

Treatment of liver metastases from colorectal cancer

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ABSTRACT

In recent years several new local as well as systemic treatment options have become available for patients with advanced colorectal cancer. A survey among Dutch hospitals revealed considerable differences in the use of diagnostic and therapeutic strategies. Radiofrequency ablation is a promising technique that is currently being investigated in a randomised trial. The role of adjuvant chemotherapy in patients with resectable liver metastases and of neoadjuvant chemotherapy in patients with nonresectable liver metastases has not been clearly established yet. The current status of local and systemic treatment options for colorectal cancer liver metastases is reviewed.

KEYWORDS

Colorectal carcinoma, liver metastases, (neo)adjuvant chemotherapy, radiofrequency ablation

Colorectal cancer is one of the most common malignant tumours, accounting for at least 1,000,000 new cases worldwide and leading to more than 500,000 deaths each year. About half of the patients with colorectal cancer develop distant metastases during the course of their disease. In recent years, much progress has been made in the systemic treatment of patients with nonresectable advanced disease.¹ This is attributed to new cytotoxic agents, such as oxaliplatin and irinotecan, as well as to the development of oral fluoropyrimidines, capecitabine and uracil-Ftorafur, that are at least as effective but less toxic than intravenous 5-fluorouracil (5-FU).^{2,3} More recently, the addition to chemotherapy of the signal transduction inhibitors cetuximab and bevacizumab, was shown to result in increased efficacy. Over a time span of some 20 years this has resulted in an improvement in the median overall survival for patients with advanced

colorectal carcinoma from eight months with supportive care alone to approximately 21 months, and of the one-year survival rate from 34 to 74%.⁴

About 10 to 15% of these patients present with metastases confined to the liver that are resectable. In this selected subgroup resection of liver metastases can result in five-year survival rates of 20 to 40%, depending on prognostic factors such as the number and size of the lesions, free resection margins and extrahepatic disease at the time of surgery.⁵ Less important factors are time between primary tumour and development of liver metastases, staging of the primary tumour and carcinoembryonic antigen (CEA) level.⁶ Approximately 61% of the patients have recurrence of disease after resection of liver metastases, with the liver as the only site of tumour activity in approximately 50%.⁷ Although formal randomised studies between chemotherapy and liver metastasectomy have not been performed, surgery is the treatment of choice for liver metastases when a radical resection appears feasible and when no clinical evidence of extrahepatic disease is present. The major reason for this is the very inferior results of systemic treatment in historic controls. However, one should be aware of a pitfall in the interpretation of this comparison, since large databases of patients with resectable disease confined to the liver who have been treated with chemotherapy alone are not available. Therefore, these historic controls consist of many patients who also have extrahepatic disease and with that a worse prognosis, which implies that the true benefit of resection over systemic therapy is unknown.

The article by Bipat *et al.* published in this issue evaluates the diagnostic and therapeutic strategies of 74 Dutch hospitals concerning patients with advanced colorectal carcinoma by means of a survey among oncology committees in the Netherlands.⁸ Liver surgery is performed

in 30 out of 73 hospitals. Neoadjuvant or adjuvant treatment combined with liver surgery and local ablative therapies is used in 71 and 64% of the participating hospitals, respectively.

The differences between the participating hospitals nicely reflect the issues of debate in the treatment of patients with metastases confined to the liver. These are: 1) What is the role of (neo)adjuvant chemotherapy in patients with resectable metastases? 2) Can primary nonresectable liver metastases become resectable after downstaging by chemotherapy? and 3) What is the benefit of local ablative therapies, such as radiofrequency ablation (RFA), when some or perhaps all lesions do not appear to be radically resectable?

The survival benefit for adjuvant chemotherapy in stage III and high-risk stage II colon carcinoma patients⁹ suggests a possible role of (neo)adjuvant chemotherapy in patients with resectable liver metastases. A phase II study using irinotecan following resection of liver metastases estimates a median relapse free survival of 45.2 months. Two-year overall survival was 85%.¹⁰ Comparing adjuvant systemic or regional chemotherapy with surgery alone shows an improved survival of adjuvant chemotherapy after hepatic resection for colorectal liver metastases in a small series.¹¹ However, convincing evidence obtained from a randomised controlled trial, supporting the use of neoadjuvant or adjuvant chemotherapy in patients with resectable colorectal liver metastases, is not yet available. The European Organisation for Research and Treatment of Cancer (EORTC) study 40983 compares preoperative and postoperative chemotherapy with 5-FU, leucovorin and oxaliplatin with surgery alone in 364 patients with potentially resectable colorectal liver metastases. The results of this study are expected in 2006.¹² Currently it is not advised to administer adjuvant chemotherapy in this setting outside the scope of clinical trials.

With respect to the second question, neoadjuvant chemotherapy might be used as an approach to increase the resectability rate of liver metastases. Downstaging with systemic chemotherapy ultimately leads to resection in 10 to 40% of primarily nonresectable liver metastases.¹³ However, again many data are obtained from small noncomparative studies. A large case series by Adam describes a five-year survival rate of 34% in 95 patients that ultimately underwent resection out of 701 patients treated with chemotherapy for downstaging of liver metastases.¹⁴ However, when the intent-to-treat principle is applied the five-year survival of the total patient cohort was only 4.6%.¹ Comparable survival rates may also be achieved in subgroups of patients with nonresectable liver metastases treated with optimal chemotherapy. Thus, the absolute benefit of resection of liver metastases

after downstaging with chemotherapy compared with chemotherapy alone in a subgroup of patients in good clinical condition without extrahepatic disease remains to be established.

The third question concerns the role of a novel experimental local therapy for primary nonresectable liver metastases: radiofrequency ablation (RFA). RFA locally destroys tumour cells by generation of high-frequency current, inducing cell death by heat induction. RFA can be performed percutaneously, via open surgery, or by laparoscopy. The role of RFA in treating liver metastases of colorectal cancer is being studied in EORTC 40004, the CLOCC study. In this study the 30-month survival rate of chemotherapy with or without RFA is established in patients with nonresectable colorectal liver metastases. Results are not yet available. However, several case series studying RFA provide promising results. In a study by Berber *et al.* 135 patients with nonresectable liver metastases underwent RFA,¹⁵ of whom 80% were previously treated with chemotherapy and 30% had extrahepatic disease at the time of RFA. The mean survival was 28.9 months after RFA and 44.6 months after diagnosis of liver metastasis. Extrahepatic tumour progression occurred in 41% of the patients. Local recurrence of disease after RFA occurred in 2 to 40%.¹⁶ Currently, the use of RFA cannot be recommended as a standard procedure in the treatment of colorectal cancer liver metastases.

In conclusion, treatment strategies for colorectal cancer liver metastases are rapidly changing. Ongoing randomised trials are assessing the role of (neo)adjuvant chemotherapy in patients with resectable liver metastases, and RFA in patients with nonresectable disease as an adjunct to chemotherapy. As mentioned by Bipat *et al.*,⁸ a national guideline, which is currently in progress, will contribute to an optimal and evidence-based use of the therapeutic options for patients with colorectal liver metastases.

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