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# The role of irinotecan in the treatment of colorectal cancer metastases: surgeons and oncologists in partnership

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**Abstract**

Resection is still the gold standard treatment for operable colorectal liver metastases. However, chemotherapy is likely to play an increasingly important role in the coming years. Many patients undergoing liver resection will eventually relapse, and adjuvant chemotherapy may help to reduce the risk of relapse. Furthermore, most patients with liver metastases present with unresectable lesions, and their chances of long-term survival are low. Neoadjuvant chemotherapy can reduce the size of the lesions, in some cases enabling them to be resected, thereby prolonging patient survival. A combination of pre- and post-operative chemotherapy may have enhanced effects on improving patient outcome, and this approach is currently being assessed. Until now, fluoropyrimidines have been the mainstay of treatment for metastatic colorectal cancer. Newer drugs, such as irinotecan, show higher activity and early reports suggest benefits in the treatment of liver metastases.


*Keywords:* Adjuvant; Colorectal; Irinotecan; Liver metastases; Neoadjuvant

## 1. Introduction

Surgical removal of liver metastases is well established as the gold standard treatment for colorectal liver metastases. Surgery has progressed from the removal of solitary metastases to multiple unilobar or bilobar metastases and to associated hepatic and extrahepatic deposits. Survival rates have increased and operative mortality has decreased (see paper by Adam in this Supplement). However, post-surgical recurrence of liver metastases occurs in up to 75% of patients. Repeat hepatic resections are feasible and are associated with survival benefits, but they are not suitable for all patients.

The treatment profile of liver metastases is changing to a more multidisciplinary approach, with chemotherapy playing an increasingly important role. Patients with resectable disease can undergo potentially curative resection (R0). Combining surgery with adjuvant chemotherapy in this setting may reduce the risk of recurrence. However, the large majority of patients (around 80%) will present with unresectable liver disease. The median survival of patients with untreated liver metastases is 4–21 months [1]. Neoadjuvant chemotherapy has been shown to downsize lesions and render them potentially resectable, thereby improving the patient's chances of prolonged survival. Thus, it is likely that neo-adjuvant and/or a combination of pre- and post-operative chemotherapy approaches may further improve resectability and survival in an increasing number of colorectal cancer patients with liver involvement.

The evaluation of chemotherapy approaches requires the use of new agents that are more active than 5-fluorouracil (5-FU)/folinic acid (FA), such as irinotecan, in well designed randomised clinical trials. In this paper we discuss evidence for the use of adjuvant and neoadjuvant

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chemotherapy combined with surgical resection for the treatment of colorectal liver metastases.

## 2. Adjuvant chemotherapy following hepatic resection

### *2.1. Adjuvant treatment using systemic delivery of chemotherapy*

Long-term results on the use of adjuvant systemic chemotherapy following hepatic resection are available from two phase III randomised trials [2,3]. In a French intergroup phase III trial initiated in 1991, patients who had undergone complete resection of liver metastases were randomised to receive bolus 5-FU/FA according to the Mayo Clinic regimen (bolus 5-FU 400 mg/m$^2$/FA 200 mg/m$^2$, days 1–5, every four weeks for cycles) ($n = 81$) or no chemotherapy ($n = 81$) [2]. There was no difference in pre-treatment patient characteristics between the groups. Adjuvant chemotherapy led to an increase in 5-year overall and disease-free survival (51% and 33%, respectively) compared with surgery alone (44% and 24%, respectively) but did not reach statistical significance (Fig. 1). Grade 3/4 toxicity was observed in one-quarter of the patients receiving chemotherapy (neutropenia 7%; thrombocytopenia 3%; stomatitis 8%, vomiting 8%; diarrhoea 8%). In the other trial, a European/North American trial, 129 patients were randomised to receive a modified Mayo Clinic regimen of 5-FU/FA following metastasectomy or no further treatment [3]. Unfortunately, this trial was closed prematurely due to slow patient accrual. Data from 107 evaluable patients showed a trend towards an advantage for chemotherapy in terms of an increase in the median disease-free (39 months versus 20 months) and overall (53 months versus 43 months) survival compared with no chemotherapy. Four-year disease-free and overall survival rates were higher in the chemotherapy arm. Although there was no statistically significant difference between the groups, the trend towards a benefit for adjuvant chemotherapy is encouraging. A non-randomised, single-centre, retrospective study has also shown a small improvement in survival with adjuvant systemic 5-FU/FA chemotherapy, but, again, this was not marked compared with surgery alone [4].

