Chapter 2

Cytoreductive surgery and HIPEC for peritoneal metastases combined with curative treatment of colorectal liver metastases
Systematic review of all literature and meta-analysis of observational studies

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Abstract

Objective: Assess the overall outcome in colorectal cancer (CRC) patients that present with a combination of peritoneal metastases (PM) and liver metastases (CRLM) after curative resection and hyperthermic intraperitoneal chemotherapy (HIPEC) in the current literature.

Methods: A systematic literature search according to the PRISMA guidelines was conducted using the PubMed database of the U.S. National Library of Medicine using the keywords: colorectal cancer, liver metastasis, extra-hepatic, peritoneal metastases, peritoneal carcinomatosis, cytoreductive surgery (CRS), HIPEC and combinations hereof. Papers focusing on CRS and HIPEC for PM combined with curative treatment of CRLM were included, provided sufficient information on survival outcomes could be extracted. Duplicate publications were excluded. Meta-analysis was performed using the method described by Tierney et al.

Results: After screening and full-text assessment of 39 papers, six articles were included containing data on combined PM and CRLM in patients treated with curative resection of both sites and HIPEC or early postoperative intraperitoneal chemotherapy (EPIC). Three articles provided enough statistical information for meta-analysis. Pooled hazard ratio (HR) was extracted from survival curves and was 1.24 (CI 0.96–1.60). A comparison was made with patients presenting with isolated PM undergoing CRS and HIPEC and with patients with disseminated disease undergoing (modern) systemic chemotherapy.

Conclusions: In the absence of randomized controlled studies, we found in this systematic review and meta-analysis of patients with a combination of colorectal metastases in the liver as well as in the peritoneum show a trend towards a lower overall survival after curative resection and HIPEC, when compared to patients with isolated peritoneal metastases after CRS and HIPEC (pooled HR 1.24, CI 0.96–1.60). However, patients with metastatic CRC show a tendency towards increased median overall survival after CRS and HIPEC combined with resection of liver metastases when compared to treatment with modern systemic chemotherapy.
Introduction

Colorectal carcinoma (CRC) is the third most common cancer worldwide. Approximately half of CRC patients develop distant metastasis, mainly through haematogenous dissemination to the liver via the portal circulation. These colorectal liver metastases (CRLM) are preferably treated by surgical resection, achieving a 5-year survival rate of 35-45%.

Distant metastases from CRC to the peritoneum, i.e. peritoneal metastases (PM) develop in 10-25% of CRC patients and in up to 25% the peritoneum is the sole site of metastasis. It is not known whether this is a different aetiology of metastasizing, and if so, if it is influenced by the (biology of) the primary tumour, the host, the metastasis or a combination of the aforementioned. Based on the observed metastasis pattern, PM is generally considered a local form of CRC dissemination. Local aggressive treatment is therefore warranted in a select group of patients presenting with PM.

Traditionally, untreated PM is associated with poor survival of about 6-12 months. Even modern systemic chemotherapy does not seem to yield any clinically significant gain in survival for patients presenting with PM. In the early 1990’s a treatment with a curative intent for patients with PM of CRC, without evidence of distant metastasis was introduced, which consists of surgery (cytoreductive surgery, CRS) combined with heated intraperitoneal chemotherapy (HIPEC).

In a prospective randomised controlled trial (RCT) a subgroup of patients - in whom there was no residual macroscopic tumour - showed a five-year survival equal to that of patients undergoing resection for CRLM’s (35-45%). Data obtained from several non-randomized comparative studies support this finding, reporting 5-year overall survival rates of up to 51%.

It is not known what percentage of CRC patients present with PM in combination with liver metastases. In combination with other distant metastases it is estimated to be approximately 75%. The presence of liver metastasis is considered a contra-indication for CRS & HIPEC. Moreover, the presence of PM is also considered a contraindication for curative resection of CRLMs.

