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Systematic review of published literature on oxaliplatin and mitomycin C as chemotherapeutic agents for hyperthermic intraperitoneal chemotherapy in patients with peritoneal metastases from colorectal cancer

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ABSTRACT

Background: The role of hyperthermic intraperitoneal chemotherapy (HIPEC) with oxaliplatin in addition to cytoreductive surgery (CRS) has recently been questioned in peritoneal metastases of colorectal cancer. Whether this applies to all published CRS/HIPEC regimens is unclear.
Methods: A systematic literature search identified 46 studies on CRS/HIPEC using either oxaliplatin of mitomycin C with at least one oncological outcome parameter
Results: Oxaliplatin and mitomycin C studies were comparable regarding extent of disease, but differed substantially regarding synchronous versus metachronous presentation, application of neo-adjuvant systemic chemotherapy, duration of HIPEC, and completeness of cytoreduction for at least one of the oncological endpoints. Severe postoperative complication rate seemed significantly higher after oxaliplatin-based CRS/HIPEC.
Conclusion: Published cohorts on oxaliplatin-based CRS/HIPEC differed essentially from MMC-based procedures, especially considering the application of oxaliplatin-containing neo-adjuvant systemic therapy and shorter exposure time to intraperitoneal chemotherapy in oxaliplatin studies. No meaningful comparison could be made regarding DFS and OS.

1. Introduction

The peritoneum is a common metastatic site in colon cancer affecting about 5–10% of patients at the time of diagnosis and accounting for approximately 30% of recurrences after curative resection (Elferink et al., 2015). Treatment with systemic therapy alone yields a median survival of a mere 17 months (Franko et al., 2010). In contrast median survival of 32 months has been documented for selected patients undergoing cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) (Baratti et al., 2016). CRS aims to eradicate all visible metastases in the abdominal cavity and pelvis, whereas the aim of HIPEC is to eradicate residual microscopic disease.

The CRS/HIPEC procedure has originally been studied as multimodal treatment and an improved survival in comparison with systemic therapy alone was demonstrated (Verwaal et al., 2003). This led to gradual adoption of this procedure The surgical component of the procedure (CRS) is crucial for oncological outcome, and completeness of cytoreduction is classified as complete (CC0), small residual disease < 2.5 mm thick (CC1) or gross residual disease > 2.5 mm (CC2). Significant variability across institutes exists regarding HIPEC, in

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particular the choice of the intraperitoneal chemotherapy (Helderman et al., 2019). HIPEC with Ox is under debate for patients with colorectal peritoneal metastases who were treated upfront with Ox based systemic therapy as it did not prolong survival compared to CRS alone (Quenet et al., 2018). Notably, exposure time in most HIPEC procedures in which OX is used is only 30 min compared to 90 min or longer with MMC. After months of systemic chemotherapy, we hypothesize that the remaining cancer cells in the peritoneal cavity may be resistant to Ox. This RCT has questioned the role of HIPEC in addition to high quality CRS in general, but it is not clear whether the regimen used in this trial can be extrapolated to other CRS/HIPEC regimens.

The aim of this systematic review was to evaluate published literature on CRS/HIPEC for PMCRC with either MMC- or OX-based regimens, regarding patient selection, use of perioperative systemic therapy, procedural characteristics, morbidity, disease-free survival (DFS) and overall survival (OS).

2. Methods

2.1. Search strategy

A comprehensive literature search was performed of the PubMed, Embase and Cochrane Library databases. Seach terms included “colorectal neoplasm”, “colon cancer”, “rectal cancer”, “peritoneal carcinomatosis”, “peritoneal metastasis”, “induced hyperthermia”, “HIPEC”, “hyperthermic intraperitoneal chemo”, “oxaliplatin” and “mitomycin C”. This process was executed in collaboration with and under the supervision of a clinical librarian, who made sure to adhere to the PRISMA criteria.

All eligible studies identified through this process, were independently screened by two reviewers and screened on title and abstract. Any conflicts were resolved by discussion until consensus was reached. The eligibility of the remaining articles was assessed by both reviewers based on screening of the full-text. Additional studies were identified through the searching of bibliographies and related citations of the articles already included.

