Cancer Treatment Reviews 39 (2013) 321–327

Contents lists available at SciVerse ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Controversy

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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ARTICLE INFO

Article history:
Received 12 July 2012
Received in revised form 5 November 2012
Accepted 6 November 2012

Keywords:
Liver metastases
Cytoreduction
HIPEC
Hepatectomy
Colorectal cancer
Peritoneal metastases
RFA
Chemotherapy

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 focussing 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 HR1.24, 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.

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Introduction

Colorectal carcinoma (CRC) is the third most common cancer worldwide.[1] Approximately half of CRC patients develop distant metastasis, mainly through haematogenous dissemination to the liver via the portal circulation.[2,3] These colorectal liver metastases (CRLM) are preferably treated by surgical resection,[3–5] achieving a 5-year survival rate of 35–45%.[4,6,7]

Distant metastases from CRC to the peritoneum, i.e. peritoneal metastases (PM) develop in 10–25% of the CRC patients and in up to 25% the peritoneum is the sole site of metastasis.[3,8] 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.[9] Based on the observed metastasis pattern, PM is generally consid-

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0305-7372/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ctrv.2012.11.003

ered a local form of CRC dissemination.[10] Local aggressive treatment is therefore warranted in a select group of patients presenting with PM.[6,11]

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.[12–14] 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).[15,16] 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%).[7,17] Data obtained from several non-randomized comparative studies support this finding, reporting 5-year overall survival rates of up to 51%.[12,18]

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%.[3,8,19] The presence of liver metastasis is considered a contraindication for CRS & HIPEC.[6,8,20] Moreover, the presence of PM is also considered a contraindication for curative resection of CRLMs.[19,21,22]

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.[6,10,23,24]

We conducted a systematic review, according to the PRISMA guidelines, focussing 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.

Inclusion- and 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.

Table 1
Search strategy.

Colorectal cancer			
AND			
Extrahepatic			
Peritoneal metastasis			
Peritoneal carcinomatosis			
Cytoreductive surgery			
HIPEC			
Liver metastasis	AND		
	HIPEC		
	Cytoreductive surgery		
	Extrahepatic		
	Peritoneal metastasis	AND	
		Cytoreductive surgery	AND
		HIPEC	HIPEC
	Peritoneal carcinomatosis	AND	
		Cytoreductive surgery	AND
		HIPEC	HIPEC

Quality assessment and data extraction

To assess study quality we used the North-England evidence-based guidelines.[25–27]

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 minimise 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.

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