

Current surgical strategies for the treatment of colorectal cancer liver metastases

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Abstract

Hepatic metastases are a common complication of colorectal cancer and affect around 50% of all patients with this disease. Surgical resection is the gold standard treatment for metastases and significantly prolongs survival. The optimum results from surgery are obtained in the following circumstances: three or fewer metastases, no extra-hepatic disease, smaller metastases, metastases confined to one lobe and clear surgical margin (>1 cm). In patients who relapse following removal of metastases, repeat resections can give the same degree of survival benefit as the original resection. Resection is only an option for a small proportion of patients, and most patients with hepatic metastases will present with unresectable disease. Strategies for treating initially unresectable disease include neoadjuvant chemotherapy aimed at downsizing the metastases and making them suitable for resection, with specific techniques such as cryotherapy and radiofrequency ablation combined with resection, portal embolisation and two-stage hepatectomies. © 2004 Elsevier Ltd. All rights reserved.

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1. Introduction

The liver is the most common, and often the only, site of metastases in patients with colorectal cancer. Approximately half of all patients with colorectal cancer will develop hepatic metastases. Among patients with untreated hepatic metastases, the median survival time has been reported to be between 4 and 21 months, depending on prognostic factors, with no long-term survivors at 5 years [1]. Surgical resection of metastases markedly increases the patient's chances of survival, and 5-year overall survival rates of 25–40% have been reported [2–7]. However, only a small proportion of patients, around 10–20%, will present with hepatic disease that is suitable for resection. The remaining majority of patients have disease that is initially unresectable disease, due either to the number, size and location of metastases or to insufficient liver reserve. Promising

treatment options for these patients include regional approaches, such as hepatic cryosurgery and radiofrequency ablation combined with resection, and neoadjuvant chemotherapy, designed to downstage the lesions to enable resection.

2. Disease characteristics influencing the success of resection

Among patients with resectable disease, there are a number of factors which have been found to influence the outcome following surgery.

2.1. The number of hepatic lesions

In general, patients with fewer hepatic lesions have a better prognosis following surgical resection than those with more lesions [7–10], although some investigators have found no effect of the number of lesions on prognosis [11,12]. In the series of 411 patients from our hospital, significantly more patients with fewer than four

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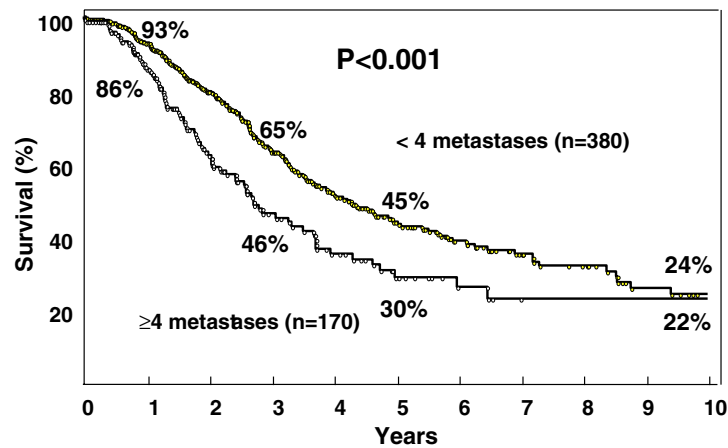


Fig. 1. Survival after liver resection of colorectal metastases according to the number of metastases. Data from 550 patients from the Paul Brousse Hospital.

metastases were alive at five years compared with those with ≥ 4 metastases (45% versus 30%, $p < 0.001$) (Fig. 1). It should be noted that by 10 years, however, the overall survival in both groups was comparable (24% and 22%). It is also worth bearing in mind that nearly one-third of the patients with ≥ 4 metastases were alive at 5 years: if hepatic disease had not been resected, few, if any, would be expected to be alive at this time. This highlights the importance of the resection of hepatic metastases even in patients with poor prognostic factors.

