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# The use of neo-adjuvant chemotherapy in patients with resectable colorectal liver metastases: Clinical risk score as possible discriminator

N. Ayez [a], E.P. van der Stok [a], D.J. Grünhagen [a,*], J. Rothbarth [a], E. van Meerten [b], A.M. Eggermont [c], C. Verhoef [a]

[a] *Department of Surgical Oncology, Erasmus MC Cancer Institute, Erasmus University, Rotterdam, The Netherlands*

[b] *Department of Medical Oncology, Erasmus MC Cancer Institute, Erasmus University, Rotterdam, The Netherlands*

[c] *Cancer Institute, Gustave Roussy Cancer Campus, Grand Paris, France*

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**Abstract**

*Aim*: The combination of surgery and chemotherapy (CTx) is increasingly accepted as an effective treatment for patients with colorectal liver metastases (CRLM). However, controversy exists whether *all* patients with resectable CRLM benefit from perioperative CTx. We investigated the impact on overall survival (OS) by neo-adjuvant CTx in patients with resectable CRLM, stratified by the clinical risk score (CRS) described by Fong et al.

*Methods*: Patients who underwent surgery for CRLM between January 2000 and December 2009 were included. We compared OS of patients with and without neo-adjuvant CTx stratified by the CRS. The CRS includes five prognosticators and defines two risk groups: low CRS (0–2) and high CRS (3–5).

*Results*: 363 patients (64% male) were included, median age 63 years (IQR 57–70). Prior to resection, 219 patients had a low CRS (neo-adjuvant CTx: N = 65) and 144 patients had a high CRS (neo-adjuvant CTx: N = 88). Median follow-up was 47 months (IQR 25–82). In the low CRS group, there was no significant difference in median OS between patients with and without CTx (65 months (95% CI 39–91) vs. 54 months (95% CI 44–64), P = 0.31). In the high CRS group, there was a significant difference in OS between patients with and without CTx (46 months (95% CI 24–68) vs. 33 month (95% CI 29–37), P = 0.004).

*Conclusion*: In our series, patients with a high CRS benefit from neo-adjuvant CTx. In patients with a low risk profile, neo-adjuvant CTx might not be beneficial.



*Keywords:* Surgery; Chemotherapy; Liver metastases; Clinical risk score

## Introduction

Colorectal carcinoma is one of the leading causes of cancer death world-wide, mostly as a consequence of metastatic disease.[1] Administration of combined chemotherapy regimens improves survival rates of patients with colorectal metastases (CRLM).[2–4] If metastases are confined to the liver, surgical resection is the most effective therapy, providing the only potential for cure.[5,6] However, cancer relapse after curative resection of CRLM is a common phenomenon, with recurrence rates up to 50% in the first 2 years.[7] In an attempt to reduce these recurrence rates, the combination of liver resection with systemic therapy, either pre-, peri- or postoperatively, is increasingly researched. Multiple studies have investigated the impact of adjuvant chemotherapy in addition to surgery for CRLM, but have failed to show survival benefit.[8,9] Recently, the mature results of the landmark EORTC 40983 trial, studying the impact of perioperative chemotherapy, were published

* Corresponding author. Dept. of Surgical Oncology, Erasmus MC Cancer Institute, P.O. Box 5201, 3008 AE Rotterdam, The Netherlands. Tel.: +31 10 7041506; fax: +31 10 7041011.

*E-mail address:* d.grunhagen@erasmusmc.nl (D.J. Grünhagen).

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showing no overall survival benefit for patients in the chemotherapy group.[10,11] Therefore, the exact role of systemic therapy in combination with resection for CRLM remains unclear. Nonetheless, some reports recommend to treat the majority of patients with CRLM with neo-adjuvant chemotherapy.[12]

In order to predict the likelihood of tumour recurrence and survival after resection of CRLM, several Clinical Risk Scores (CRS) have been developed.[5,13–18] The most widely used and validated CRS has been described by Fong et al., in 1999.[15] In this publication, 5 independently prognostic clinical variables for survival after surgery for CRLM are identified. Furthermore, 2 risk groups (high/low) are characterized: patients with a high risk profile have significantly worse overall survival rates as compared to patients with a low risk profile. Although all CRLM may well be regarded as "high risk", this CRS may explain, at least in part, the relative lack of efficacy of systemic therapy when combined with surgery in the metastasized setting. It is not uncommon in other types of malignancies (e.g. breast, primary colon) to reserve the use of adjuvant chemotherapy to those patients with the most advanced disease (highest risk profile). The present retrospective study aimed to evaluate overall survival outcome in patients with and without neo-adjuvant chemotherapy, stratified by their clinical risk profile as described by Fong.

