Colorectal Liver Metastases—Enhancing Outcomes Through Combination Treatments

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Abstract

Colorectal liver metastases are common and should be considered for treatment in a multidisciplinary setting. Surgery is the treatment of choice providing the metastases are resectable. In recent years the benefit of neoadjuvant chemotherapy has been established to downstage metastases and render them amenable to surgical excision. This aspect, as well as the role of adjuvant chemotherapy, is discussed and critically appraised in this article.

Keywords

Colorectal liver metastases, neoadjuvant treatment, adjuvant treatment

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Colorectal liver metastases (CRLMs) are common and can either present at the time of initial colorectal cancer diagnosis (synchronous) or develop later (metachronous). There has been increasing interest in the treatment of CRLMs in recent years due to the development of new therapies and improving prognoses. A major factor in the treatment of CRLMs is the need for detailed discussion of individual patients in a multidisciplinary environment involving specialists with a wide range of interests. Accordingly, a treatment plan and follow-up can be devised at an early stage. The importance of this approach cannot be overemphasized.

Surgery

Surgery is the most important treatment modality for patients with CRLMs. Appropriate surgery in selected patients will result in long-term survival of up to 40%;[1,2] this percentage has increased over the last two decades. There have been developments in surgical technique, including portal vein embolization and safer liver division and resection, as well as improvements in post-operative management. As a result, resections are now more extensive and, due to improving expertise, are associated with reduced post-operative morbidity and mortality. A general principle is to resect all macroscopic disease, aiming for a potentially curative resection. In order to achieve this, it may be necessary to combine surgical excision with ablation, e.g. radiofrequency ablation, intra-operatively or percutaneously, in the post-operative period. Often this avoids an unacceptably dangerous major resection; for example, an extended right hemi-hepatectomy can be combined with radiofrequency ablation of smaller lesions on the left side of the liver. However, it should be noted that initially only 15–20% of patients are suitable for surgical resection.[3] As a result, an attempt to increase the resectability rate with additional treatments has been advocated.

Neoadjuvant Chemotherapy

There is increasing interest in the role of pre-operative or neoadjuvant chemotherapy to downsize liver metastases in an attempt to achieve resection of previously unresectable CRLMs. Accordingly, such treatment increases the proportion of patients able to achieve long-term survival. Recent studies have described resection rates of up to 20% in patients with initially unresectable liver metastases, with five-year survival rates in these patients approaching 50% (see *Table 1*).[4–7] However, it should be emphasized that in order to achieve optimum results, careful selection is essential. Recent studies have demonstrated a strong correlation between response rate to chemotherapy and subsequent resection rate, which in selected patients may be 20–50% compared with 1–20% in non-selected patients. As shown in *Table 1*, various chemotherapy regimes have been advocated and several have been subjected to prospective clinical trials. The overall conclusions are, in summary: folinic acid, fluorouracil, and irinotecan (FOLFIRI) and 5-fluorouracil (5-FU), leucovorin, and oxaliplatin (FOLFOX) are equally effective (response rates of 56 and 54%, respectively[8]), and 5-FU, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) is superior to FOLFIRI[9] (response rates of 60 and 34%, respectively, and radical resection rates of 36 and 12%, respectively). Other studies have demonstrated response rates between 8 and 41% following administration of oxaliplatin- or irinotecan-based regimes; again, in these terms selection may be crucial. It would appear that three-drug combinations have a higher response rate and a higher resection rate, without any significant impact on either toxicity or surgical safety. These

