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Current Perspective

# Adjuvant chemotherapy after resection of liver metastases from colorectal cancer

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ABSTRACT

Colorectal liver metastases are common and found in almost 50% of patients with colorectal cancer. Surgical excision, whenever possible, is the optimum form of treatment and should be carried out with the intention of removing all macroscopic disease (R0 resection). However, recurrence frequently occurs within the remaining liver as well as at extra-hepatic sites. The role of adjuvant systemic chemotheraphy in an attempt to reduce the incidence of recurrence has been investigated in several studies. This review discusses the possible incorporation of adjuvant systemic chemotheraphy following liver resection.



## 1. Introduction

Colorectal liver metastases are common and found in almost 50% of patients with colorectal cancer. Approximately 30% of these patients present with liver metastases at the time of initial diagnosis of the primary tumour (synchronous), whereas the remainder develop in the subsequent post-operative period (metachronous).

The optimum treatment for colorectal liver metastases is surgical resection. In many studies, the 5-year survival following liver resection ranges from 25% to 40%.[1–3] The survival, however, in non-resected patients is barely 18 months.[4]

It has been estimated that approximately 85% of patients with liver metastases have disease which is considered to be unresectable at presentation. Liver resection should aim to remove all macroscopic disease if optimum outcome is to be achieved. In recent years, attempts have been made to increase the resectability rate by neoadjuvant (downstaging or 'up-front') chemotherapy. As a result of the substantial improvement in neoadjuvant combination chemotherapy, response rates and survival have improved (Table 1).

Nevertheless, it should be recognised that patients who develop recurrence after liver resection have disease predominantly within the remaining liver. Often this occurs in isolation, although it is frequently combined with extra-hepatic disease. It is assumed that micro-metastases were present at the time of initial liver resection in the remaining lobes but could not be detected by the present day scanning techniques. In order to deal with this theoretical possibility, the question of adjuvant chemotherapy following liver resection has been raised and several studies relating to this therapeutic intervention have been reported (see Table 2).

For any adjuvant therapy, a number of issues are of supreme importance and require consideration. These are, firstly selecting patients most likely to benefit and therefore, secondly avoiding unnecessary toxicity in patients who would not benefit thus ensuring that the degree of toxicity does not overshadow any minimal benefit in terms of overall survival. In order to deal with this dilemma, prospective randomised clinical trials are necessary and a few have been carried out.

It is important to define adjuvant chemotherapy in this situation. Neoadjuvant chemotherapy is given to downstage liver metastases so that the subsequent liver resection with

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**Table 1 – Resection rates following neo-adjuvant chemotherapy**

| Study | Regimen | Response rate (%) | Resection rate (%) | Median survival (months) |
|---|---|---|---|---|
| Wein[5] | 5FU/FA | 42 | 17 | |
| Giacchetti[6] | 5FU/FA + Oxal. | 59 | 51 | 24 |
| Alberts[7] | Folfox 4 | 60 | 40 | 26 |
| Masi[8] | 5FU/FA/Oxal/CPT | 72 | 26 | 26 |

**Table 2 – Adjuvant systemic chemotherapy following liver resection**

| Study | Median FU months | ADJ treatment | Median PFS months | Median overall survival months |
|---|---|---|---|---|
| Mitry et al.[17] | Not reported | 5 FU/FA versus surgery | 26.4 versus 18.6 ($p = 0.059$) | 61.1 versus 46.9 ($p = 0.125$) |
| Portier et al.[18] | 87 | 5 FU/FA versus surgery | 24.4 versus 17.6 ($p = 0.028$) | 62.1 versus 46.4 ($p = 0.13$) |

the removal of all macroscopic disease is feasible.[9] This might be combined with post-operative chemotherapy also. However, in patients in whom all macroscopic disease has been resected, adjuvant chemotherapy is given with the objective of reducing the incidence of hepatic recurrence as well as extra-hepatic metastases, which hopefully will translate into an improvement in a median survival. It is this aspect which will be discussed in this review concentrating on randomised studies.

Although neoadjuvant studies will not be considered, nevertheless, it should be recognised that pre-operative chemotherapy may have a role to play in the selection of appropriate patients. By assessing a response to pre-operative chemotherapy, it is theoretically possible to predict the patients whose tumours are most likely to respond to post-operative adjuvant chemotherapy. This is based on the assumption that any viable micro-metastases present in the remaining liver are likely to respond in a similar fashion.

## 2. Selection

Appropriate imaging is essential to recognise the extent of liver metastases. Numerous studies have investigated the relative diagnostic performance of ultrasound, CT, MRI and FDG-PET as well as PET-CT.[10,11] Accurate imaging is necessary to determine not only the resectability but also the prevalence of extra-hepatic disease which may determine the efficacy of liver resection. Appropriate evaluation of the lungs is particularly important. PET-CT has demonstrated a high level of sensitivity for the detection of extra-hepatic metastases thus altering the decision for surgery. Unnecessary laparotomy can be avoided in significantly more patients undergoing FDG-PET scanning than with other investigations.[11] This is highly desirable. Surgeons should have a high degree of certainty that a laparotomy will result in a beneficial resection before embarking on this. Accordingly, the results of pre-operative scanning are crucial and the importance of discussion of each patient in a multi-disciplinary environment cannot be overemphasised.