## Patients and methods

Between January 2000 and December 2009, all consecutive patients who underwent liver resection for CRLM were analysed. Patients were assessed by Fong's CRS and excluded from the analysis if they had missing data to calculate the CRS and/or extrahepatic disease. Calculation of the CRS was based on clinical data at diagnosis of CRLM. The clinical prognosticators in Fong's CRS were: (1) node positive status of primary tumour (pathological), (2) disease-free interval from the primary to discovery of the liver metastases $<12$ months, (3) number of metastases $>1$ (radiological), (4) size of the largest metastases $>5$ cm (radiological) and (5) preoperative CEA level $>200$ ng/ml.[15] Each criterion is assigned one point. The prognostic value of this scoring system has been verified by independent research groups.[19,20] We identified two risk groups: low risk (CRS 0–2) and high risk (CRS 3–5), in concordance with the original study. The rationale for dividing patients in two risk groups was to evaluate whether the CRS may play a role in explaining the relative lack of efficacy of chemotherapy when combined with surgery in the metastasized setting.

### *Chemotherapy*

Erasmus MC Cancer Institute is a tertiary referral hospital for patients with CRLM. In our treatment protocol, perioperative chemotherapy is not standard of care for patients with CRLM. All patients in this study were assessed by a dedicated liver surgeon in a multidisciplinary meeting with respect to resectability before potential administration of chemotherapy. Patients in our hospital received neo-adjuvant chemotherapy in case of multiple ($\geq$4), synchronous metastases. However, a large proportion of patients in this study received neo-adjuvant chemotherapy in the referring hospital, after which patients are transferred to our unit for liver surgery. The reason for administering one type of chemotherapy over another was based on local treatment protocols. All patients received a combination of 5-fluorouracil (5-FU)/Capecitabine and Oxaliplatin or Irinotecan, with or without Bevacizumab. The response to neo-adjuvant systemic therapy was assessed after two or three cycles by CT scan (according to RECIST[21]) and carcinoembryonic antigen levels. Further treatment strategy was determined on basis of the tumour response and extent of the disease. When the liver metastases were resectable, a laparotomy was planned at least three weeks after the last course of neo-adjuvant chemotherapy. Bevacizumab had to be excluded from the last course of chemotherapy to ensure an interval of at least six weeks. All patients included in this study had resectable CRLM, resectability of liver metastases was assessed by a liver surgeon at diagnosis. None of the patients received standard adjuvant systemic therapy after liver surgery.

Patients were included after 2000, as from then on modern chemotherapy and biologicals were available. In our unit, the definition of resectability has not changed since 2000 (i.e. possibility of an R0 resection, the feasibility of securing vascular in- and outflow as well as biliary drainage to the remaining segments, and a future liver remnant of at least 20–30%)

### *Follow-up*

Follow-up after resection of CRLM consisted of clinical examination and measurement of CEA every 3 months. Abdominal imaging (ultrasound, CT-thorax-abdomen) was performed at 3, 6, 9 and 12 months in the first year, every 6 months the second year and once per year thereafter. If recurrent disease occurred, palliative or curative treatment strategies were considered by the multidisciplinary team.

### *Outcome*

Overall survival (OS) was defined as the interval in months between resection of CRLM and death, or the date of last follow-up. Disease-free survival (DFS) was defined as the interval in months between resection of CRLM and recurrence, death without recurrence, or date of last follow-up without recurrence.

### *Statistics*

Descriptive values are expressed as median (interquartile range (IQR)). Variables were compared by means of chi-