2.2. Study selection

Studies were eligible for inclusion if they described patients with PMCRC who were treated with CRS/HIPEC using either OX or MMC as chemotherapeutic agent. Studies had to report on at least one oncological outcome measure (DFS or OS) and/or severe postoperative complication rate. Severe postoperative complications were defined as any complication requiring surgical, endoscopic or radiological re-intervention or re-admittance to the intensive care unit (ICU). A maximum of 15% appendiceal primary tumors within the colorectal cohort was accepted when no distinction was made in primary outcome measures.

Exclusion criteria were: case reports, patients described with PM originating from a tumor other than of colorectal origin or more than 15% of appendiceal origin, any chemotherapeutic agent other than OX or MMC given intraperitoneally, and early postoperative intraperitoneal chemotherapy (EPIC) protocols. The arbitrary threshold for appendiceal origin was chosen as these tumors usually show a more benign biological behaviour, and overrepresentation in a study would compromise the ability to extrapolate the data for our purposes. No restrictions were made based on language or date of publication. The latest search was performed on March 2nd 2018.

2.3. Quality assessment

Methodological quality of the included articles was assessed by two independent reviewers using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Cohort Studies. A study was considered to be of high quality if a minimum of six out of the 11 questions that make up this checklist were answered with ‘yes’. This cut-off value was chosen through discussion and ultimate consensus between the two reviewers.

2.4. Data extraction

Both reviewers performed the search independently. The data was extracted from each of the included articles independently, after which the separate data extraction tables were combined into one. General study characteristics included first author, year of publication, study design, exclusion criteria, chemotherapeutic agent, sample size and median follow-up duration. Clinico-pathological and procedural characteristics included ratio of synchronous to metachronous PMCRC, Peritoneal Cancer Index (PCI) or Dutch Region Count, completeness of cytoreduction, duration of the total CRS/HIPEC procedure and duration of HIPEC, perfusion characteristics, and perioperative systemic chemotherapy (CT) regimens. Extracted surgical and follow-up items were: blood loss, hospital and ICU stay, severe postoperative complication-rate, hematologic toxicity, postoperative mortality rate, reoperation rate, costs, DFS and OS.

2.5. Assessment of comparability between MMC and OX studies

Comparability of procedural characteristics included duration, temperature and dosage of chemoperfusion. In addition, four factors were chosen to assess the comparability of MMC and OX studies. These were the ratio of synchronous to metachronous PMCRC, the administration of neo-adjuvant systemic chemotherapy, the extent of PMCRC as preferably defined by the PCI, and CC score. All four criteria were assessed for survival outcomes, with the exception of neo-adjuvant systemic chemotherapy when assessing the comparability for the severe postoperative complication rate. Systemic chemotherapy was thought not to significantly influence postoperative complications, considering that a chemotherapy-free interval of a few weeks is often applied, with restricted application of targeted agents such as bevacizumab. CC-score of zero or one was used as discriminator, corresponding to R-scores of 1 (no residual macroscopic disease) and 2a (macroscopic residual disease up to 2.5 mm), respectively.

2.6. Outcome measures

The main outcome measures of this study were severe postoperative complication rate, DFS and OS.

2.7. Statistical analysis

Meta-analysis was performed using RStudio. Pooled proportions with 95% confidence intervals (95% CI) were calculated for the one-, three-, and five-year OS and DFS rates in both groups, as well as for the severe postoperative complication rate using the inverse variance method with a Random Effects Model. To evaluate the heterogeneity in outcomes of the studies per agent, the I^2 statistic was calculated. In case of $I^2 > 50\%$, heterogeneity was considered to be high. Conclusions on comparability of the studies for each of the outcome parameters were made based on educated observation through the joint effort of two reviewers (DW & LB). A random effect meta-regression was used to compare pooled proportions for severe complications. Two-sided p-values < 0.05 were considered to indicate statistically significant difference.