2.2. The resection margin

The existence of tumour cells in the surgical resection margin negatively influences survival [7,12–14]. Scheele *et al.* [14] showed that patients with incomplete radical resection of hepatic metastases had a similar survival to patients with untreated resectable hepatic metastases. In both groups, the median survival was approximately 1 year shorter than in patients with completely resected hepatic metastases. The size of the resection margin is associated with poor prognosis [8,9,15–17], and obtaining a clear resection margin of 1 cm is generally the recommended surgical approach. While resections with smaller margins may not adversely affect survival in some patients, evidence of a correlation between narrow margins and extensive disease (e.g., a high number of metastases, bilateral sites and extended hepatectomy) [17] points to generally poorer prognosis in these patients.

2.3. Extra-hepatic disease

Another factor which has been shown to adversely influence outcome is the existence of extra-hepatic disease, frequently in the lung, the second most common site for colorectal metastases. Most of the studies pub-

lished to date looking at extra-hepatic disease have shown a significant negative impact on survival compared with no extra-hepatic disease [5,7,11,18]. In a series of 425 patients who underwent liver resection of colorectal metastases at our hospital between 1981 and 1998, 36% of 341 patients with no extra-hepatic disease were alive at five years compared with 23% of 68 patients with extra-hepatic disease. However, this difference in survival did not reach statistical significance. As with the number of colorectal metastases, there was no difference between the two groups in survival at 10 years (19% and 16%, respectively). The value of the surgical management of patients with both pulmonary and hepatic metastases is still unclear. However, data from a number of analyses have revealed that around one-third of patients treated in this way are alive at five years (Table 1), demonstrating the usefulness of aggressive pulmonary/hepatic metastases resection in improving the outlook of this poor prognostic group.

2.4. Other factors

Patient outcome following hepatic resection is also negatively influenced by the diameter of the largest metastasis (large versus small) [7,9], the hepatic distribution of the metastases (bilobar versus unilobar) [12] and hepatic lymph node involvement [19].

2.5. Predicting response

Fong *et al.* [7] developed a scoring system for predicting which patients derive the greatest survival benefit from hepatic resection. This system is based on a number of largely pre-surgical characteristics: extra-hepatic disease, node-positive primary tumour, the length of the disease-free interval between primary tumour and metastasis, the number of hepatic tumours, the largest hepatic tumour, the level of carcinoembryonic antigen and

Table 1
Operative mortality associated with surgical resection of hepatic colorectal metastases

Reference	Date of series	No. of patients	Early mortality (%)
Fortner <i>et al.</i> , 1984 [29]	1971–1982	58	7.0
Scheele <i>et al.</i> , 1995 [11]	1960–1992	1718	4.4
Bakalakos <i>et al.</i> , 1998 [12]	1978–1993	301	1.1
Gayowski <i>et al.</i> , 1994 [6]	1981–1991	204	0.0
Jatzko <i>et al.</i> , 1995 [30]	1984–1992	66	4.5
Scheele <i>et al.</i> , 1995 [11]	1989–1992	114	1.8
Elias <i>et al.</i> , 1998 [16]	1984–1996	187	2.0
Fong <i>et al.</i> , 1999 [7]	1985–1998	1001	2.8
Adam <i>et al.</i> , 2003 [39]	1988–1996	95 ^a	0.0

^a Initially non-resectable patients only.

a positive resection margin. In their analysis, in which one point was assigned for each criterion, 14% of patients with a score of 5 were long time survivors, suggesting that even with bad prognostic factors, long-term remission is possible with surgery.

3. Resection techniques

In terms of the surgical technique used, small metastases (≤ 5 cm) on the surface of the liver can be removed by simple wedge resection [2]. For tumours larger than 5 cm, or where there are multiple metastases, a major liver resection is required. As our understanding of the anatomy of the liver and the role of resection in the treatment of colorectal metastases has improved, the aggressiveness of liver resections has increased. Typical resections include right and left lobectomies, right and left trisegmentectomies and left lateral segmentectomy, and many resections now involve removing over 50% of the liver [20]. Intra-operative ultrasound (IOUS), which for over 15 years has been used to scan the liver during surgery [21], is mandatory for the evaluation of the resectability of colorectal metastases. It is also an extremely useful tool for assisting surgeons to identify areas of vasculature within the liver and so help with resection. IOUS has high sensitivity and specificity [22] and, in a retrospective evaluation, revealed more information than pre-operative computed tomography [23]. This additional information can lead to a change in the surgical procedure in patients in whom new findings are made [23,24].