Since both separate sites of metastasis have been curatively treated by surgery, cases have been reported of patients with PM of CRC that have been treated with a combination of resection, including that of liver metastases and HIPEC. This has proven to be feasible.

We conducted a systematic review, according to the PRISMA guidelines, focusing on papers reporting the clinical outcomes of patients with a combination of PM and CRLM, treated with CRS and HIPEC combined with curative treatment for the concomitant CRLM. In addition, a meta-analysis of published data was performed.
Materials and Methods

Literature search

A systematic literature search was conducted using the PubMed database of the U.S. National library of Medicine using the following keywords: colorectal cancer, liver metastasis, extra-hepatic, peritoneal metastases, peritoneal carcinomatosis, cytoreductive surgery, HIPEC and combinations hereof (Table 1) Papers focussing on cytoreductive surgery and HIPEC for peritoneal metastases combined with curative treatment of CRLM, but providing enough information on survival outcome after treatment with curative intent were included.

These search terms were employed in order to include as many publications as possible on the subject. Additional papers were incorporated by manually cross-referencing from publications retrieved in the initial search. Only full-text papers in English were included that have been published between 1990 and April 2012. Considerable effort was made to detect possible duplication of published data by reviewing the institutions, authors and period of follow-up reported.

Table 1: Search strategy

<table>
<thead>
<tr>
<th>Colorectal cancer</th>
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<td>extrahepatic</td>
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<td>peritoneal metastasis</td>
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<td>peritoneal carcinomatosis</td>
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<td>cytoreductive surgery</td>
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<td>HIPEC</td>
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<tr>
<td>liver metastasis</td>
<td>AND</td>
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<td></td>
<td>HIPEC</td>
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<tr>
<td>cytoreductive surgery</td>
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<td>extrahepatic</td>
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<tr>
<td>peritoneal metastasis</td>
<td>AND</td>
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<td></td>
<td>cytoreductive surgery</td>
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<td>peritoneal carcinomatosis</td>
<td>AND</td>
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<td></td>
<td>cytoreductive surgery</td>
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<td>HIPEC</td>
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Inclusion- & Exclusion criteria

Initially, all available observational cohort studies were considered. Studies on CRC patients with peritoneal- in combination with liver metastases, treated with a combination of CRS & HIPEC and curative treatment of the liver metastases were included for individual review. Additional review was conducted when deemed necessary. Studies in which data on the PM in combination with CRLM curatively treated with CRS & HIPEC and hepatic resection or an ablative technique could not be extracted from the published article were excluded from the final analysis. When studies overlapped or duplicated, those articles with more complete data on the subgroup of interest were retained.

Quality assessment & Data extraction

To assess study quality we used the North-England evidence-based guidelines. Categories of evidence:

Ia: Evidence obtained from meta-analysis or randomized controlled trials
Ib: Evidence obtained from at least one RCT
IIa: Evidence obtained from at least one well-designed controlled study without randomization
IIb: Evidence Obtained from at least one other type of well-designed controlled study without randomization
III: Evidence obtained from well-designed non-experimental descriptive studies such as comparative studies, correlation studies and case studies
IV: Evidence obtained from expert committee reports or opinions, or clinical experiences of respected authorities

We extracted relevant data from all full-text articles. These included the following parameters: First author, year of publication, study design, level of evidence, study population characteristics, number of patients in the PM in combination with CRLM group as a percentage of the entire study population, time of follow-up, and all available survival data.

To ensure accuracy and minimize bias, all noticed discrepancies were discussed and settled through consensus discussion.