3. Results

3.1. Literature search

A total of 642 studies were identified through electronic searches of PubMed (175), Embase (441) and Cochrane Library (Simkens et al., 2019). After duplicate removal, 510 studies were screened based on title and abstract, resulting in a further exclusion of 375 studies. Full-

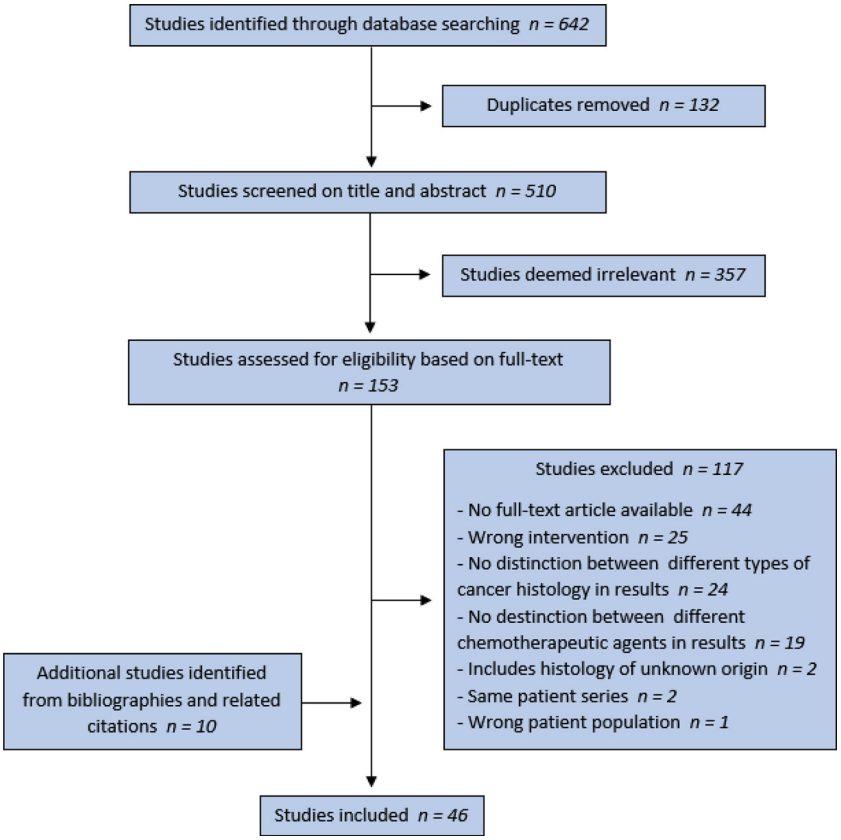

Fig. 1. Flowchart showing selection process.

text screening of the remaining 153 studies, led to exclusion of 117 studies. After cross-referencing, an additional 10 studies were included. A total of 46 studies qualified for data-extraction (Fig. 1).

3.2. General study characteristics

The general study characteristics of all included studies are shown in Table 1. All studies have been published between 1996 and 2018. Six out of 46 studies were prospective cohort studies and the remaining 40 studies had a retrospective design. Of all studies included, six were comparative cohort studies on MMC versus OX, 28 were cohort studies on MMC and 12 on OX. Common exclusion criteria were 'distant metastases' or 'extra-abdominal metastases', 'incomplete cytoreduction', 'poor performance status' and 'unresectable disease'. A total of 3516 patients were included in the final analysis, of whom 2768 patients received MMC and 748 received OX. Median follow-up ranged from 10 months to 63 months. Median follow-up could not be extracted for 25 studies, due to median follow-up times concerning multiple different subgroups.

3.3. Quality assessment

Assessment of methodological quality showed 41 studies to be of high quality. Of the five studies deemed to be of lower quality, one was a comparative study, three reported on MMC only and one on OX only. This leads to five/six comparative studies being considered to be of high quality and 25/28 studies on MMC and 11/12 of the studies on OX being of high quality. Confounding factors or limitations to the study concerned the retrospective study design in nearly all studies or the sometimes incomplete reporting of patient and tumor characteristics. Moreover, the relatively small patient population was often named as a limitation and a selection bias was frequently identified. This bias arose as patients were often selected according to strict criteria (i.e. good physical condition and no systemic metastases), leaving a population with overall favorable conditions.

3.4. Procedural characteristics of MMC- and OX-based HIPEC procedures

Out of all 46 included studies, a mere two studies failed to specify the procedural characteristics of the HIPEC procedure. These were 'Tan et al. (2017)' and '(Ching et al., 2015)', both reporting on MMC. All other studies showed highly similar procedural characteristics. Intraperitoneal perfusion with MMC lasted 90 min in nearly all studies (range: 60–150 minutes) and the perfusate was generally maintained at 42 °C (range: 38.5 °C–43 °C). The dosage was set at 35 mg/m^2 (range: 10 mg/m^2 - fixed dosage of 60 mg) in the vast majority of the studies reporting on MMC. Perfusion with OX lasted 30 min in all studies but one ('Elias et al., 2006a', 35 min). The perfusate was generally maintained at an intraperitoneal temperature of 43 °C (range: 41 °C–44 °C) and in all but two studies the dosage was set at 460 mg/m^2 (exceptions: 'Leung et al., 2016' & 'Kirby et al., 2014', both reporting a dosage of 350 mg/m^2). In the majority of the studies, the OX was diluted in a 5% dextrose/glucose perfusate of a volume of nearly always 2 L/m^2.