studies are extremely important and demand our attention. Patients with apparently unresectable disease who are otherwise fit should be considered for neoadjuvant therapy in a multidisciplinary setting. The role of biological agents in this situation has also been extensively investigated. The two agents studied are bevacizumab (vascular endothelial growth factor [VEGF] monoclonal antibody) and cetuximab (epidermal growth factor receptor [EGFR] monoclonal antibody). Bevacizumab has been shown to improve the objective response rate and prolong survival: in one study, the response rate was 45–70% when combined with 5-FU, leucovorin, and irinotecan.[10] Cetuximab has been reported to result in resection rates of 19–30% in unselected patients.[11] Patients refractory to conventional chemotherapy can be switched to cetuximab-based regimes, hence increasing the total proportion of initially unresectable patients to approximately 20%. It is suggested that the resectability rate should be an end-point in randomized trials. There is a concern that these agents will result in an increase in post-operative morbidity and possible mortality. Studies have demonstrated that post-operative morbidity is correlated with the number of cycles of chemotherapy and not necessarily the type of chemotherapy. There are two major concerns concerning this matter: steatohepatitis (recognized particularly in patients with a high body mass index [BMI]) and vascular changes resulting in increased post-operative hemorrhage. However, there is controversy related to these complications and several studies have failed to demonstrate any increased risk for morbidity or mortality.[12] A few reports on the role of hepatic arterial infusion chemotherapy as neoadjuvant treatment have been described. Using these techniques, resection rates between 6 and 47% are reported.[13] Nevertheless, few centers utilize this technique in preference to systemic chemotherapy.

Peri- and Post-operative Adjuvant Chemotherapy

Controversies exist relating to the role of adjuvant chemotherapy following curative surgical resection. The European Organization for Research and Treatment of Cancer (EORTC) trial 40983 randomized 364 patients into a two-arm study. Patients received either FOLFOX-4 followed by surgery and post-operative FOLFOX-4 over three months or surgery alone. There was some improvement in disease-free survival with peri-operative chemotherapy. In patients in whom the metastases were subsequently resected, progression-free survival in resected patients was 42.4 versus 33.2% in unresected patients (hazard ratio [HR] 0.73; p=0.025), indicating a favorable response.[13] In this study, there were no major differences in post-operative complications. A new study is being devised in which cetuximab is added to the chemotherapy regime alone or with bevacizumab. These results are awaited with interest.

Radiofrequency Ablation

There is increasing interest in the role of radiofrequency ablation of liver metastases. Numerous reports have suggested improvements in survival in patients with unresectable disease. Five-year survival rates between 23 and 58% and even 10-year survival rates of up to 25% have been reported.[14,15]

Table 1: Resection Rates Following Neoadjuvant Chemotherapy

	Regimen	Response Rate (%)	Resection Rate (%)	Median Survival (months)
Wein[4]	5-FU/FA	42	17	NR
Giacchetti[5]	5-FU/FA + oxal.	59	51	24
Alberts[6]	Folfox-4	60	40	26
Masi[7]	5-FU/FA/oxal./CPT	72	26	26

5-FU = 5-fluorouracil; CPT = camptothecin; FA = folinic acid; FOLFOX = 5-FU, leucovorin, and oxaliplatin; NR = not reported; oxal. = oxaliplatin.

This is a relatively minimally invasive technique associated with a low incidence of toxicity. Radiofrequency ablation can be used to extend the role of surgery by enabling a hemi-hepatectomy to be performed with radiofrequency ablation of lesions in the adjacent lobe carried out either percutaneously or intra-operatively. Other studies have even suggested that patients with resectable disease can be treated with radiofrequency ablation, thus avoiding the problems of major surgery.[16–18] In the same way that surgery is combined with chemotherapy, so radiofrequency ablation should be combined with appropriate chemotherapy. There is no doubt that such therapy must be discussed in a multidisciplinary meeting, and careful selection is essential to achieve good results.

Conclusion

All otherwise fit patients with CRLMs should be referred to a multidisciplinary specialist team in order to ensure that the most effective therapy is initiated. Surgery has a major role and, whenever possible, all resectable disease should be removed. Patients whose disease is extensive and inoperable may be converted to operable disease by appropriate neoadjuvant therapy, and this treatment should be considered and discussed with the patient. Undoubtedly, increased resection rates can be achieved and therefore outcome improved. Patients who have undergone appropriate resection with removal of all macroscopic disease may benefit from adjuvant chemotherapy with the addition of biologic agents. Several studies are currently ongoing. It is important to remember the role of radiofrequency ablation in increasing resectability rates and dealing with recurrent disease following surgery. A combination of radiofrequency ablation with chemotherapy may be used to downstage inoperable disease towards a resectable state. All treatments require careful selection in order to ensure that only appropriate patients are subjected to these extensive and potentially toxic treatments. ■

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