (95 per cent c.i. 1·2–8) per cent. However, in recent years there have been more impressive reports. These have resulted from combination chemotherapy (5-FU, vincristine and lomustine methyl CCNU)[23], by combining 5-FU with immunomodulatory drugs such as levamisole[24] or by biomodulating 5-FU with leucovorin[25]. In the Intergroup study, for example, 352 patients with Dukes B_2 and 971 patients with Dukes C disease were randomized to surgery alone or surgery with 5-FU and levamisole for 1 year[24]. In patients with Dukes C disease there was a significant reduction of 41 per cent in the risk of cancer recurrence (chiefly within the liver) and a corresponding reduction in mortality of 33 per cent. This initial improvement corresponded with an absolute survival benefit of approximately 5 per cent which was maintained at 5 years. The survival benefit for patients with B_2 disease did not reach conventional levels of significance and there was no reduction in the incidence of liver metastases.

Three cooperative groups evaluated 5-FU and leucovorin individually but because their protocols were so similar their data was pooled to allow a combined analysis[26]. Patients with Dukes B and C disease were randomized to surgery alone or surgery followed by 5-FU and leucovorin administered for 5 days every 28 days for 6 months. The crude rate of recurrence in the liver was twice as high in the control group compared with the treatment group. Overall, the chemotherapy group had significantly lower rates of an adverse event (35 per cent lower) and death (22 per cent lower) than the control group. However, the 3-year overall survival rate for patients with Dukes B disease was not significantly different between the control and chemotherapy groups. There was a statistically significant improvement in overall survival only in patients with Dukes C lesions (hazard ratio for overall survival 0·7 (95 per cent c.i. 0·53–0·92)). Accordingly there is now considerable evidence of a survival benefit for systemic chemotherapy in patients with Dukes C disease, but considerable uncertainty of benefit for those with Dukes B lesions. This survival improvement correlates with a similar reduction in the incidence of liver relapse in the first 2–3 years following colorectal resection.

If hepatic micrometastases exist, it could be argued that the incidence of overt liver metastases might be reduced by selectively delivering high-dose chemotherapy to the liver through the portal venous system. Any effect on inhibition of occult micrometastases should be associated with an improvement in survival. Any benefit, however, would more likely be demonstrated in patients with Dukes C disease.

This hypothesis has been tested in ten published studies of adjuvant cytotoxic portal vein infusion in primary colorectal cancer. Portal vein cytotoxic infusion is usually commenced at operation or in the immediate postoperative period, and given continuously for the first 7 days after surgery. This short perioperative therapy is in marked contrast to long-term chemotherapy when 5-FU is given systemically for 6 months; toxicity is reduced as, indeed, is cost. An original hypothesis-generating trial demonstrated a significant reduction in the incidence of liver metastases with survival benefit[27]. Nine subsequent trials have demonstrated improvement to a lesser extent. For example, a Swiss group[28] has recently reported a 25 per cent incidence of relapse confined to the liver in the control arm compared with 12 per cent in the portal vein infusion group in node-positive patients. Overall, portal vein infusion reduced the risk of recurrence by 21 per cent (hazard ratio 0·9 (95 per cent c.i. 0·62–1·00); $P = 0{\cdot}051$) and the risk of death by 26 per cent (0·74 (95 per cent c.i. 0·57–0·97); $P = 0{\cdot}026$). The major risk reduction was in patients with Dukes C disease as, indeed, was the overall absolute survival improvement.

A meta-analysis of all ten published trials of portal vein cytotoxic infusion, including a total of 3499 patients, has provided confirmatory evidence[29]. Overall, portal vein infusion was associated with a mean(s.d.) 18(6) per cent

reduction in the annual risk of death from any cause with a 20(6) per cent reduction in death from colorectal cancer. Interestingly in this meta-analysis, overall survival diverged significantly at 2 years and at 5 years was 64 per cent in the portal vein infusion group *versus* 59 per cent in the surgery-only group. The benefit was significantly greater for patients with Dukes C disease (54·2 per cent *versus* 46·6 per cent) than for those with Dukes B lesions (76·3 per cent *versus* 72·1 per cent).

It is well known that over 90 per cent of patients developing colorectal liver metastases do so within 2 years of primary surgery. The observation that significant benefits from portal vein infusion occur after 2 years is consistent with an effect on the natural history of occult liver metastases. A diminution in their rate of growth and development into overt metastases would have overall survival benefits only after approximately 2 years.

The published results of both adjuvant systemic chemotherapy for 6–12 months and portal vein infusion for 1 week are roughly comparable, with an approximate 5 per cent improvement in absolute survival at 3 years. The major benefits from both treatments occur in patients with lymph node-positive disease. This is entirely consistent with the hypothesis that chemotherapy inhibits occult hepatic micrometastases rather than producing systemic effects outside the liver. Subsequent relapse in extrahepatic organs is also inhibited, since extrahepatic metastases spread from liver metastases.

There is now sufficient evidence to recommend that patients with Dukes C disease who are otherwise sufficiently fit should receive adjuvant cytotoxic chemotherapy. There is still significant uncertainty, however, with regard to the benefits for patients with Dukes B lesions. Randomized trials in patients with Dukes B disease should therefore include a surgery-only arm.