3.5. Severe postoperative complications

In the meta-analysis on severe postoperative complication rate 17 articles on MMC and 10 articles on OX were included. A proportion of 21% in the cohort receiving MMC developed severe postoperative complications, versus a proportion of 30% in the cohort treated with OX (Figs. 2 and 3).

Significant heterogeneity was observed in both groups. Comparability of the MMC and OX studies was assessed for three of four predefined criteria.

Table 1
General study characteristics.

Author, year	Study design	Chemotherapeutic agent assessed	Exclusion criteria	Sample size	Median follow-up
Van Eden et al., 2017	Retrospective cohort, single centre	Mitomycin C versus Oxaliplatin	Cytoreduction score > R2a Secondary HIPEC	MMC: 104 Ox: 73	MMC: 32.7 months Ox: 14.0 months
Hompes et al., 2014	Retrospective cohort, dual centre	Mitomycin C versus Oxaliplatin	Cytoreduction score > CC1	MMC: 56 Ox: 39	MMC: 5.1 years Ox: 2.8 years
Prada-Villaverde et al., 2014	Retrospective cohort, multicentric	Mitomycin C versus Oxaliplatin	Incomplete cytoreduction (> CC-1) Poorly differentiated or Signet Ring cell carcinomas	MMC: 418 Ox: 166	–
Leung et al., 2016	Retrospective cohort, single centre	Mitomycin C versus Oxaliplatin	PC of appendiceal origin Distant metastases PCI > 20 before 2013, PCI > 15 from 2013 onwards	MMC: 96 Ox: 106	–
Rouers et al., 2016	Retrospective cohort, single centre	Mitomycin C versus Oxaliplatin	PCI > 15	MMC: 13 Ox: 8	24.9 months
Simkens et al., 2016	Retrospective cohort, single centre	Mitomycin C versus Oxaliplatin	ECOG > 3, PCI score > 20, distant metastases (except for < 4 resectable LM), Cytoreduction Score > CC2, cytoreduction resulting in short bowel syndrome	MMC: 184 Ox: 26	–
Ching et al., 2015	Retrospective cohort, single centre	Mitomycin C	ECOG > 2 Distant metastases	35	24.7 months
Winer et al., 2014	Retrospective cohort, single centre	Mitomycin C	Distant metastases Poor performance status Unresectable disease on preop. imaging	30	4.4 years
Varban et al., 2009	Retrospective cohort, single centre	Mitomycin C	–	142	14.6 months
Gusani et al., 2007	Retrospective cohort, single centre	Mitomycin C	–	28	–
Van Oudheusden et al., 2014	Retrospective cohort, single centre	Mitomycin C	–	268	12.7 months
Simkens et al., 2017	Retrospective cohort, single centre	Mitomycin C	Cytoreduction score > R2a	133	22.9 months
Shen et al., 2008	Retrospective cohort, single centre	Mitomycin C	–	121	86 months
Braam et al., 2014	Retrospective cohort, multicentric	Mitomycin C	Distant metastases No peritoneal recurrence	132	26.2 months
Chua et al., 2011	Retrospective cohort, multicentric	Mitomycin C	–	55	–
Tabrizian et al., 2014	Retrospective cohort, single centre	Mitomycin C	–	51	15.7 months
Haslinger et al., 2013	Retrospective cohort, single centre	Mitomycin C	Distant metastases ECOG > 2	38	–
Hsieh et al., 2017	Retrospective cohort, single centre	Mitomycin C	–	32	–
Kuijpers et al., 2014	Retrospective cohort, single centre	Mitomycin C	–	71	47 months
Swellengrebel et al., 2009	Retrospective cohort, single centre	Mitomycin C	Poor performance status Extra-abdominal metastases Inoperable intra-abdominal disease	92	31 months
Frøysnes et al., 2016	Retrospective cohort, single centre	Mitomycin C	PC of appendiceal origin	119	42 months
Shen et al., 2004	Retrospective cohort, single centre	Mitomycin C	–	77	15 months
Glehen et al., 2004	Retrospective cohort, single centre	Mitomycin C	Age > 70, extra-abdominal or liver metastasis, renal or myocardial failure, systemic chemotherapy < 1 month before inclusion, central nervous system disease, World Health Organization performance status < 2A	53	59.5 months
Witkamp et al., 2001	Prospective cohort, single centre	Mitomycin C	Distant metastases, unresectable disease, abnormal findings in blood examinations, poor performance status	29	38 months