## 3. Principles of surgery

The aim of surgery is to remove all macroscopic disease resulting in an R0 resection (clear resection margins). It has been recognised that providing the patient has a normally functioning liver pre-operatively, at least 30% of the liver should remain after surgery in order to avoid the danger of liver failure. In general, a surgical margin of approximately 10 mm is recommended but this depends to a degree on the anatomical location.[12] The presence of adjacent lymph node involvement should not necessarily be considered an absolute contraindication to resection.[13] In addition, the presence of a limited number of small lung metastases is in itself not considered an absolute contraindication.[14]

It is probably best to avoid simultaneous major resections of both the colon and the liver because of the high complication rate and the detection of an increased number of liver or distant metastases after an interval of 2–3 months.

The benefit of treatment in a specialist centre with all appropriate multi-disciplinary facilities has been recognised increasingly over the last few years.

## 4. Adjuvant chemotherapy

Post-operative adjuvant chemotherapy has been advocated following liver resection to theoretically destroy any dormant malignant cells in the remaining liver. Numerous randomised clinical trials have demonstrated the benefit of adjuvant systemic chemotherapy following resection of stage III colon cancers and therefore this principle might be extrapolated to patients with liver metastases. Adjuvant chemotherapy can be delivered in two ways:

### 4.1. *Hepatic arterial infusion (HAI)*

A cannula is positioned in the hepatic artery at the time of liver resection for post-operative infusion chemotherapy. There have been seven randomised trials on HAI involving 592 patients. A systemic review has been carried out but no significant advantage for hepatic artery chemotherapy was

found in the meta-analysis, measuring overall survival and calculating survival based upon 'intention to treat'. (95% confidence interval = –0.1189 to 0.2885, or a hazard ratio of 1.089, an 8.9% survival advantage for the control group, 95% confidence interval of the hazard ratio = 0.887).[15] In addition, it was noted that adverse events related to hepatic artery therapy were common including five therapy related deaths. Intra-hepatic recurrence was more frequent in the control group (97 patients versus 43 in the HAI group).

One of the studies, however, showed a positive result with an overall survival at 2 years of 86% compared to 72% with a systemic therapy alone. In this study, the rates of adverse events were similar in the 2 groups.[16]

Nevertheless, although recurrence in the remaining liver appears less in the hepatic artery chemotherapy treated patients, overall survival is not improved and may even be favoured in the control group. Post-operative complications are also greater in patients receiving hepatic arterial infusion chemotherapy compared to a systemic chemotherapy.

### 4.2. *Adjuvant systemic chemotherapy*

Although there have been two randomised trials reviewing the role of adjuvant systemic chemotherapy following liver resection, these have been unsatisfactory and did not recruit the targeted number of patients to provide sufficient statistical power.[17,18] An important recent phase III EORCT study has recently reported benefits from peri-operative chemotherapy after surgical resection. This multi-centre trial randomised 364 patients to receive surgery alone ($n = 182$) or surgery + FOLFOX 4 chemotherapy with 6 cycles before and 6 cycles after ($n = 182$). On further evaluation, several patients in each arm were found to be ineligible for inclusion resulting in 152 patients in the surgery group alone and 150 patients in the chemotherapy and surgery group.[19]

On an intention to treat analysis, there was no statistically significant difference in progression free survival between the 2 groups ($p = 0.058$). A second analysis was performed including only patients who had undergone surgery. In this group, progression free survival at 3 years was 32% versus 42.4% in the adjuvant chemotherapy group ($p = 0.025$). This statistically significant difference was translated into a progression free survival benefit of 9.2%. Overall survival is still being assessed and was not available in this report.

Needless to say, there were a number of adverse events in the peri-operative chemotherapy group including neutropenia, diarrhoea and neurological toxicity. There were more reversible post-operative complications in patients receiving chemotherapy compared to surgery only (25% versus 16%, $p = 0.04$). The conclusion from this study was that progression free survival was improved. Future studies are being established utilising different chemotherapy regimes with the addition of biologically active substances, e.g. cetuximab.

The data from this single randomised trial are impressive and suggest a possible benefit for peri-operative systemic chemotherapy following resection of liver metastases. Nevertheless, the results of overall survival are awaited. There is an increased toxicity associated with these regimes, and therefore care needs to be taken in determining a relevant protocol. In patients with localised disease suitable for resection, whether additional chemotherapy should be added needs to be discussed in the context of a multi-disciplinary meeting. It would appear that patients at a high risk of recurrence following resection can reasonably be offered adjuvant chemotherapy, whereas patients with solitary metastases (or limited disease) may not benefit sufficiently to overcome the disadvantage of toxic side-effects.

## 5. Conclusion

Although there are strong theoretical arguments in favour of adjuvant systemic chemotherapy following resection of liver metastases, the evidence to suggest an improvement in survival following this regime is still lacking. Selection of patients is crucial. Patients with localised solitary metastases should undergo resection aiming for a curative R0 resection. Whether these patients will subsequently benefit from addition of chemotherapy is still unknown. Patients with more extensive disease in whom there is still doubt about R0 resection might benefit from additional systemic chemotherapy.

Accordingly, it is still not possible to provide a blanket recommendation with regard to adjuvant chemotherapy following liver resection. The evidence from the EORTC trial is promising and certainly provides support for adjuvant therapy to be considered in individual patients. Further studies are awaited with interest.

## Conflict of interest statement

None declared.

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