A phase III randomised trial investigating the benefit of adding irinotecan to 5-FU/FA as adjuvant therapy following complete resection of hepatic metastases is currently under way (Fig. 2). Since the previously described trials were initiated, infusional (with or without bolus) 5-FU/FA regimens have come to be accepted as being less toxic and thus have largely replaced bolus 5-FU/FA in many centres. This practice has been reflected in the design of the phase III trial, in which patients are randomised to receive intermittent bolus and infusional 5-FU/FA according to the modified de Gramont schedule (FA 400 mg/m$^2$ as a 2-h infusion followed by 5-FU 400 mg/m$^2$ IV bolus followed by 5-FU 2400 mg/m$^2$ as a 46-h infusion), either alone or in combination with irinotecan (180 mg/m$^2$ d1). Treatment is intended to continue for six months (12 cycles). The study aims to recruit over 550 patients from 83 centres in 17 countries by the end of 2004.

Finally, the effects of combining pre- and post-operative chemotherapy in patients with up to four potentially resectable liver metastases is being investigated in a European Organization for Research and Treatment of Cancer (EORTC) trial (see Section 4 for more details).

### *2.2. Adjuvant treatment using hepatic arterial infusion of chemotherapy with or without systemic chemotherapy*

Hepatic arterial infusion (HAI) is a way of delivering high concentrations of cytotoxic drugs directly to

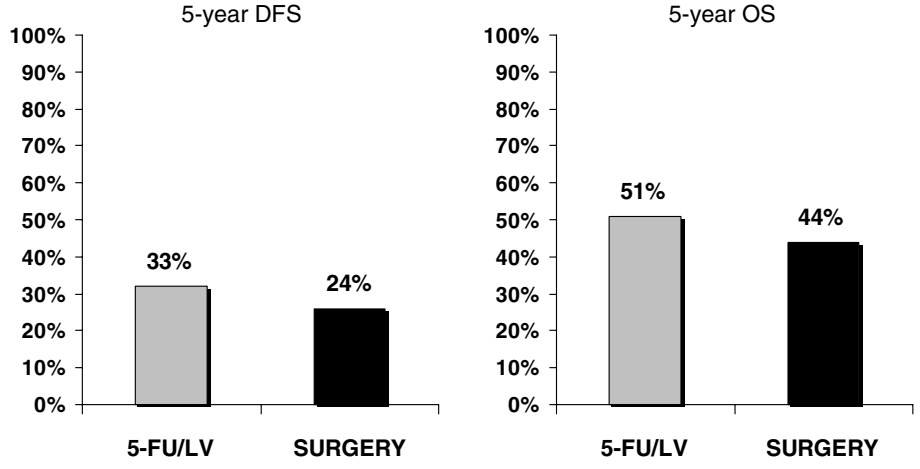


Fig. 1. Adjuvant chemotherapy with systemic 5-FU/FA following surgical resection of hepatic metastases [2].

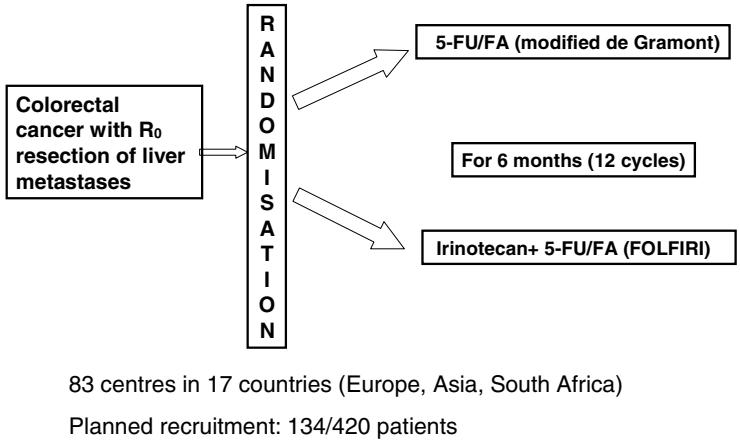


Fig. 2. Irinotecan/5-FU/FA compared with 5-FU/FA as adjuvant chemotherapy in patients undergoing resection of colorectal liver metastases – a phase III trial.

malignant tissue. The technique is based on the understanding that metastases derive their blood supply largely from the hepatic artery whereas healthy hepatocytes are supplied mainly by the portal vein. In addition, delivery of cytotoxic drugs directly to the metastases reduces the likelihood of systemic toxicity (reviewed in [5]). The mortality rate associated with HAI is low (about 1%) [6].