Statistical analysis

Survival outcomes reported in the included series was the main area of interest. The median overall survival was the outcome used to report the initial comparison between the different cohorts.
In the absence of randomized controlled trials on this subject, we further assess the survival outcomes of patients curatively treated for the combination of PM and CRLM versus PM alone by subsequently analysing included series with comparative cohorts. They were included in the meta-analysis on the condition that the published article provides enough statistical information to do so. All included studies were weighed using the inverse variance, the precision, to assess the effects of the cohorts included. Hazard ratio (HR) was used as measure for comparison in the meta-analysis, which was extracted from each published cohort included from the Kaplan-Meier by using the method previously described by Tierney et al. 28. The subsequent pooled HR and its corresponding 95% confidence interval (CI) were subsequently calculated using a fixed model as described by DerSimonian et al. 29 For the generation of the corresponding figures, we utilized a web-based meta-analysis tool 30. Further statistical analysis of the data was performed using the statistical package for the social sciences (SPSS Inc, Chicago IL) version 18 for OSx.

Results

We identified a grand total of 939 publications for screening and selection. Fig. 1 shows the flowchart depicting the literature search and selection process.

Observational studies and meta-analysis

After meticulous screening and selection, six articles of interest remained. Reasons for excluding 33 full-text articles are summarized in figure 1, one of which is exclusion of 4 duplicate or overlapping publications (based on same patient cohort in time). To correct for this, we included the most recently published article with complete data on the subgroup of interest in our analysis. The remaining six articles provided minimally the median overall survival of the group with a combination of PM and CRLM curatively treated with CRS and HIPEC in combination with hepatectomy, radio-frequency ablation (RFA) or cryosurgery. All eligible studies were published in between 2004 and 2010. Representing data on a total of 139 patients, with the biggest cohort being included in the most recent study, comprising of 70 patients. 21 The follow-up per study ranged from 1 month up to five years. 20,21,31-34 All studies reported overall survival for this particular subpopulation. It was only possible to extract individual patient data from 1 study 32. The median overall survival reported ranged from 6 months and 36 months (fig.2). Figure two depicts reported range of overall survival reported in these six studies in contrast to the range in overall survival reported in literature on 1) several (sub)groups of patients presenting with isolated PM treated with CRS and HIPEC 6,7,12,18,35-38 and 2) patients extracted from several series with PM of CRC treated with (modern) systemic chemotherapy, including biologicals. 13,14,39-41
Figure 1: Flowchart of inclusion of the studies.

All patients in the six analysed studies underwent CRS and HIPEC or EPIC for the treatment of the PM of CRC. The treatment of CRLM varied per study. All main characteristics of these studies are summarized in table 2.

By considering the known prognostic factors affecting treatment outcome after CRS and HIPEC for patients with PM of CRC as described previously, some aspects stand out that differ between the studies; We noticed that there is considerable difference between the baseline characteristics of the population undergoing CRS plus HIPEC (PCI, presence of malignant ascites, occlusive syndrome). The methods of reporting the total intra-abdominal disease burden, excluding the CRLM, differ per study. In some the Gilly method is applied and in others the peritoneal cancer index is utilized. Overall, the PCI range can be broken down into PCI ≥ 11-20 and PCI ≤ 11. Two studies also included patients with PCI ≥ 11-20, while the remaining four studies included predominantly patients with PCI ≤ 11. Overall in all six studies the cohort reported is comprised predominantly of patients in whom an R0 resection was achieved. Elias et al only included patients (100%) in which an R0 was achieved.
Table 2: Main characteristics of six articles included in the qualitative analysis

