Complete Radiological Response of Colorectal Liver Metastases after Chemotherapy: What Can We Expect?

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Key Words

Missing metastasis • Disappearing metastasis • Complete pathological response • Colorectal cancer • Liver metastasis • Chemotherapy • Hepatic intra-arterial chemotherapy

Abstract

Missing metastases, also called vanishing or disappearing liver metastases, concern about 5% of patients with colorectal liver metastasis undergoing chemotherapy, and this phenomenon is likely to become more frequent in the near future, with the widespread use of highly efficient chemotherapy. As their definition is highly dependent on the quality of initial imaging, a DLM on preoperative computed tomography scan should be systematically confirmed by a second imaging modality, ideally magnetic resonance imaging. It is important to note that a complete clinical response does not mean a complete pathologic response. Currently, there are no absolute criteria of a complete pathologic response. However, treatment with neoadjuvant and adjuvant hepatic arterial infusion in patients <60 years old with an initially low carcinoembryonic antigen level that normalizes under chemotherapy and who have no detectable lesion on both computed tomography and magnetic resonance imaging is probably more likely to yield a complete pathologic re-

sponse. Whatever their treatment, patients with DLM run a high risk of recurrence that could be decreased with the use of HAI. Despite a high recurrence rate, the overall 5-year survival rate of patients with DLM ranges from 40 to 80%. Having a DLM should no longer be a contraindication to hepatic surgery since long-term survival is expected in these highly chemosensitive patients. The use of adjuvant HAI in addition to efficient systemic chemotherapy could reduce the risk of hepatic relapse.

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Introduction

Recent improvements in the care of patients with colorectal liver metastasis (CRLM) would not have been possible without the widespread use of adjuvant and neoadjuvant chemotherapy with a multidisciplinary approach. Nevertheless, when complete resection is possible, aggressive surgical treatment remains the cornerstone of the management of these patients and the only hope for cure.

The use of neoadjuvant chemotherapy remains controversial [1] when CRLM are initially resectable, but it is widely used [2] allowing better patient selection, assess-

Table 1. Main published series reporting management and outcome of colorectal liver metastases vanishing under chemotherapy

First author, year	Patients with DLM, %	Use of HAI	Patients with recurring DLM, %	Median overall survival	Overall survival, %	Author's conclusions
Benoist [10], 2006	6.5	no	79	–		In most cases, a complete response on CT scan does not mean cure
Elias [11, 12], 2007	7	yes	38	NR	94 (3 years)	DLM are definitively cured in 62% of cases, adjuvant HAI might play a major role
Fiorentini [16], 2008	–	yes	–	–	–	–
Tanaka [13], 2009	36	yes	–	–	69.2 (5 years)	Little correlation between response to chemotherapy on imaging and pathologic response. Liver surgery should be performed even after a complete response on imaging since these patients have a favorable outcome
Auer [14], 2010	9	yes	44	NR	65 (5 years)	Approximately 66% of DLM exhibited a true complete response
Van Vledder [15], 2010	23.8% of patients undergoing resection	no	59	NR	63.5 (5 years)	Survival was comparable in patients with untreated DLM, in spite of high intrahepatic recurrence rates in these patients

HAI = Hepatic arterial infusion; NR = not reached; DLM = disappearing liver metastases.

ment of sensitivity to chemotherapy or possible downstaging of metastases. When metastases are initially unresectable, systemic or intra-arterial hepatic chemotherapy is initially the only therapeutic option. In a subset of patients, the ensuing tumor shrinkage allows liver resection with a curative intent, leading to long-term survival or even cure in these selected patients [3–5]. With the availability of new regimens and active drugs, including targeted therapy, a complete radiological response of CRLM (fig. 1), i.e. the disappearance of liver metastases on preoperative imaging, is becoming more common. On average, this concerns 5% of patients [6] and as many as 38% [7] depending on the chemotherapy regimen used. Additionally, a pathologic complete response, i.e. the disappearance of viable tumor cells on pathologic examination, is observed in about 10% of patients [6] and in as many as 24% [8] in some series.