(*continued on next page*)

Table 1 (*continued*)

Author, year	Study design	Chemotherapeutic agent assessed	Exclusion criteria	Sample size	Median follow-up
Chia et al., 2019	Retrospective cohort, single centre	Mitomycin C	Distant metastases ECOG ≥ 2	23	18.5 months
Tan et al., 2017	Prospective cohort, single centre	Mitomycin C	–	61	–
Schneebaum et al., 1996	Retrospective cohort, single centre	Mitomycin C	Extra-abdominal or liver metastases	15	10 months
Mercoli et al., 2019	Retrospective cohort, single centre	Mitomycin C	Distant metastasis	45	–
Zanon et al., 2006	Prospective cohort, single centre	Mitomycin C	< 3 weeks since prior chemotherapy, age < 18 or > 75 years, ASA > 2, ECOG > 2, unresectable disease, abdominal RT, pregnant / breast-feeding, stroke / myocardial infarction < 6 months ago, mental confusion, extra-abdominal metastases Hematopoietic performance: absolute neutrophil count < 1500 mm3, platelet count < 100,000 mm3 Hepatic performance: (AST) and (ALT) > 3 x normal upper limit; bilirubin > 1.5 x normal upper limit Renal performance: creat clearance < 60 ml/minute	25	–
Klaver et al., 2011	Retrospective cohort, single centre	Mitomycin C	PC presentation > 18 months after start of adjuvant systemic chemotherapy	21	–
Glehen et al., 2003	Prospective cohort, single centre	Mitomycin C	Age > 65 Extra-abdominal or liver metastases Poor cardiorespiratory / renal status	26	–
Iversen et al., 2013	Retrospective cohort, single centre	Mitomycin C	Age > 70-75, Cytoreduction Score > 2, ASA score ≥ III, PC extent > 5 regions, extraperitoneal disease, invasive growth into the retroperitoneal space / abdominal wall, massive disease involvement of the small bowel or its mesentery, more than one stenosis of the small bowel because of PC, disease involvement of the hepatic pedicle or the pancreas	34	16.0 months
Desantis et al., 2014	Retrospective cohort, single centre	Mitomycin C	Age > 75 Poor cardiac, renal, hepatic, bone marrow function	74	–
Franko et al., 2010	Retrospective cohort, multicentric	Mitomycin C	–	67	–
Elias et al., 2009	Retrospective cohort, multicentric	Oxaliplatin	Huge or symptomatic PC, extra-abdominal metastases, poor performance status, age > 65, disease progression after 2-3 months of neoadjuvant chemotherapy	48	63 months
Gervais et al., 2013	Retrospective cohort, single centre	Oxaliplatin	Synchronous hepatic metastases	25	–
Elias et al., 2006b	Prospective cohort, single centre	Oxaliplatin	Poor performance status, age > 70, extra-abdominal metastases, evidence of bowel obstruction, abundant ascites, bulky clinical / radiological PC, incomplete resection of all visible / detectable disease, liver metastases > 2, minimal follow-up < 30 months since HIPEC	23	–
Elias et al., 2006a	Retrospective cohort, single centre	Oxaliplatin	Poor performance status, age > 65, extra-abdominal metastases, occlusive disorders, abundant ascites, bulky clinical / radiological PC, rapid progression of PC under i.v. chemo	30	55 months
Turrini et al., 2012	Retrospective cohort, single centre	Oxaliplatin	–	26	–
Van Leeuwen et al., 2007	Retrospective cohort, single centre	Oxaliplatin	Extra-abdominal metastases Karnofsky performance score < 60	38	–
Ceelen et al., 2008	Retrospective cohort, single centre	Oxaliplatin	–	32	–
Cavaliere et al., 2006	Retrospective cohort, multicentric	Oxaliplatin	–	11	16 months
Mura et al., 2007	Retrospective cohort, single centre	Oxaliplatin	Cytoreduction Score > 0	9	–
Quenet et al., 2011	Prospective cohort, dual centre	Oxaliplatin	ECOG > 2, age > 75, extra-abdominal metastases, liver metastases > 3, evidence of bowel obstruction, abundant ascites, bulky clinical / radiological PC	43	–
Rodríguez Silva et al., 2017	Retrospective cohort, single centre	Oxaliplatin	Age < 18 / > 70, PCI > 26, Cytoreduction Score > CC1, life expectancy < 12 weeks, ECOG > 2, extra-abdominal metastases, > 2 LM, biliary / ureteral obstruction, severe cardiac / lung / liver / kidney / neurological conditions that contraindicate surgery, intestinal obstruction, inadequate hematologic and hepatic balance	30	–
Kirby et al., 2014	Retrospective cohort, single centre	Oxaliplatin	PC > 15 without LM PC > 10 with 3+ LM	15	–