<table>
<thead>
<tr>
<th>1st author</th>
<th>Year of Publication</th>
<th>PM + CRLM</th>
<th>Number of patients (as % of total study population)</th>
<th>Median OS (mths)</th>
<th>PM Treatment method</th>
<th>HIPEC / EPIC compound</th>
<th>HIPEC method</th>
<th>Per-operative systemic chemotherapy used</th>
<th>CRLM treatment method</th>
<th>LE</th>
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<tr>
<td>Carmignani</td>
<td>2004</td>
<td>subpopulation</td>
<td>16 (59.3%)</td>
<td>15.2</td>
<td>CRS + HIPEC/EPIC</td>
<td>MMC / 5-FU</td>
<td>Coliseum technique</td>
<td>Unknown</td>
<td>Resection or left in-situ</td>
<td>III</td>
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<tr>
<td>Kianmanesh</td>
<td>2007</td>
<td>subpopulation</td>
<td>16 (37%)</td>
<td>36.0</td>
<td>CRS + HIPEC</td>
<td>MMC - Cisplatin</td>
<td>Unknown</td>
<td>Resection</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>Chua</td>
<td>2009</td>
<td>subpopulation</td>
<td>16 (29.1%)</td>
<td>*</td>
<td>CRS + HIPEC/EPIC</td>
<td>MMC / 5-FU</td>
<td>Unknown</td>
<td>Resection</td>
<td>III</td>
<td></td>
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<tr>
<td>Varban</td>
<td>2009</td>
<td>subpopulation</td>
<td>14 (9.9%)</td>
<td>23.0</td>
<td>CRS + HIPEC</td>
<td>MMC</td>
<td>Closed technique</td>
<td>Resection, Cryo-surgery</td>
<td>III</td>
<td></td>
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<tr>
<td>Cavaliere</td>
<td>2010</td>
<td>subpopulation</td>
<td>7 (6.2%)</td>
<td>6.0</td>
<td>CRS + HIPEC</td>
<td>MMC - Cisplatin + Oxaliplatin</td>
<td>Closed technique + closed</td>
<td>5-FU + Leucovorin</td>
<td>Unknown</td>
<td>III</td>
</tr>
<tr>
<td>Elias</td>
<td>2010</td>
<td>subpopulation</td>
<td>70 (15.9%)</td>
<td>24.7</td>
<td>CRS + HIPEC/EPIC</td>
<td>MMC / 5-FU</td>
<td>Multiple</td>
<td>5-FU + Leucovorin</td>
<td>Unknown</td>
<td>III</td>
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* MMC = Mitomycin C, RFA= Radio-Frequency Ablation, LE= Level of Evidence
* The median overall survival could not be extracted, however it was possible to calculate the corresponding HR using the Tierney et al method
One study also included patients with malignant ascites and occlusive syndrome, both factors that have been reported to negatively impact survival after treatment. Data on lymph node status and response to adjuvant chemotherapy were not available for further analysis.

Furthermore, two out of six studies provided detailed description of the associated CRLM. The number reported ranged from 1-7, with a median of 1. The article by Varban et al also reported a median diameter of 3 cm, ranging from 0.4-12 cm. The remaining publications did not provide data on the number, site and diameter of the associated CRLM. In light of the overall either retrospective or not-controlled nature of the studies, we performed a meta-analysis of available observational studies. For the meta-analysis, three out of six studies assessed in detail provided sufficient statistical information for adequate analysis. A combined total of 100 patients were included in these studies with a combination of PM and CRLM of CRC. When compared to CRC patients whom present with isolated PM, the calculated HR was 1.24 (CI 0.96-1.60).

![Median Overall Survival Reported in Months](image)

**Figure 2:** Reported median overall survival in several subgroups of patients presenting with PM of CRC.

Modern SC = Cohort of PM patients treated with modern systemic chemotherapy (irinotecan, oxaliplatin, biological) 14,18,39,39-41. 5-FU based SC = chemotherapy regiment based on 5-FU. Combined treatment of PM & CRLM with CRS & HIPEC = Patients presenting with combination of PM and liver metastasis treated with CRS and HIPEC. CRS & HIPEC = Good quality non-randomized comparative trials on patients with isolated PM treated with cytoreduction and HIPEC. CRS & HIPEC - Only CR0 = Patients presenting with isolated PM in which complete cytoreduction was achieved, followed by HIPEC. Arrow: Reported Median Overall Survival extracted from only Randomized Controlled Trial conducted by Verwaal and colleagues.
Discussion