Liver resection

Additional support for the hypothesis can be found by a critique of the reported data on liver resection for localized metastatic disease. Conceptually it seems illogical that resection of solitary or localized metastatic disease within the liver should have a favourable effect on survival. However, in the absence of prospective randomized trials, carefully documented prospective studies and clinical audit report median 3- and 5-year survival rates of 40 per cent and 25 per cent respectively[30]. These survival data following resection of liver metastases are similar to what would be expected in patients who undergo primary colorectal resection of Dukes C disease. It would appear that resection of localized liver metastases downstages Dukes 'D' to Dukes C disease.

As mentioned previously, the majority of micrometastases that exist within the liver remain dormant and presumably never develop into overt metastatic disease. Metachronous overt liver metastases become clinically apparent within 2 years of colorectal resection. Other metastases within the liver should have appeared by that time and the fact that they are still dormant indicates that they are unlikely to develop into overt liver metastases. Interestingly, this is supported by the observation that resection of metachronous metastases is associated with improved survival compared with resection of synchronous metastases. This suggests that patients with synchronous metastases have more aggressive tumours, which have grown at the same rate as the primary tumour and which are less likely to benefit from resection than a metachronous tumour of slower growth rate. This is supported by the reported independent prognostic variables that influence 3- and 5-year survival rates following liver resection. These are the degree of differentiation of the primary tumour, whether the adjacent lymph nodes are involved, and whether the tumour is synchronous or metachronous[30,31].

There is, therefore, an argument for adjuvant systemic chemotherapy following liver resection, particularly if one considers that the disease may be downstaged by surgery from a Dukes 'D' to a Dukes C equivalent which, as mentioned previously, is an indication for adjuvant systemic chemotherapy. In addition, approximately 50 per cent of patients who relapse after liver surgery do so with extrahepatic metastases. A randomized trial comparing liver resection with liver resection and systemic chemotherapy is being undertaken under the auspices of the European Organisation for Research and Treatment of Cancer (EORTC).

Hepatic arterial infusion

There is additional information available from studies utilizing hepatic arterial cytotoxic infusion for established multiple liver metastases. Patients with multiple metastases unsuitable for resection might be eligible for treatment by means of intrahepatic arterial chemotherapy. Numerous studies have shown that this approach achieves a higher locoregional control rate than systemic chemotherapy, although few studies have demonstrated an overall improvement in survival[32]. This is to be expected. Even if multiple liver metastases respond to high-dose locoregional chemotherapy, this is unlikely to affect the development of extrahepatic metastases, if such lesions develop from liver metastases. Once again, the characteristics of the primary tumour and the length of time from resection of the primary lesion to the development of liver metastases appear to determine the response rate[33,34]. The combination of locoregional cytotoxic chemotherapy with systemic chemotherapy is more likely to yield favourable survival rates and preliminary studies support this[35].

Conclusions

Liver metastases represent a major determinant of outcome following apparently successful curative colorectal resection. The majority of patients have hepatic micrometastases which remain dormant, but undoubtedly a proportion develop the necessary mechanisms for growth and stimulation of a neovascular circulation.

Patients with Dukes C disease have a greater propensity for development of liver metastases and it is this group of patients who benefit most from adjuvant systemic chemotherapy. There are few reasons for not offering patients with Dukes C disease (provided that they are fit enough) adjuvant cytotoxic chemotherapy. Presently available data suggest that the benefits from 6 months of treatment with 5-FU and levamisole or folinic acid are equivalent to those of a 1-week portal vein infusion with 5-FU, although the combination of the two could be additive. Patients with Dukes C disease should be considered for randomization into the QUASAR ('quick and simple and reliable') study in which high- and low-dose 5-FU and folinic acid are being compared with high- and low-dose 5-FU and levamisole. This trial is accruing

patients at a rapid rate. The situation in patients with Dukes B lesions is less certain since they are less likely to have hepatic micrometastases and are thus less likely to benefit. Accordingly, such patients should be offered the opportunity of randomization into a trial such as the QUASAR study, with a surgery-only arm. Because of the natural history of hepatic micrometastases and because the majority of overt metastases develop within 2 years, such adjuvant trials are unlikely to demonstrate significant benefits in overall survival within 2 years of surgery.

In patients with localized colorectal liver metastases, liver resection probably downstages Dukes 'D' to Dukes C disease and so such patients should be considered for adjuvant systemic chemotherapy by randomization into the ongoing EORTC study of liver resection alone *versus* liver resection plus systemic chemotherapy. In patients with multiple liver metastases locoregional chemotherapy has a higher response rate than systemic chemotherapy. However, there is evidence that this should be combined with systemic treatment. A randomized trial, under the auspices of the Medical Research Council in the UK, is comparing locoregional chemotherapy with systemic chemotherapy and appropriate patients should be considered for inclusion within this study. Data from adjuvant trials, as well as studies involving the metastatic process and haemodynamic changes, should be utilized when determining a logical strategy for treating patients with resected colorectal cancer.

It is recognized that all these strategies are of little value if the primary cancer surgery is not performed to the highest standard. Surgeons are aware of their responsibility in this regard to ensure a low locoregional recurrence rate. Only when this is satisfactorily achieved will the benefits of any additional therapy be apparent.

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Announcement

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Applications should be sent to Mr J. R. C. Sainsbury, Company Secretary, The British Journal of Surgery Society, Department of Surgery, The Royal Infirmary, Lindley, Huddersfield HD3 3EA, UK by 28 June 1996.

J. R. C. Sainsbury