One of the problems concerning missing metastases is that the definition of a complete radiological response depends on the quality and completeness of preoperative imaging. Some CRLM are still detectable during surgery. However, when there is a complete radiological response and CRLM are no longer detectable during surgery (i.e. complete clinical response), this is not always associated with a complete pathologic response [9].

The increasing incidence of ‘missing metastases’, also called ‘vanishing metastases’ or ‘disappear/ing/ed metastases’ led several teams during the last years to report their experience of patients with disappeared liver metastases (DLM) following preoperative chemotherapy [10–16], analyzing patient outcome and the significance of a complete radiological response (table 1). Nevertheless, the results of these publications are sometimes conflicting, highlighting the need for a review of the literature because this clinical problem is likely to become more frequent in the near future with the widespread use of highly efficient chemotherapy [17].

The aim of this work was to best determine our attitude toward patients with disappeared CRLM, and (1) to determine the predictive factors associated with the occurrence of disappeared metastases, (2) to question the significance of a vanishing metastasis on preoperative imaging, (3) to assess when complete clinical responses are associated with cure or long-term survival, i.e. either a complete pathologic response on the operative specimen, or no recurrence when lesions are left in situ, and (4) to assess the impact of these DLM on disease-free survival and the overall prognosis.

Fig. 1. Complete radiological response. **a** CT scan before systemic chemotherapy. Three colorectal liver metastases were visible (2 in segment VII, one in segment V). **b** CT after chemotherapy. The 3 metastases showed a complete radiological response after 10 courses of systemic LV5FU2 plus oxaliplatin (FOLFOX).

Results

Predictive Factors for the Occurrence of DLM

In their recent report, using various systemic preoperative chemotherapy regimens, Van Vledder et al. [15] at Johns Hopkins Hospital analyzed the predictive factors for the occurrence of DLM, comparing patients with ($n = 40$) and without ($n = 128$) DLM. In the univariate analysis, the median size of CRLM prior to chemotherapy was significantly smaller in CRLM that had disappeared when compared to the size of CRLM that had not disappeared during chemotherapy (1 vs. 2.1 cm; $p < 0.001$). In addition, patients with DLM had more frequently synchronous liver metastases (over 3). They were initially unresectable and treated with a higher total number of cycles. In the multivariate analysis, only an initial number of metastases exceeding 3 (OR 13.1; $p < 0.001$) and a high number of courses of preoperative chemotherapy (OR 1.18; $p = 0.03$) were independent predictive factors for the occurrence of DLM. It is noteworthy that the definition of a DLM is highly dependent on the quality of preoperative imaging, and overall, in 45% of patients, a metastasis was detected during surgery at the site where it had disappeared on imaging.

From a clinical point of view, we believe that particular attention should be paid to patients with small numerous

metastases undergoing prolonged preoperative therapy, especially with a new-generation drug, or if it is administered via the hepatic artery, since these patients run a high risk of developing DLM.

From a Complete Radiological Response to a Complete Clinical Response

Response to chemotherapy is assessed on imaging studies performed before and after chemotherapy according to RECIST (response evaluation criteria in solid tumors) [18]. In a recent systematic review of randomized and nonrandomized trials of neoadjuvant systemic chemotherapy for resectable CRLM [6], the mean rate of complete radiological response was 4%, and was capable of attaining 38% [6]. However, if the rate of complete radiological response depends on the type and duration of chemotherapy, it is also influenced by the quality and completeness of preoperative imaging.

In the 5 main series of patients with DLM, a complete radiological response of at least one CRLM was described in 6.5–36.5% of the patients [10–15]. In these series, the diagnosis of a complete radiological response after chemotherapy was usually based on a transabdominal ultrasound and a triple-phase helical computed tomography (CT) scan with 5-mm reconstructions. Imaging was completed selectively at the discretion of the treating phy-

sicians, by magnetic resonance imaging (MRI), ultrasound with contrast agent (Sonovue) injection and/or a fluorodeoxyglucose (18F) (FDG)-PET in a subset of patients [11, 13, 14]. It is noteworthy that one of the higher rates of DLM (nearly 40%) was observed in a series of patients who underwent CT arterial portography before and after the chemotherapy [13]. Ninety percent of these patients were treated with intra-arterial chemotherapy.