Currently the presence of liver metastasis is a contraindication for treatment of diagnosed peritoneal metastases (PM) with cytoreductive surgery (CRS) and hyperthermic intra-peritoneal chemotherapy (HIPEC). Conversely, the presence of PM is considered a contraindication for curative resection of CRLMs. Despite the fact that presence of CRLM is officially a contraindication for CRS and HIPEC, there is a selected group of patients presenting with a combination of CRLM and PM of CRC that are curatively treated by an aggressive surgical approach. In 2008 consensus was reached which stated that concomitant liver metastases are only to be resected when confined to three or less well-resectable lesions. In addition eligible patients should have a good performance status and low co-morbidity. Literature also reports that disease which responds adequately to neo-adjuvant systemic chemotherapy, i.e. reduction of overall tumour burden or no progressive disease during treatment, as having a less aggressive tumour biology. This is cited as a favourable factor in selecting patients for this aggressive approach. After analysis of the available data, we found that there are no prospective randomized controlled trails for this particular subgroup of PM of CRC patients. The selected group of patients undergoing this aggressive approach mostly consists of those with three or less, well resectable CRLM and relatively low PCI. During our systematic review of published literature we also identified a total of eight reviews, however three were centred on CRLM and extrahepatic disease in general without the addition of CRS and HIPEC, three reviewed only CRS and HIPEC in patients with isolated PM and the remaining two included data on patients with PM in combination with CRLM. One article centred
largely on CRLM and extrahepatic disease and discussed one study by Elias et al in their manuscript. The review article published more recently, in 2009, discussed a number of studies included in our review as well. However, they did not apply the PRISMA guidelines in their literature search and due to the timeframe in which their analysis was performed they did not include two publications on the subject published in 2009. Both these studies are of importance, because they were published after the 2008 consensus was reached and thus have included a carefully selected group of patients with mostly less than three CRLMs. In addition, the size of the published original series in literature is relatively small and of an observational nature. Therefore, we performed a meticulous (meta-) analysis of the available data, in the absence of randomized trials. This first meta-analysis of the published data will facilitate clinical decision-making and aid in identifying the boundaries of our treatment in this group of metastatic CRC patients.

As depicted in table 2 the included studies varied in different treatments administered. Not only for PM of CRC, but also for the associated CRLM. For PM, comparison is a challenge, because the studies vary in respects to the intra-peritoneal regimen used (EPIC vs HIPEC), i.e. the procedure is not standardized. With variations in exposure techniques, administered drugs, doses, duration, optimal temperature and flow rates, makes the comparison between the different cohorts of patients a difficult task. Also different systemic chemotherapy was administered, even though it has been reported that modern chemotherapeutic regimens do not seem to alter the outcome in this subgroup of metastatic colorectal cancer patients. One tendency observed in reporting was that studies prior to the consensus meeting of 2008 do include patients with concomitant CRLM, but reported no detailed data on the number, site, resectability and diameter of the lesions. Thus no conclusion can be drawn on the baseline variables concerning the present CRLMs in our analysis. However, two out of four studies published after 2008 have reported the presence of CRLM in more detail. These included patients with median 1 CRLM, ranging from 1-7, with limited PCI (mostly ≤11). Both studies show promising treatment results, with median overall survival rates ranging from 23-36 months. In addition, they report no statistically significant difference in overall survival between patients with isolated PM and those with concomitant CRLM. However, in one study they also point out that the peritoneal cancer index of the patients with a combination of PM and CRLM is significantly lower at baseline when compared to those with isolated PM.

