Chemotherapy and surgery: new perspectives on the treatment of unresectable liver metastases

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Liver metastases concern half of patients with colorectal cancer, and are frequently unresectable, jeopardizing patient outcome. Owing to increased efficacy, chemotherapy can render initially inoperable patients amenable to potentially curative resection. The 34% 5-year and 20% 10-year survival of patients resected following neoadjuvant chronomodulated chemotherapy with 5-fluorouracil, folinic acid and oxaliplatin is similar to that of patients whose disease was operable at diagnosis. Recently, a group of 16 patients were treated with irinotecan and became resectable after treatment. Their survival (56% at 3 years) matches that of patients treated with other forms of chemotherapy. The poor prognosis of patients with non-resectable hepatic metastases might now be improved by the combination of chemotherapy and surgery.

Introduction

Approximately 50% of colorectal primaries are complicated by liver metastases [1–3]. When these metastases can be surgically resected, patients can expect a longer survival, with a median overall survival (OS) of around 3 years [3, 4]. This compares with a median OS of around 15–20 months with regional or systemic chemotherapy. However, only 10% to 20% of patients with hepatic metastases have resectable disease at the time of presentation. This grim outlook has stimulated the development of neoadjuvant treatments aiming to improve resectability, of which chemotherapy is the most widely used, with the advantage of treating both liver metastases and of preventing and treating extrahepatic disease.

Principles of surgery for resectable liver metastases

Surgery is the only potentially curative treatment, and therefore should be the first therapeutic option in patients with resectable disease. The main risk of surgery is post-operative liver failure relating to the volume of the resected liver [5]. The quality of hepatic tissue that may be altered by chemotherapy is also important, as is the degree of ischemic damage related to maneuvers of vascular occlusion during heptectomy.

Increasing knowledge of liver anatomy, better control of intra-operative bleeding and the use of intra-operative ultrasound (which acts as ‘the eye of the surgeon within the liver’) has been improving outcome [6]. In a series of 1066 resections of liver metastases from different primaries, carried out at the Paul Brousse Hospital, operative mortality (death within 2 months) is now only 1.1%. Other series have reported similar results [7–9].

In the resection of liver metastases, several principles have been established. First, provided that a margin of 1 cm around the tumor is respected, the amount of liver resected has no prognostic significance [10]. Secondly, provided that resection is complete, the type of resection (anatomical or wedge) does not influence outcome [11]. Thirdly, palliative surgery has no place: resection of liver metastases must be all or nothing. Patients undergoing less than complete resection experience the same outcome as unresected patients [12].

In a series of 526 patients resected for colorectal metastases at our institution between 1980 and 1999, the 5-year survival rate was 37% and the 10-year survival rate 22%, similar to our previous reports [6, 13]. Although encouraging, these figures do mean that approximately two-thirds of patients achieve no long-term survival benefit from surgery. Factors predictive of recurrence and poor prognosis include Dukes’ stage disease, larger volume and number of metastases, the presence of extrahepatic disease and high pre-operative carcinoembryonic antigen levels [11].

The best outcome is obtained when patients have no comorbid conditions, three or fewer metastases, no extrahepatic disease and clear surgical margins following resection [5]. However, there are no hard and fast rules. For example, although 5-year survival in patients with fewer than four metastases is 38% while that in patients with a greater number is only 23%, surgery offers patients in the latter group a one in four chance of long-term survival, which they could not have hoped for without resection (Figure 1). The same is true of patients with concomitant extrahepatic tumors, in whom 5-year survival is still 23% provided that extrahepatic tumor is resectable (Figure 2). It is therefore appropriate to propose liver resection whenever feasible and potentially curative, irrespective of prognostic factors.

Surgery of non-resectable liver metastases downstaged by chemotherapy

Although 80% to 90% of patients with colorectal cancer liver metastases are not resectable at diagnosis, their chance of
being alive at 5 years, even with gold standard chemotherapy, is no more than 2% [6, 12–14].

It is in this context that chemotherapy can have a critical role in transforming at least a proportion of unresectable patients into patients in whom surgery is possible.

The Paul Brousse Hospital series from 1988 to 1996 contains data on 872 patients, 701 of whom (80%) presented as non-resectable [15]. In half of these cases, the reason was multinodular disease; in others, the metastases were judged too large or ill-located, or with extrahepatic tumor presumably precluding a curative approach. Of these 701 patients, 95 (13%) were eventually resected as a result of treatment.

In the group of patients resected following chemotherapy, the 5-year survival rate is 34%. These figures almost exactly match those seen in patients whose disease was resectable at the outset (Figure 3).

The morbidity and mortality associated with resection of initially inoperable liver metastases is acceptable. In the series presented, no patients died within 2 months of surgery (operative mortality 0%). Twenty-three per cent experienced peri-operative morbidity, including two post-operative hemorrhages requiring further surgery, four cases of biliary leaks and 12 fluid collections, four of whom infected but were treated non-operatively.

The majority of patients of this initial series received oxaliplatin-based chrono-modulated chemotherapy.

More recently, since irinotecan is registered in combination with 5-fluorouracil, a small group of 16 patients became resectable following treatment with irinotecan. Their mean age was 54 years, the mean tumor size 46 mm and mean number of nodules eight. Patients received a mean of eight pre-operative cycles of chemotherapy. They underwent a limited hepatic resection (one or two segments) in four cases (25%), and a major hepatectomy (three or more segments) in 12 (75%). The 53% 3-year survival of these 16 irinotecan patients matches that of the 123 treated with other forms of chemotherapy (Figure 4). Nine are alive and four disease-free at a median follow-up of 2.9 years (Figures 5 and 6).

The treatment of liver metastases requires close collaboration between oncologists and surgeons. Currently, active chemotherapy is a means of improving outcome of initially unresectable patients by allowing tumor downstaging and secondary liver resection. In certain patients, other additional surgical procedures are needed to achieve resectability. In multiple unilobar disease, when the projected remnant liver is <30% of the total liver, portal embolization can induce hypertrophy of the healthy liver, leading to resectability [16]. In multiple bilobar disease, in situ destruction of residual non-resectable tumors by radiofrequency or cryosurgery may be associated with liver resection to achieve potential radicality of the procedure. Two-stage hepatectomy is also an alternative for those patients whose tumors could not be resected in a single procedure [17].

In conclusion, surgery remains the gold standard treatment for patients with resectable liver metastases. For patients with non-resectable metastases, improvements in chemotherapy have resulted in significant benefit of survival. However, long-term survival is only exceptionally obtained with chemotherapy alone. Encouraging data are now emerging with the combined use of
neoadjuvant chemotherapy and surgery. The long-term remission increasingly observed in unresectable patients treated by this combined approach opens new perspectives for a category of patients otherwise doomed to a rapid fatal outcome.

**Disclosure**

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**References**

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**Figure 5.** Abdominal computed tomography scan of a patient with unresectable synchronous liver metastases at time of diagnosis.

**Figure 6.** Abdominal computed tomography scan of the same patient after 11 courses of chemotherapy with irinotecan. Tumor downstaging allowed further hepatic resection.