The risk of post-operative liver insufficiency increases with the volume of liver removed. This risk is high where there is less than 25% of the tissue remaining and relatively low in the presence of more than 40% of hepatic tissue. Clearly, the need to retain sufficient healthy hepatic tissue has to be balanced alongside the complete removal of malignant tissue. Therefore, it is generally recommended that at least 30% of hepatic tissue remain following resection to avoid the possibility of post-operative liver failure.

4. Repeat resections for recurrent liver metastases

Despite the improvements in survival seen following an initial hepatic resection, two-thirds to three-quarters of patients with successfully resected metastases will eventually suffer recurrence of their disease. In patients with good prognostic factors, repeat hepatic resection for recurrent metastases is worthwhile and can produce long-term survival rates in the region of those obtained after first resection [25,26]. Among a group of 64 patients treated at the Paul Brousse Hospital who underwent 83 repeat hepatectomies (mainly second hepatectomies [77%]), we observed 5-year overall and disease-free survival rates of 41% and 26%, respectively [27]. There was no increase in operative mortality or morbidity, or operative bleeding. An interval of more than one year between hepatectomies was independently related to survival. Recently, we have performed a retrospective analysis on patients undergoing a third hepatectomy between 1984 and 2000 and compared the results with patients from the same series who underwent first and second hepatectomies [28]. Of the 60 patients undergoing a third hepatectomy, there was a 5-year overall survival rate of 32% from the time of the third hepatectomy. This was higher than that seen in patients who were not eligible for a third hepatectomy (3-year overall survival rate of 5%) or in whom resection was not achieved (2-year overall survival rate of 15%, $p = 0.0001$), and similar to that observed in patients undergoing a second hepatectomy (5-year overall survival of 27%). The estimated 5-year survival rate of all sixty patients undergoing a third hepatectomy was 65% from the time of the first hepatectomy.

5. Complications of resection

The radical resection of such a major organ as the liver is bound to be associated with post-operative complications and this is indeed the case. Complication rates of between 20% and 50% have been reported (reviewed in [20]). The most serious complications are liver

Table 2

Resection of colorectal hepatic and/or pulmonary metastases improves patient prognosis

Reference	Hepatic and/or pulmonary resection	No. of patients	5-year survival (%)
McAfee <i>et al.</i> , 1992 [40]	Pulmonary	139	31
Okumura <i>et al.</i> , 1996 [41]	Hepatic and pulmonary	39	33
Murata <i>et al.</i> , 1998 [42]	Hepatic and pulmonary	30	44
Regnard <i>et al.</i> , 1998 [43]	Hepatic and pulmonary	43	11
Kobayashi <i>et al.</i> , 1999 [44]	Hepatic and pulmonary	47	31

failure and haemorrhage, both of which are relatively rare, occurring in up to 5% and 3% of cases, respectively. Other complications include biliary leak or fistula and peri-hepatic abscess, myocardial infarction, sympathetic pleural effusions, pneumonia and pulmonary embolism. Despite these complications, the risk of early (operative) death is relatively low. Data from as far back as 40 years ago from patients undergoing resection show operative mortality rates of between 0% and 7% [5,6,11,12,16,17,20,29,30] (Table 2). Improvements in surgical techniques and aftercare in recent years have reduced the operative mortality rate to less than 2%.

6. The treatment of initially unresectable liver metastases

6.1. Physical approaches

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. Such regional approaches involve destroying the tumour cells *in situ*. Hepatic cryosurgery is a technique that involves inserting a cryoprobe into the tumour and using a number of freeze/thaw cycles to destroy the tumour (reviewed in [31]). We have shown this to be a useful approach, in combination with systemic chemotherapy, in the treatment of malignant liver tumours [32]. In radiofrequency ablation, energy emitted from a radiofrequency electrode placed in the centre of the lesion (using ultrasound or computed tomography) leads to the generation of intense heat and consequent coagulative necrosis of tumour tissue (reviewed in [31]). This technique can be performed percutaneously and is associated with a low level of complications, but it is unsuitable for the treatment of relatively large tumours. The relative efficacies of cryosurgery and radiofrequency ablation require continued investigation.