We extracted data from three studies for a meta-analysis according to the Tierney method. We found a pooled HR of 1.24 (CI0.96-1.60). This indicates that patients with a combination of PM and CRLM at first glance seem to fare less well when compared to patients with isolated PM treated with CRS and HIPEC. However, this finding is not statistically significant. To date, patients that are excluded from CRS & HIPEC are usually referred to the oncologist for best systemic therapy in a palliative setting. Currently, there
is no data available to compare patients that present with a combination of PM and CRLM of CRC, treated with either curative resection and HIPEC or best systemic chemotherapy. In recent years there has been considerable progress in overall survival with modern chemotherapy regiments in metastatic colorectal cancer. 59,60 However, results from data extracted from the CAIRO series and an article by Franko and colleagues show that median overall survival in patients with isolated PM, treated with several systemic chemotherapy regiments ranges from 5.2 to 23.9. (Fig. 2) 13,35,39-41 One obstacle in interpreting this data is however the fact that CRS and HIPEC patients are a highly selected group of patients in contrast to the rather heterogeneous population of metastatic colorectal cancer treated with systemic chemotherapy. 14,18 The study conducted by Franko et al does however contain a large number of patients presenting with PM in combination with CRLM (62.7%). 14 The reported median overall survival for the entire cohort was 12.7 months. The data extracted from the studies used are of moderate quality, due to the fact that some cohorts were rather small in size. As a result the ultimate result of the meta-analysis could be considerably influenced by the effect of one rather large study containing seventy patients. 21 The confidence interval ranging from 0.96 to 1.60 does imply a statistical uncertainty of this calculated HR. However, in light of the paucity of data concerning this particular subgroup of patients we still feel that our approach is scientifically valid and useful for facilitating clinical decision-making and identifying the boundaries of our treatment in this group of metastatic CRC patients.

Based on current literature and our most recent findings, patients presenting with a combination of PM and CRLM of seem to fare less well when compared to patients presenting with isolated PM. However, this could be explained as due to the additional tumour burden if one considers the abdomen as a whole. Nonetheless, based on our analysis there is currently no evidence to support exclusion of patients with additional metastases to the liver from aggressive, potentially curative, treatment. Figure 2 also shows a tendency towards better overall survival in carefully selected patients with a combination of PM and CRLM who are treated with curative resection of both sites plus HIPEC. Taking into consideration the abovementioned, careful assessment of the current literature and the available data for meta-analysis suggest that a combination of CRS and HIPEC with curative treatment for CRLM will in all likelihood result in improved survival, compared to treatment with modern systemic chemotherapy alone. However, further research comparing the different treatment modalities in a well-defined and matched subgroup of CRS and HIPEC patients is necessary.

Prediction of the patients in whom the disease will be restricted to local growth in both sites versus those in which it will disseminate further and shift via the haematogenous and/or the lymphatic route will prevent futile surgical intervention. But until we reach the era in which molecular markers can lead the way in treatment decisions in this population we...
will have to rely on clinical and pathological parameters, such as the aggressiveness of the
tumour (chemotherapy response), resectability and overall intra-abdominal tumour burden.
In conclusion, overall the international reported experience with cytoreductive surgery
and HIPEC for peritoneal metastases combined with curative treatment of colorectal liver
metastases is limited, as highlighted by the small amount of literature retrieved on the subject.
In the absence of randomized controlled studies, we found in this systematic review and
meta-analysis of a selected group of patients with a combination of colorectal metastases
in the liver as well as in the peritoneum seem to have a lower median overall survival
after curative resection and HIPEC, when compared to patients with peritoneal metastases
only after CRS and HIPEC. However, when patients were treated with CRS and HIPEC
and curative treatment of liver metastases, we found indications for improved (median)
overall survival as compared to patients treated with modern systemic chemotherapy. 13,14,21
In addition, a recent study on the specific complications associated with hepatobiliary
procedures in CRS and HIPEC patients reports a low rate of said complications. 61 Hence,
there is currently no solid evidence on which to validate exclusion of carefully selected
patients from potentially curative resection and HIPEC.
Twenty-five percent of patients that are eligible for curative resection of liver metastases
will not undergo treatment due to presence of extrahepatic disease, mostly peritoneal
metastases. 62 In addition, a currently unknown proportion of potential CRS and HIPEC
candidates are also excluded due to haematogenous spread to the liver. Keeping in mind
these statistics, we consider further studies on cytoreductive surgery and HIPEC for
peritoneal metastases combined with curative treatment of colorectal liver metastases to
be warranted.
Chapter 2 | CRS & HIPEC for combination PM and CRLM

References


