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# Metástasis hepáticas del carcinoma colorrectal

## Multimodality treatment of liver metastases from colorectal cancer

R. Adam

Liver metastases are the major cause of death in patients with colorectal cancer. Surgical resection is now recognised as the most effective treatment for liver metastases resulting from colorectal cancer and from a high proportion of other primary tumours. The ability to resect disease is associated with 5-year survival rates of 30-50%<sup>1,2</sup>. Generally the surgeon is faced with two different situations as outlined below:

### Primarily Resectable metastases

Only a minority of patients with liver metastases (10-20 percent) are initially candidates for potentially curative resection. For those who do undergo surgery, prognostic factors of recurrence are well known and include mainly the number and size of metastases, the presence of extra-hepatic disease, the degree of invasion of the primary tumour and for some series the synchronous or metachronous pattern of the metastases. Irrespective of this, liver resection should be considered as it remains the only chance of long-term remission (5 year survival: 30-40 percent) and sometimes of cure for these<sup>1,2</sup>. Patients are only candidates for surgery if they have no unresectable extra-hepatic disease, if all liver deposits can be resected and if sufficient liver parenchyma can be preserved to avoid post-operative liver insufficiency. The goal of surgery for liver metastases is to remove all the metastatic sites, if possible with a free clearance margin of 1 cm. Incomplete treatment is not associated with a benefit in survival. Despite radical treatment, recurrences are still observed in 60 to 80 percent of patients, one third of these through isolated metastases of the liver. Repeat liver resection in these patients will give a survival benefit of 30-40% at 5 years and should be considered in all cases for which liver resection is potentially curative. Post-operative mortality and morbidity after a repeat resection do not differ from those reported after a first resection. The 5-year survival rate of repeat hepatectomies is also similar, around 30-40% in most reported series<sup>3-5</sup>.

### Initially unresectable Metastases

When liver metastases are initially unresectable, recent strategy is to convert them into resectable metastases through neoadjuvant chemotherapy or adjuvant technical procedures<sup>6</sup>.

#### 1. Neoadjuvant chemotherapy

The last few years have seen a great improvement in chemotherapy-induced responses by the addition of newer agents such as oxaliplatin or irinotecan to the standard 5-FU/FA regimens. A major contribution offered by these more efficient regimens is that upon re-evaluation, approximately 15% of initially unresectable patients are found to be resectable and can undergo a potentially curative resection. At Paul Brousse Hospital, 701 patients with unresectable colorectal liver metastases were treated with neoadjuvant chemotherapy combining 5-fluorouracil, folinic acid and oxaliplatin, between February 1988 and September 1996. Our strategy was to reconsider liver resection in all patients whose tumors were adequately downstaged by neoadjuvant chemotherapy. After resection the patients were followed every three months and received adjuvant postoperative chemotherapy for 6 to 8 course.

Out of the 701 initially unresectable patients, 95 (14%) were found to be resectable on reevaluation after a mean of 9 courses of chemotherapy, and underwent a potentially curative resection. The main causes of initial irresectability were large (9 patients), ill located (12 patients), and multinodular liver tumors (48 patients) or concomitant extrahepatic metastases (26 patients).

There was no perioperative mortality and the complication rate was 23%. Associated surgical procedures included 28 repeat hepatectomies, 11 cryotherapies, 12 concomitant GI tract resections and 20 pulmonary resections. The overall five years survival was 35% from the time of resection, similar to that reported for primarily surgical candidates and 39% from the onset of chemotherapy<sup>7,8</sup>.

Recent results showed that secondary resectability could also be achieved with irinotecan-based chemotherapy regimens.

However, the combination of chemotherapy and conventional surgery is sometimes insufficient to achieve radical treatment.

## 2. Specific techniques aiming at improving respectability

Three different situations may be encountered with for each, a possible therapeutic solution:

### a. Portal embolisation

When only a small anatomical part of the liver is tumour-free, and is insufficient to allow hepatic regeneration after extensive hepatectomy, preoperative portal vein embolisation may be indicated to induce atrophy of the liver to be resected and hypertrophy of the future remnant liver. In our center, PVE is performed systematically when the estimated rate of remnant functional liver parenchyma is <30%, mainly when prolonged chemotherapy is anticipated<sup>9</sup>. Following embolisation, a previously unfeasible liver resection is possible 60% of the time with a mortality rate comparable to that observed following primary liver resections<sup>9</sup>.

### b. Resection combined with cryotherapy or radiofrequency

When the initial cause of unresectability is the presence of multi-nodular bilateral metastases, new methods of ablation, such as cryosurgery or radiofrequency ablation, can be combined with hepatic resection<sup>10, 11</sup>. Cryotherapy is a treatment by which tumours are destroyed by freezing at temperatures of -180°C and the treated area left *in situ*. Radiofrequency is based on the production of tissue necrosis induced by local temperatures of 100°C produced at the tip of a probe directed at the centre of the tumor. Coagulation necrosis of treated zones has been histologically proven in resected specimens<sup>12</sup>. However, following removal of the majority of metastases through major hepatectomy, the residual tumours must be limited in number (<3) and in size (<30mm) to achieve a real efficacy of the treatment.

### c. Two-stage hepatectomy

Complete treatment is sometimes impossible with a single procedure either because the remaining tumours are too numerous, exceed 30 mm in size or are in close contact with critical vascular or biliary structures. In such cases, an incomplete resection is not indicated because of the absence of a significant survival benefit as compared to non-operated patients<sup>13</sup>. We recently proposed to reconsider liver resection in selected patients whose liver metastases could be resected by two sequential hepatectomies using for the second resection, the hypertrophy induced by the first liver resection<sup>14</sup>. The overall strategy should be curative. Two stage hepatectomies are often associated with prolonged chemotherapy and repeat liver resections and are arduous, but may prolong survival in some patients who would otherwise be candidates for a very poor outcome (3 year survival: 30 percent).

With the help of efficient chemotherapy, the surgeon now has a number of means to extend the limits of resectability. These can be successfully integrated and adapted to the needs of each individual patient with the objective of offering a chance for successfully long term survival.

## Conclusion

Resection, when feasible, is still the best treatment for liver metastases. The indications for surgery, as a potentially curative strategy for liver malignancy, may now include previously irresectable cases owing to the efficacy of chemothe-

rapy to downstage tumor disease and to the combination of conventional resection with adjuvant techniques such as cryotherapy or radiofrequency.

The management of patients with liver metastases is based on a multimodal treatment strategy, which uses all the available treatments including chemotherapy, other adjuvant treatments such as portal embolisation, local ablative therapy, two-stage resections, repeat hepatectomies and resection of extra-hepatic metastases. The surgeon must integrate all these so as to coordinate and adapt the treatment to each individual patient, and thereby extend the limits of resectability. In this way, it may become possible to increase the proportion of patients who are candidates for resection from current levels at 10 to 20%. Further developments in adjuvant treatments, based on the molecular biology of liver tumours, will be needed to lower recurrence and improve long term disease-free survival.

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