Results are available from three randomised trials using adjuvant HAI with a fluoropyrimidine, with or without systemic chemotherapy, following hepatic resection. The earliest reported trial, a German Cooperative group study in 226 patients who received HAI with 5-FU/FA, was terminated early when an interim analysis showed little benefit of adjuvant chemotherapy and, in fact, an increased risk of death [7]. In the subsequent two trials, chemotherapy comprised HAI with floxuridine (a 5-FU derivative that shows high hepatic extraction when delivered by HAI) together with systemic infusion of 5-FU (alone or with FA) or other chemotherapy. Using this approach, Kemeny *et al*. showed an improvement in the two-year survival rate of patients receiving chemotherapy (86% versus 72%, $p = 0.03$) [8]. An intergroup study also showed a benefit with this regimen, with a four-year disease-free survival rate of 46% compared with 25% for patients receiving surgery alone ($p = 0.04$) [9]. However the increased rates of extrahepatic failure observed with HAI alone provided the rationale for combining HAI and systemic chemotherapy.

The feasibility of combining systemic administration of irinotecan with HAI with floxuridine and dexamethasone as adjuvant chemotherapy after hepatic resection has been shown [10,11]. In a phase I/II study involving 96 patients, the maximum tolerated dose (MTD) of irinotecan in the combination was 200 mg/m$^2$ every two weeks [10]. At a median follow-up of 26 months, the two-year survival rate was 89% and all 27 patients treated at the MTD were alive. In another study, 185 patients with unresectable 5-FU-resistant hepatic metastases underwent surgical cytoreduction followed by adjuvant chemotherapy with systemic irinotecan and HAI floxuridine [11]. The recurrence rate was lower and the progression-free survival and overall survival times longer with post-operative chemotherapy compared with no further treatment.

## 3. Pre-operative chemotherapy

### *3.1. Oxaliplatin-based neoadjuvant chemotherapy*

Results from four analyses (dominated by data from one institution) of the efficacy of oxaliplatin in combination with 5-FU/FA as neoadjuvant therapy for initially unresectable colorectal liver metastases are shown in Table 1 [12–15]. The use of pre-operative oxaliplatin/5-FU/FA led to the downsizing of lesions such that between 14% and 43% of patients were able to undergo potentially curative resection. The five-year survival rates of these resected patients ranged from 35% to 50% [12–14], similar to those achieved with surgery in patients with initially resectable disease [16–18].

Table 1
Oxaliplatin/5-FU/FA neoadjuvant chemotherapy for colorectal liver metastases

| No. of evaluable patients | Patients able to undergo resection (%) | 5-year overall survival rate (%) | Reference |
|---|---|---|---|
| 330 | 16 | 40 | Bismuth *et al.* [12] |
| 151 | 51 | 50 | Giacchetti *et al.* [13] |
| 701 | 14 | 39 | Adam *et al.* [14] |
| 131 | 43 | 37 (4-year survival) | Rivoire *et al.* [15] |

Table 2
Irinotecan/5-FU/FA-based neoadjuvant therapy for colorectal liver metastases

| Dose of drug (mg/m$^2$) | | No. evaluable patients | Response rate (%) | Patients able to undergo resection (%) | Median overall survival (months) | Reference |
|---|---|---|---|---|---|---|
| Irinotecan | 5-FU/FA | | | | | |
| 180 | 400/200<br>1200 48-h CI | 40 | 48 | 33 | >19 | Pozzo *et al.* [34] |
| 260 | 400/400<br>2400 46-h CI | 55 | 53 | 31 | Not reached in resected patients | Ducreux *et al.* [20][a] |
| 180 | 200 24-h CI | 32 | NR | 34 | 37 (resected patients) | Slater *et al.* [22] |
| Various (retrospective analysis) | | 46 | 63 | 71 | 35 | Clavero-Fabri *et al.* [21] |
| 180 | 400/200<br>600 CI | 28 | 56 | 11 | NR | Ho *et al.* [35][b] |
| 180 | 400/200<br>600 22-h CI | 31 | 48 | 35 | 20.5<br>(not reached in patients with completely resected metastases) | Zelek *et al.* [23] |

[a] Data as of October 2003.
[b] Interim analysis. 5-FU, 5-fluorouracil; FA, folinic acid; CI, continuous infusion; NR, not reported.