In the setting of missing metastases, particular attention should be paid to preoperative imaging, since FDG-PET and CT sensitivity are lowered by neoadjuvant chemotherapy [19, 20], probably because of changes in the liver parenchyma. Thus, Angliviè et al. [20] recently reported that chemotherapy, more than 3 CRLM and steatosis >30% were independent risk factors for inadequate staging of CRLM by CT scan. MRI is not widely performed for the preoperative assessment of liver metastases partly because of its cost and limited availability. Nevertheless, its accuracy for detecting CRLM seems higher than that of a CT scan, as recently reported in a meta-analysis [21]. In the Memorial Sloan Kettering Cancer Center experience [14], among 89 DLM on CT scan in 27 patients, an additional MRI was performed for 44 DLM, and an FDG-PET in 54. Overall, of the 7 DLM (8%) detected at the site of its disappearance, 6 were detected by MRI and 1 by FDG-PET. In our opinion, and because of the major clinical implication of DLM, all missing metastases on triple-phase CT should be confirmed by another imaging modality, ideally by MRI since it appears that the sensitivity of MRI is superior to that of CT based on a per lesion analysis [21], and MRI often depicts vestiges of the metastasis. Particular attention should be paid in patients who develop steatosis during chemotherapy or chemotherapy-associated steatohepatitis. Moreover, the inability to observe the DLM on MRI was recently associated with a pathologic complete response or a durable complete clinical response [14]. Adequate preoperative evaluation of these metastases should allow us to accurately plan surgical resection preoperatively, and to avoid, when possible, intraoperative changes in strategy.

Despite an extensive preoperative evaluation, some DLM are found during open surgical exploration. In the published experience, surgical exploration was meticulous, including complete liver mobilization and careful exploration, palpation and ultrasonographic exploration, and a macroscopic residual disease was observed at the time of laparotomy at the site of the disappeared CRLM in 11–30% of patients [10, 13, 14] or in 27–45% of the patients exhibiting DLM [12, 15]. As expected, persistent tumor at the site of DLM was less frequent in patients whose

DLM were determined with preoperative MRI [11, 12, 14]. Pathologic examination of DLM seen at surgery showed the presence of viable tumor cells in 55–65% of cases [10–15]. This highlights the fact that a complete radiological response does not necessarily mean a complete pathologic response, and in contrast, a complete pathologic response can occur in a visible metastasis [9]. In the study by Benoist et al. [10], univariate analysis showed no preoperative predictive factor for the intraoperative persistence of macroscopic remnants of DLM, but the type of imaging performed was not tested in the statistical analysis.

From a clinical point of view, DLM on preoperative CT scan should be systematically confirmed by a second examination, ideally MRI. If the disappearance is confirmed, the intraoperative examination should be carefully done with palpation and ultrasonography after full liver mobilization.

From a Complete Clinical Response to a Complete Pathological Response

The true complete response rate of CRLM could be defined as CRLM exhibiting either a complete pathologic response, or no recurrence if left in situ. The rate of complete pathologic responses among metastases with a complete clinical response is discordant, ranging from 20 to 100%. In the study by Benoist et al. [10], the pathologic examination of the sites of 15 initially resectable CRLM not seen on preoperative imaging or during surgery showed the presence of viable tumor cells in 12 of them (80%). In contrast, in the study by Tanaka et al. [13], a complete pathologic response was present in all resected liver metastases with a complete clinical response ($n = 28$). When they considered predictive factors for the occurrence of at least one CRLM having complete pathologic response [13] in those patients, the initial median number of CRLM was higher (8 vs. 5, $p = 0.012$), a partial response on preoperative imaging was more frequent (83 vs. 40% of patients, $p = 0.005$), as were the rates of patients' CRLM exhibiting a complete clinical response (69 vs. 17% of patients, $p < 0.001$) than in patients without DLM. Additionally, Adam et al. [9] found that a complete pathologic response was more frequent in young patients (<60 years) with a small lesion (<3 cm), a low initial carcinoembryonic antigen (CEA) level (<30 ng/ml), and in those exhibiting either a complete or partial radiological response after chemotherapy.

