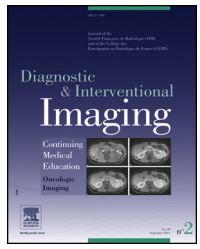
Diagnostic and Interventional Imaging (2014) **95**, 513—523



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Liver, lung and peritoneal metastases in colorectal cancers: Is the patient still curable? What should the radiologist know

C. Dromain*, C. Caramella, P. Dartigues, D. Goere, M. Ducreux, F. Deschamps

Department of diagnostic imaging, Gustave-Roussy Institute, 39, rue Camille-Desmoulins, 94805 Villejuif cedex, France

KEYWORDS
Liver;
Peritoneum;
Oncology;
Tumor excision;
Colorectal metastases

Abstract Regardless of the advances in chemotherapy, the only curative treatment for colorectal metastases is surgery, which must be complete and excise all of the metastatic sites of disease. Thanks to advances in neoadjuvant chemotherapy and also to alternative techniques, such as radiofrequency ablation, however, surgical treatments have become available to a larger number of patients and have improved patient survival. The aim of this article is to describe the different treatment strategies for colorectal metastases and to examine the role of imaging in defining the resect ability of these metastases. The key factors in the radiological report in the initial and post-chemotherapy assessments are described.

Metastases from colorectal cancer are common and develop in 40 to 60% of the patients. The existence of metastases classifies patients into M1 of the TNM classification and stage IV of the UICC/AJCC classification. External or common iliac lymph node involvement is also deemed to be M1.

The primary metastatic site is the liver. After colorectal cancer has developed, 40 to 50% of the patients will develop liver metastases and synchronous liver metastases, i.e. those present at the time when the colorectal cancer is discovered are found in 15 to 20% of the cases. The cumulative incidence of metachronic liver metastases, i.e. those discovered after treatment for the primary tumor is around 15% at 5 years. The risk of

* Corresponding author.
E-mail address: clarisse.dromain@gustaveroussy.fr (C. Dromain).

http://dx.doi.org/10.1016/j.diii.2014.03.011

developing metastases correlates with the stage of the primary cancer and liver invasion is also a major prognostic indicator and therefore a major treatment challenge. Whilst liver metastases are present in approximately 30% of all patients with colorectal cancer, they are responsible for approximately 2/3 of the deaths [1].

The other sites for colorectal cancer metastases are rarer and include the lungs, peritoneum and pelvic abdominal lymph nodes. These are often combined with liver metastases.

Treatment strategies

Preoperative chemotherapy has become a standard treatment in the initial management of patients with metastases. Regardless of the advances in chemotherapy, however, the only curative treatment for metastatic colorectal cancer remains surgery for the primary tumor and the metastases. This surgery must be complete (R0), excising all of the metastatic disease sites. It has become available to a larger number of patients because of advances in neoadjuvant chemotherapy and in surgery and also as a result of alternative treatment techniques, particularly, percutaneous or preoperative ablation therapy techniques. The surgical treatment options for metastases must therefore be considered routinely and reassessed throughout the patient's management.

Chemotherapy

Neoadjuvant chemotherapy

The purpose and choice of neoadjuvant chemotherapy vary depending on the possibilities for surgical resection, which is currently the only curative treatment for metastatic colorectal cancer. Its purpose is to reduce the risk of recurrence and therefore increase overall survival in metastatic disease, which can be resected from the outset, to make the patient operable by obtaining a response in potentially resectable disease and to increase disease free survival in metastatic disease, which has ''never'' been resectable.

Chemotherapy in metastatic colorectal cancer has changed greatly in recent years with the sequential use of chemotherapy with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI), which have doubled median survival times, increasing from 11 months to approximately 21 months [2,3]. Survival has also recently been improved by the introduction of new pharmacological agents, particularly the biotherapies and with the identification of predictive indicators for treatment response or failure. The addition of bevacuzimab or FOLFIRI as the first line treatment increases the likelihood of objective tumor response to 63%, with a median survival of 28 months, which has never yet been achieved in this situation [4]. More recently, cetuximab, an epidermal growth factor receptor, (EGF-R receptor) combined with FOLFIRI, has also achieved an overall survival of 23.5 months [5] in first line treatment as a result of determining the tumor KRAS status, which enables a group to be selected which benefits from this treatment.

In order to increase the resectability of metastases (particularly liver), it is now possible to offer selected patients a combination of 3 cytotoxic agents and a biotherapy with bevacizumab or cetuximab. These intensive treatments can achieve response rates of over 70% with tumor control as high as 100% and a resectability rate of approximately 70%, although this is at the cost of significant toxicity.

A new method of chemotherapy administration by slow intravenous hepatic infusion (SIHCA) has been developed to treat colorectal metastases, which are inoperable from the outset and located only in the liver. Hepatic intra-arterial chemotherapy requires an intra-arterial catheter to be introduced either by laparotomy or percutaneously by radiology and uses drugs, which have a high, first pass hepatic extraction rate. These enable higher concentrations to be achieved within the tumor and therefore a better response to treatment than the same chemotherapy administered systemically ($\times$5—10 for 5FU, $\times$4 for oxaliplatin compared to systemic chemotherapy) [6]. The treatment regimen currently used is a combination of intra-arterial chemotherapy (5FU/FUDR, irinotecan or oxaliplatin) and systemic chemotherapy, which achieves particularly high response rates and overall survival rates ranging from 74 to 92% and 20 to 40 months, respectively. IHCA has also been shown to be effective in patients who have failed treatment after several lines of systemic chemotherapy [7]. In particular, the use of oxaliplatin IHCA combined with LV5FU2 has produced response rates of 54% in patients in disease progression after treatment with systemic oxaliplatin [8]. Because of the high response rates obtained, this type of treatment is indicated particularly in patients with single, potentially resectable liver metastases. A recent study in 87 patients with liver metastases deemed to be unresectable and treated with IHCA (oxaliplatin) + LV5FU2 reported a resectability rate of 26% with a significant 56% gain in 5-year survival compared to 0% in the group of patients who were not treated surgically [9]. In another phase II study (the CHOICE study), in 36 patients treated with a combination of intra-arterial oxaliplatin and FU/LV + cetuximab, the response rate was 86% with a resectability rate for liver metastases of 48% (ASCO 2010).

Postoperative chemotherapy

The purpose of postoperative chemotherapy is to reduce the local recurrence rate and to increase progression-free survival and overall survival in patients. This is mostly adjusted in terms of the histological response. If a good histological response is achieved, it is standard practice to repeat the same chemotherapy as was used preoperatively.

Surgery

Surgery remains the only curative treatment for colorectal cancer metastases. For this reason, it should be considered routinely and discussed again at the different stages in patient management in a multidisciplinary team meeting. This discussion is based on the risk/benefit balance of surgery, which requires the following criteria to be assessed:

- the patient's background, whether it is compatible with anesthesia and resection of the metastases;
- oncological restrictions: the total absence of unresectable tumor sites;