### 3.2. Irinotecan-based neoadjuvant chemotherapy

In the last few years, irinotecan has been investigated in the neoadjuvant setting with encouraging results.

Systemically administered irinotecan, in combination with systemic 5-FU/FA, as neoadjuvant chemotherapy enabled between 30% and 70% of patients with initially unresectable liver metastases to undergo potentially curative resection (Table 2) [19–23]. Survival times of up to 37 months in resected patients have been reported. Treatment is generally well tolerated, the main toxicities being neutropenia and diarrhoea.

Pozzo *et al.* reported results of a single-centre study using irinotecan (180 mg/m$^2$) with bolus and infusional 5-FU (400 mg/m$^2$ bolus and 1200 mg/m$^2$ continuous infusion)/FA (200 mg/m$^2$) as neoadjuvant therapy for patients with unresectable metastases. Treatment was repeated every two weeks and response was assessed every 12 weeks (six cycles) [19]. As of October 2003, among 40 evaluable patients, there was a response rate of 48%, including two complete responses. As a result of treatment, 33% of patients were able to undergo potentially curative liver resection (Table 2). As expected, resection rates were greater among patients who achieved a partial or complete remission compared with those with stabilised disease. No resections could be performed in patients with disease progression. At a median follow-up of 19 months, all patients were alive. Treatment was well tolerated: grade 3/4 haematological toxicity and gastrointestinal toxicity were reported in 35% and 13% of patients, respectively.

The use of a higher dose of irinotecan (260 mg/m$^2$) in combination with bolus and infusional 5-FU/FA as first-line therapy in metastatic colorectal cancer has been investigated by Ducreux and colleagues [20]. 5-FU/FA was administered according to the De Gramont schedule (FA, 200 mg/m$^2$; 5-FU 400 mg/m$^2$ bolus and 600 mg/m$^2$ 22-h continuous infusion for two days every 15 days) or a simplified version of it. As of October 2003, 55 patients had been treated and efficacy data are available for 44 of them. Over half of these patients, 53%, achieved an objective response (partial response). Following treatment, 17 patients (31%) underwent surgery with curative intent for liver and/or lung metastases (Table 2). Eleven of these patients, that is one-fifth of all the patients treated, had complete R0 resections. At a median follow-up of 16.3 months, overall survival had not been reached in resected patients. Grade 3/4 neutropenia was observed in 75% of patients, and was associated with fever in 11% of patients. Grade 3/4 diarrhoea was reported in 15% of patients.

In another study, investigators reported the benefits of a relatively aggressive approach using systemically administered irinotecan/5-FU/FA combined with HAI delivery of pirarubicin (60 mg/m$^2$) [23]. This led to the resection of lesions in 35% of patients with initially unresectable disease. The median progression-free survival time was higher amongst those patients with completely resected metastases than among the whole group (20.2 vs 9.1 months). Similarly, median overall survival was 20.5 months over the whole group but had not been reached among those with completely resected metastases. The main toxicity was grade 3/4 neutropenia, which was observed in 78% of patients.

#### 3.2.1. Regional administration of irinotecan

In some cases, regional delivery of chemotherapy can be an alternative to surgery for the control of liver metastases. Initial studies have shown that HAI with irinotecan either alone or in combination with 5-FU/FA is an effective strategy and can rescue patients whose disease has progressed on systemic chemotherapy [24,25].

Table 3
Irinotecan/oxaliplatin/5-FU/FA – a triplet combination as neoadjuvant chemotherapy for colorectal liver metastases

| Dose of drug (mg/m$^2$) | | | No. evaluable patients | Response rate (%) | Patients able to undergo resection (%) | Median overall survival (months) | Reference |
|---|---|---|---|---|---|---|---|
| Irinotecan | Oxaliplatin | 5-FU/FA | | | | | |
| 175 | 100 | 3800 48-h infusion/200 | 42 | 71 | 26 | 26.5 | Falcone *et al.* [27] |
| 175 | 110 | 650–800/250 | 40<br>18[a] | 28<br>50 | NR | NR | Comella *et al.* [29][b] |
| 180 | 85 | 400/400<br>2400 46-h CI | 13 | 80 (of 10 patients) | 62 | NR | Ychou *et al.* [28] |

[a] Dose-finding study: this figure represents assessable patients from the final two cohorts who were receiving the highest tolerated doses of 5-FU.
[b] Immature data; 5-FU, 5-fluorouracil; FA, folinic acid; NR, not reported; CI, continuous infusion.

