



Review

Management of disappearing colorectal liver metastases

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Abstract

The development of new potent systemic treatment modalities has led to a significant increase in survival of patients with colorectal liver metastases. In the neo-adjuvant setting, these modalities can be used for patient selection, down staging, and conversion from non-resectable to resectable liver metastases. In addition, complete radiological disappearance of metastases can occur, the phenomenon of disappearing liver metastases.

Because only a small percentage of these patients (0–8%) have a complete radiological response of all liver metastases, most patients will undergo surgery. At laparotomy, local residual disease at the site of the disappeared metastasis is still found in 11–67%, which highlights the influence of the imaging modalities used at (re)staging. When the region of the disappeared liver metastasis was resected, microscopically residual disease was found in up to 80% of the specimens. Alternatively, conservative management of radiologically disappeared liver metastases resulted in 19–74% local recurrence, mostly within two years.

Obviously, these studies are highly dependent on the quality of the imaging modalities utilised. Most studies employed CT as the modality of choice, while MRI and PET was only used in selective series.

Overall, the phenomenon of disappearing liver metastases seems to be a radiological rather than an actual biological occurrence, because the rates of macroscopic and microscopic residual disease are high as well as the local recurrence rates. Therefore, the disappeared metastases still require an aggressive surgical approach and standard (re)staging imaging modalities should include at least CT and MRI.

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Background

Approximately 50% of patients diagnosed with colorectal cancer will develop metastatic disease during the course of their disease.¹ Over recent years, increasingly effective systemic treatment regimens, loco-regional treatment modalities and a more aggressive surgical approach has led to continuously improving survival outcome of patients with metastatic colorectal cancer.^{2,3} Three year overall survival (OS) rates up to 75% have been described when

combining these treatment strategies in patients with extensive metastatic colorectal cancer.⁴

Neo-adjuvant systemic treatment can be considered in patients with initially resectable metastatic colorectal cancer, although it is doubtful whether this translates into a meaningful overall survival advantage.^{5,6} The EPOC trial showed no overall survival benefit for patients undergoing perioperative chemotherapy, although it was only powered to investigate progression free survival and included more than 50% of patients with a single liver metastasis.^{6,7} More important is its use to downsize metastatic disease to more easily resectable or more parenchyma-sparing resections; to convert initially unresectable disease to resectable disease; or to subject patients and the biology of their disease to a test of time, for example in patients with liver metastases and multiple indeterminate lung

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lesions or patients with synchronous bilobar liver metastases.

Depending on the chosen regimen, neo-adjuvant systemic treatment can lead to an objective radiological response in approximately 65% of patients.⁸ In addition, complete radiology disappearance of metastases can occur, the phenomenon of disappearing liver metastases (DLMs). This phenomenon is described as the complete disappearance of liver metastases upon cross-sectional imaging such as CT, PET or MR; also called a complete radiological response. It is described in up to 37% of patients after neo-adjuvant systemic therapy.^{9–14} However, local residual disease at the site of the disappeared metastasis could still be found in 11–67% at laparotomy.^{13,15} Furthermore, there is a clear difference between complete radiological and complete pathological response. When the areas of the disappeared liver metastases were resected, microscopically residual disease was found in up to 80% of the specimens.⁹

Debate continues about the optimal treatment regime for DLMs. This review provides an up-to-date overview of the existing literature on disappearing liver metastases and a discussion of management options.

Neo-adjuvant systemic treatment of colorectal liver metastases

Palliative treatment regimens in the nineties for patients with unresectable metastatic colorectal cancer consisted of fluorouracil–leucovorin based regimens and provided a median OS of 8–12 months.¹⁶ In more recent years, new combinations of capecitabine, oxaliplatin, irinotecan, bevacizumab, cetuximab, and panitumumab have had a significant impact on survival, with an improvement of the median survival rate to almost 30 months.² Recently, the new antiangiogenic drug aflibercept and the multikinase inhibitor regorafenib have been tested on their efficacy in previously treated metastatic colorectal cancer patients with promising results.^{17,18}

An increasing number of patients with colorectal liver metastases undergo neo-adjuvant systemic therapy.⁸ The increasing number of patients with initially unresectable or marginally resectable disease converted by evolving systemic regimes to resectable disease is an important indicator of the improving efficacy of modern multidisciplinary management. Adam et al. showed that 12.5% of patients that were initially unresectable were downsized to resectability with systemic therapy that mainly consisted of 5-fluorouracil and leucovorin combined with oxaliplatin.¹⁹ Although most patients in this group needed further resection for recurrent disease, the 5-year OS was 33%. A systematic review by Lam et al. investigating the outcomes of downsizing systemic therapy and rescue liver surgery in patients with initially unresectable colorectal liver metastases showed an objective radiological response in 64% (range 43–79%) of patients after systemic chemotherapy and 22.5% eventually underwent macroscopically curative

liver resection.²⁰ The median overall survival in this group was 45 months. A more recent Japanese study showed a conversion rate of 40.1% in a cohort of 137 patients who underwent oxaliplatin-based systemic treatment for initially unresectable colorectal liver metastases.²¹

In randomized controlled trials, the highest response rates were seen in patients who receive FOLFOXIRI (66%) and FOLFOX + cetuximab (68%).^{22,23} Triplet systemic therapy with FOLFOXIRI plus bevacizumab did not improve response rates but reportedly had a negative impact on grade 3 and 4 events.²⁴

Recent data provide evidence that liver-targeted drug delivery via hepatic artery infusional chemotherapy (HAI) could improve response and conversion rates in patients with liver metastases. Most studies use floxuridine, a 5-FU analogue, for HAI because of its high hepatic extraction rate that limits systemic toxicity and allows its use in combination with systemic therapy. A recent phase 2 prospective non-randomised cohort study from the same institute included 49 patients (2007–2010) for HAI with floxuridine combined with systemic therapy with unresectable colorectal liver metastases.²⁵ The median number of tumours was 14 and 65% were previously treated patients. The overall response rates were 76% (4 complete responses) and 47% of patients achieved conversion to resection at a median of 6 months from treatment initiation. Eighty per cent of patients had recurrent disease at a median follow up of 39 months. At the moment, the results of multiple randomized trials are awaited. [Table 1](#) shows the preoperative treatment regimens in the studies that describe disappearing liver metastases. Although treatment regimens vary widely in these studies, a significant proportion was treated with HAI.

The use of neo-adjuvant systemic therapy in patients with initially resectable disease is under debate. A meta-analysis by Wang et al. of 1896 patients in 10 studies including the EPOC trial showed no overall survival benefit for patients receiving perioperative chemotherapy.²⁶ The impact in these cases of neo-adjuvant systemic therapy on DLMs is unclear. Factors that were independently associated with DLMs were metastases number >3 and the number of courses of preoperative chemotherapy in the study by van Vledder et al., while HAI, normalized CEA levels, and disappearance of metastases on MR were associated with a true clinical response in the study by Auer et al.^{14,15}

Diagnostic modalities

Multiple studies describe the phenomenon of disappearing liver metastases.^{9–15,27–29} To assess the extent of the phenomenon of DLMs it is important to evaluate diagnostic modalities utilised. Are these diagnostic modalities simply unable to detect small remnant liver metastases?

Available studies on DLMs show a wide range of preoperative and intra-operative imaging modalities employed for restaging of colorectal liver metastases after neo-

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