The heterogeneity in the rates of complete pathologic responses reported might be due to the type, duration and number of lines of chemotherapy administered be-

fore surgery. In fact, a higher rate of complete pathologic responses among CRLM with a complete clinical response was observed in patients who had neoadjuvant hepatic arterial infusion (HAI) [11–14]. Thus, in the study by Elias et al. [11], the histological analysis of the resected CRLM (still visible on imaging) showed a complete pathologic response in 86% of the patients who had received HAI preoperatively compared to 22% in those who had not ($p < 0.02$). Also, a higher rate of complete pathologic response might be observed in patients with initially unresectable CRLM, transformed to resectable lesions by chemotherapy and therefore selected on their responsiveness to chemotherapy.

When CRLM with a complete clinical response were left in place, the rate of recurrence in situ ranged from 38 to 74%. As expected, higher rates of recurrence in situ were observed in the series of patients with a lower rate of CRLM exhibiting a complete pathologic response. Thus, in the series by Benoist et al. [10], a recurrence in situ was observed in 23 of the 31 CRLM left in place (74%) in 12 patients with initially unresectable CRLM. This is in accordance with the complete pathologic response rate of 20% reported in our experience when patients only received systemic chemotherapy. In other series of patients with disappeared CRLM on imaging and at surgery, the in situ recurrence rates were more concordant, ranging from 38 to 47%, which signifies that no recurrence was observed in situ in 53–62% of the patients. The discrepancy between these results and those previously published by Benoist et al. [10] seems to be mainly due to the administration of neoadjuvant and/or adjuvant HAI chemotherapy in addition to systemic chemotherapy. In fact, in the study by Tanaka et al. [13], 90% of patients appear to have received HAI postoperatively, and in the study by Elias et al. [11], hepatic recurrence was significantly decreased among those 75% of the patients who had received postoperative HAI. In the study by Auer et al. [14], the authors reported that normalization of the CEA level, the inability to detect the lesion by MRI and the use of HAI chemotherapy were independent predictive factors for a true complete response. Thus, the risk of hepatic recurrence appears to be decreased when the rate of true complete pathologic responses is increased (by neoadjuvant HAI), and when adjuvant HAI is administered.

From a clinical point of view, it is noteworthy that a complete clinical response does not mean complete pathologic response. To date, there are no absolute criteria for complete pathologic response, but treatment with neoadjuvant and adjuvant HAI in patients <60 years old with an initially low CEA that normalizes under chemo-

A recent analysis of 27 patients operated on for CRLM at the Gustave Roussy Institute, in whom untreated DLM were left in place, showed that 19 of the 27 patients (70%) relapsed, 14 (52%) with intrahepatic lesions (isolated or not) and 5 with extrahepatic lesions alone, after a median follow-up of 55.4 months. The intrahepatic recurrence rate was significantly lower in patients who had received adjuvant HAI (4 intrahepatic recurrences in the 15 patients who had received adjuvant oxaliplatin-based HAI), 26.6 versus 83.3% (10 intrahepatic recurrences in the 12 patients who had not received adjuvant oxaliplatin-based HAI; $p = 0.006$). Recurrences occurred at the site of the missing CRLM in only 9 of the 27 patients (33.3%). All patients who developed a recurrence at the site of the missing metastasis also had a hepatic recurrence elsewhere in the liver, which either occurred at the same time (6/9), before (1/9) or after (2/9) the relapse of the missing CRLM.

rence rate was 66.6%, comparable to the recurrence rates observed when some DLM are left untreated. All of these patients had received postoperative chemotherapy, but none had received HAI.

From a clinical point of view, most patients with a DLM initially have extensive disease, with numerous initially unresectable and bilobar lesions. Consequently, it is not surprising that they run a high risk of either intra- (at the site of the DLM or elsewhere) or extrahepatic recurrence. This recurrence rate seems to be lower if the DLM is resected, or when adjuvant HAI is administered.

Overall Survival

The 5-year overall survival rate of patients with DLM ranges from 40 to 80% [11, 14, 15], which is higher than what might have been expected in this setting. In our experience focused on patients with initially unresectable but highly chemosensitive disease who underwent surgery leaving DLM in place, prolonged overall survival was observed. In fact, patients were highly selected according to their response to chemotherapy and the stability of the disease. Also, the persistent absence of DLM on imaging had to be verified over at least 3 months before surgery. This very unusual chemosensitivity might explain the higher rate of complete pathologic responses and the prolonged survival obtained in these selected patients compared to that in most other series.