When only a small portion of the liver is tumour-free and is insufficient to allow hepatic regeneration after extensive hepatectomy, pre-operative portal vein embolisation (PVE) can be used. The aim of this is to induce atrophy of the section of liver to be resected and at the same time cause hypertrophy of the remnant liver. In a small series of 30 patients with initially unresectable

liver metastases, PVE enabled resection to be carried out in 63% [33]. Five-year survival rates were similar in patients undergoing PVE followed by resection and those with resectable disease who had undergone resection alone (40% and 38%, respectively).

An alternative to PVE is hepatic arterial infusion (HAI). HAI delivers high concentrations of cytotoxic agents directly to the liver metastases and has been used for many years as an alternative to systemic chemotherapy. In patients with initially unresectable liver metastases there is some evidence that HAI can downstage the disease to enable resection to take place [34].

In some patients, for example those with multiple metastases, complete resection is not possible even after the use of the techniques described above. A potential approach to the treatment of these patients is two-stage hepatectomy, in which as many lesions as possible are removed in an initial resection and the remaining tumours are resected following a period of time to allow liver regeneration [35]. Although this technique is often associated with prolonged chemotherapy and repeat resections, and carries a relatively high risk of post-operative complications, it increases the proportion of patients with resectable disease and can lead to long-term remission.

6.2. Neoadjuvant chemotherapy

In patients with initially unresectable liver metastases, neoadjuvant chemotherapy is used to downstage disease to enable resection to be performed [36,37].

We have investigated the use of neoadjuvant chemotherapy for initially unresectable disease in a series of 87 patients whose disease became resectable following neoadjuvant chemotherapy, mainly with oxaliplatin-based regimens: there was a 5-year survival rate of 35% from the time of resection [38]. This rate is remarkably similar to that observed in patients whose disease was resectable at presentation and who did not receive neoadjuvant chemotherapy. No operative mortality was observed over the entire group. In view of the efficacy of irinotecan in the treatment of colorectal cancer, its use in the neoadjuvant setting was an obvious extension. Preliminary data from our hospital suggest that irinotecan is at least as effective in survival terms as other types of chemotherapy when used as neoadjuvant therapy for initially

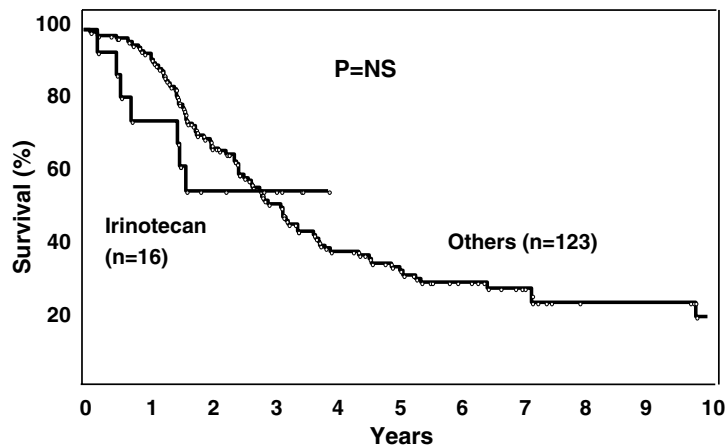


Fig. 2. Overall survival after the surgical resection of initially unresectable hepatic metastases following neoadjuvant chemotherapy with irinotecan and other chemotherapy regimens. From [39] with permission of Oxford University Press.

unresectable disease [39] (Fig. 2). Among 35 patients receiving neoadjuvant irinotecan followed by liver resection, the median overall survival was 45 months.

7. Conclusions

Liver resection is the gold standard treatment of colorectal hepatic metastases and the only approach with a chance of long-term survival. However, chemotherapy has a key role to play in the treatment of such metastases, and the management of patients requires close collaboration between the oncologist and the surgeon. Resection should be discussed as first-line therapy in cases of resectable metastases and after chemotherapy when metastases are considered unresectable. The decision of if and when to resect should be based on pre-treatment tumour and patient characteristics. However, even patients with less than optimum prognostic characteristics may benefit. For example, between one-quarter and one-third of patients with extra-hepatic disease and multiple metastases (generally regarded as poor prognostic factors) may gain a survival benefit from the resection of hepatic metastases.

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