

# Treatment (with a curative intent) of extrahepatic colorectal metastases

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## Introduction

The detection of extrahepatic metastases (EHM) from colorectal cancer is commonly considered a contraindication to resection of associated liver metastases (LM), and also, ever increasingly, a relative contraindication to resection of the primary tumour if asymptomatic. Progress in the understanding of the metastatic process, in imaging, in surgical techniques and in chemotherapy, are gradually modifying this attitude.

## Background

It has been proven that the surgeon's awareness of synchronous metastases decreases his/her technical performance when resecting the primary, and influences the curability of the colorectal resection [1].

New chemotherapy regimens allow downstaging of unresectable metastases to such an extent that close to 20% become resectable.

We must underline that, unfortunately, the definition of unresectability is different according to the teams, it changes with time, and finally should, in our opinion, be based only on technical criteria and not on oncological criteria (as proven below).

The importance of the chemosensitivity of the metastases when faced with the choice of a curative strategy for multiple LM or EHM has been demonstrated: for hepatectomised patients with  $\geq 4$  LM, the 5-year survival rate was 37% in patients with chemosensitive lesions versus 8% in patients with chemoresistant disease [2].

## Peritoneal carcinomatosis (PC)

A new approach combining cytoreductive surgery (CRS) and intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) is indicated in patients with moderate PC, chemosensitive disease and a good general status. A randomised Dutch trial using i.p. mitomycin at 41°C showed that the 3-year survival rate

was 3-fold higher (36%) in the experimental arm than in the control arm (10%) [3]. Using HIPEC exclusively after complete CRS of the PC, our group recently reported a 48% 5-year survival rate in 30 colorectal patients with PC who received i.v. oxaliplatin at 43°C and i.v. 5-FU plus leucovorin [4]. This is exactly the same survival rate as after resection of LM. We have been using a tri-therapy during HIPEC (i.p. oxaliplatin plus irinotecan, and i.v. 5-FU-leucovorin) for 3 years and are awaiting the latest results. This aggressive approach gives rise to mortality and morbidity rates of 4–5% and 40–50% respectively.

## Lung metastases

Lung metastases must be treated like liver metastases. Between 1991 and 1995, 645 patients who underwent metastasectomy had a 5-year survival rate of 37% [5], which is similar to that obtained with hepatectomy during the same period. Selected patients (n = 81) from the Memorial Sloan Kettering presenting with liver metastases and lung metastases, synchronously or not, who underwent surgery had a 5-year survival rate of 30% [6]. Recently, percutaneous radiofrequency ablation yielded a local efficacy rate of 87% and a survival rate of 70% at 2 years in 89 patients (de Baere IGR 2007). It is indicated that the intent is curative, when there are less than five metastases and their diameter is less than 4 cm. It requires a technical platform with CT scan and general anaesthesia.

## Ovarian metastases (OM)

Two considerations must be taken into account for these metastases. 22% are synchronous to the primary. After resection of OM, the risk of developing PC is close to 70% and prophylactic therapy with HIPEC should be considered. Metachronous metastases occur in 88% of cases, mainly in the peritoneum or in the liver. More importantly, our team recently showed that OM progressing under chemotherapy (88%) failed to

achieve an objective response while 57% of objective responses were obtained in the liver in the same patients with concomitant LM [7]. This chemoresistance leads clinicians to propose early surgery for OM, before they become symptomatic.

### **(R)Evolution in colorectal metastases: Is the multiplicity of metastatic sites less important than their total number?**

The concept that the prognosis of metastases is better when limited to only one organ is inconsistent with recent studies on circulating tumour cells and the pathophysiology of metastases. At variance with this concept is the crude overall 5-year survival rate of 29% that we reported in 75 patients who underwent hepatectomy with resection of EHM [8], with the message that EHM do not absolutely contraindicate hepatectomy for colorectal LM.

This article deals with the same topic but with a new concept: interpreting the results of the resection of metastases, not according to the sites, as is the case conventionally, but according to the total number of lesions, regardless of the number of invaded sites.

We recently demonstrated that after resection the prognosis is, to a greater extent, associated with the total number of resected metastases (located inside and outside the liver), than with the site of these metastases (whether inside the liver alone or not) [9]. 308 colorectal patients underwent hepatectomy between 1987 and 1999. Eighty-four of them (27%) also underwent resection of miscellaneous EHM. The overall 5-year survival rate was 32% for all the series. In the multivariate analysis, when the total number of resected metastases was considered, each LM and each EHM being counted as one lesion, the total number of metastases (whatever the site, inside and outside the liver) had a greater prognostic value than the criterion 'presence or absence of EHM'. Considering the total number of resected metastases (whatever the site), 5-year survival rates were  $38 \pm 4\%$  in the group with 1–3 metastases,  $29 \pm 5\%$  in patients with 4–6 metastases and  $18 \pm 5\%$  in patients with more than 6 metastases ( $p = 0.002$ ).

**Conclusion:** When resectable, the presence of EHM is no longer a contraindication to hepatectomy. More importantly, the total number of the metastases, whatever the location, exerts a stronger prognostic impact than the site of these metastases.

For the first time, this study showed that for resectable metastatic colorectal tumours, the total number of metastases, whatever the location, is a

more important prognostic factor than the site of the metastases. It thus appears that one LM associated with one EHM virtually has the same prognostic value as two isolated LM. In addition, the liver as the first site of disease extension no longer appears as a site of predilection for resection of metastases, but seems to be on a par with any other site.

### **Conclusion**

Faced with advanced cancers which always reflect a disseminated process, a new approach is to combine a complete resection of macroscopic disease with cure of residual microscopic disease with chemotherapy. In the concept of treating macroscopic and microscopic tumour components differently (but using a combined approach), complete resection of colorectal metastases is more important than the sites of these metastases. Thus, extrahepatic metastases are no longer a contraindication to hepatectomy. The total number of resected metastases, whatever the site, maintains a strong prognostic impact.

This is both true for the treatment of peritoneal carcinomatosis as for that of any type of colorectal metastases. When applicable, this approach results in a 40–50% 5-year survival rate for LM, for PC, and for different EHM.

In the future, the logical application of this principle should be to rapidly test the chemosensitivity of the tumour targets in patients first, then to completely resect the metastases when feasible, and to continue the efficient chemotherapy after resection. In this setting, surgery and chemotherapy will therefore be equally important for cure.

### **Conflict of interest statement**

None declared.

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