No statistically significant difference in overall survival was found between patients with DLM left untreated and patients in whom all the original sites were treated (median survival 65 vs. 45 months, $p = 0.31$) in the study by Van Vledder et al. [15]. Also, in our recent analysis, overall survival was not significantly different between patients who had a recurrence from DLM left in place and those who did not relapse ($p = 0.77$). In the experience reported by Tanaka et al. [13], the best survival rate was observed among patients in whom all the CRLM achieved a complete pathologic response, but it was also improved ($p = 0.001$) in patients exhibiting a complete pathologic response in at least one lesion compared to those with no response. As recently reported, a complete pathologic response under chemotherapy is a strong predictive factor for improved survival [9, 22]. Adam et al. [9] reported a 5-year overall survival rate of 76% in 29 patients (among 767 consecutive patients with CRLM) who achieved a complete pathologic response after resection of a CRLM treated with neoadjuvant chemotherapy compared to 45% in patients without a complete pathologic response ($p = 0.004$).

From a clinical point of view, despite a high recurrence rate, overall survival of patients with DLM, most of whom

have initially extensive disease, ranges from 40 to 80% at 5 years. This is likely due to patient selection based on high chemosensitivity, and in our opinion, justifies an aggressive surgical approach and the continuation of the same chemotherapy in an adjuvant setting.

Discussion

Chemotherapy is more and more used before hepatectomy, allowing a subset of patients with initially unresectable disease to undergo liver resection. With the increasing efficiency of chemotherapy regimens and novel drugs, a complete radiological response of CRLM is now more frequently observed. The prediction and assessment of a complete pathologic response of CRLM after neoadjuvant chemotherapy is mandatory in order to tailor surgical resection. This is still impossible, since there is no clear correlation between a complete pathologic response and a complete clinical/radiological response. Moreover a complete clinical response can occur without a complete pathologic response, especially with the use of targeted therapy.

Two situations can thus be distinguished. First, when CRLM are initially resectable, we advise surgeons and oncologists to carefully reevaluate the lesion after a few cycles ($n < 4$) of chemotherapy in order to avoid the disappearance of the CRLM and to promptly resect it. If chemotherapy cannot be stopped, or if the metastasis is very likely to disappear, an alternative option is to mark the CRLM with coils [23] and to resect or ablate the site during hepatic surgery. Finally, if some DLM still cannot be found during surgery, the site of the DLM should be resected if a major hepatectomy is not required. Otherwise, the decision to undertake a major hepatectomy should be discussed by a multidisciplinary team. The decision should be made based on the aggressiveness of the disease, the patient's condition and operative risks, and it should take into account the risk of relapse even after resection of the DLM. In fact, performing a major hepatectomy to resect the site of the DLM may not decrease the recurrence rate, as shown in the study by Benoist et al. [10]. On the contrary, the prognosis could be worsened by reducing the possibility of a second hepatectomy, which was performed in 38% of the patients in our updated experience.

In the second situation, when CRLM are unresectable and become resectable under chemotherapy, resection or destruction of all visible lesions is recommended, but leaving a DLM in situ should not contraindicate hepatectomy with a curative intent. The goal of this aggressive

surgical approach is to reduce the recurrence rate as much as possible in the liver at the site of the missing CRLM or elsewhere. It is of course important to continue the same efficient chemotherapy postoperatively in these highly chemosensitive patients. Adjuvant HAI seems to be of major importance in these patients in order to reduce the risk of hepatic recurrence, and should be used if possible.

In conclusion, in patients with highly chemosensitive but initially unresectable CRLM, which become resectable during a curative attempt but with a missing CRLM left in place, long-term survival is expected, despite a high

recurrence rate. Having a missing CRLM should no longer be a contraindication to hepatic surgery if complete resection of all other lesions is possible. The postoperative use of HAI could reduce the risk of hepatic relapse.

Disclosure Statement

Sébastien Gaujoux was a recipient of a research grant from the European Society of Surgical Oncology (ESSO) and the Association Française de Chirurgie Hépatobiliaire et de Transplantation Hépatique (ACHBT).

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