### *3.3. Irinotecan/oxaliplatin/5-FU/FA – triple-drug combinations for neoadjuvant chemotherapy*

The activity of the individual anti-tumour agents, irinotecan, oxaliplatin and 5-FU/FA, in colorectal disease prompted investigation into the benefits of combining the three agents. In the first clinical case reported with this combination as first-line therapy in metastatic colorectal cancer, six cycles of treatment led to a 70% reduction in tumour size in the liver [26].

A number of preliminary studies have used the triplet combination as neoadjuvant therapy, and the results of three phase I and II studies using various dosing regimens in initially unresectable disease are shown in Table 3 [27–29]. Following treatment with bolus irinotecan and oxaliplatin, and bolus and infusional 5-FU/FA, between one-quarter and two-thirds of patients were eligible for resection [27,28]. The most relevant toxicities observed were grade 3/4 neutropenia (and febrile neutropenia) and diarrhoea.

### *3.4. The impact on patient outcome of tumour response to neoadjuvant therapy*

The success of neoadjuvant chemotherapy depends on the control of tumour progression prior to resection. Adam and colleagues recently published the results of a study in which patients with more than three hepatic metastases underwent neoadjuvant chemotherapy, mainly with 5-FU/FA and irinotecan or oxaliplatin [30]. The liver resection performed was macroscopically complete and potentially curative. For patients in whom disease was downstaged or stabilized following chemotherapy, the 5-year survival rate was good (58% and 45%, respectively). However, none of the patients who underwent resection with tumour progression were alive at five years. Similar findings were reported by Allen *et al.* [31]. They showed that there was no difference in the 5-year survival rate between patients receiving neoadjuvant chemotherapy prior to resection and those receiving no chemotherapy (43% and 35%, respectively). However, when the comparison was made between patients whose disease did not progress while on neoadjuvant chemotherapy and those not receiving chemotherapy, the former group had a significantly improved survival (85% versus 35%, $p = 0.03$). These results point to tumour response to neoadjuvant chemotherapy being a good prognostic indicator of survival.

## 4. Combining pre- and post-operative chemotherapy

Pre-operative chemotherapy is of value not only for downsizing tumours in initially unresectable disease, but may improve the outcome in patients with resectable disease [32,33]. In a retrospective analysis of 71 patients with multiple bilobar metastases, neoadjuvant chemotherapy prior to surgery was associated with a significantly better 5-year survival rate and fewer extended hepatectomies than surgery alone [33]. It is logical, therefore, to combine pre-operative and post-operative chemotherapy in an attempt to further improve survival. The EORTC is currently enrolling patients with up to four potentially resectable liver metastases to such a trial. Randomisation is to either surgery alone or in conjunction with pre- and post-operative oxaliplatin/5-FU/FA. The primary endpoint of the trial is a 40% improvement in 3-year progression-free survival.

## 5. Conclusions

Although surgery remains the standard treatment for resectable hepatic metastases, the benefits of chemotherapy are being increasingly recognised, especially with regard to facilitating the resection of initially unresectable liver metastases. As such, the management of patients with hepatic metastases requires a multidisciplinary approach. Adjuvant chemotherapy following total or partial resection of colorectal hepatic metastases may have important survival advantages. It is necessary to determine the impact of this approach with new drugs/regimens with greater activity than 5-FU/FA. Irinotecan, which is now a standard agent in the treatment of metastatic colorectal cancer, is an obvious candidate and is being investigated in a randomised

phase III trial. For patients with initially inoperable liver metastases, neoadjuvant chemotherapy can enable resection in some cases. Recent recommendations from a French expert meeting recommend the use of either irinotecan or oxaliplatin in combination with 5-FU/FA, with treatment being guided only by tolerability and contra-indications. For both adjuvant and neoadjuvant chemotherapy, the optimum route/s of administration of chemotherapy – systemic, HAI or a combination of both – also requires clarification.

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