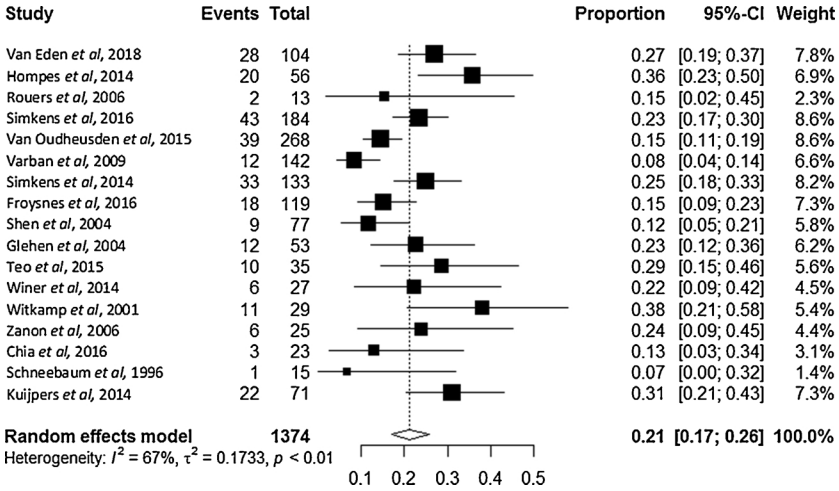

Fig. 2. Forest plot showing postoperative complications for the MMC cohort.

3.5.1. Synchronous / metachronous PMCRC

Nine out of the 17 MMC articles and five out of the 10 OX articles reported this characteristic. Of the five articles in which OX was used, one study did not differentiate between the included subgroups. The MMC cohort seems to have a higher percentage of synchronous PM when compared to the OX cohort, with a pooled percentage of 56% versus 45%, respectively.

3.5.2. Extent of peritoneal metastases

Thirteen of the 17 articles on MMC and eight of the 10 articles on OX reported data on this clinico-histopathological characteristic. As the extent of PM was noted in a variety of ways between the studies, exact percentages of a PCI-score below or above a certain cut-off value could not be calculated. For this reason, comparison was performed through observation and discussion between two reviewers. The MMC and OX cohorts appeared to be comparable in terms of extensiveness of PM, with the median PCI ranging from 8 to 12 and 7.58 to 12, respectively.

3.5.3. Optimal cytoreduction

Sixteen out of the 17 MMC studies and nine out of the 10 OX studies reported data on the completeness of cytoreduction. However, one study could not be used for comparison, as no distinction was made between the CC-scores of zero, one and two [12]. Hence, ultimately 15 articles on MMC versus nine articles on OX were included in this comparison. Optimal cytoreduction appears to have been reached in a higher percentage of the OX group compared to the MMC group, with pooled percentages of 99% and 88%, respectively.

Despite the fact that the MMC cohort seemed to be at a slight disadvantage when compared to the OX cohort, it was decided that formal statistical comparison was justified. Comparing the 30% severe complication risk after OX with the corresponding 21% after MMC resulted in a p-value of 0.046. This suggests an overall higher risk of developing severe postoperative complications when treated with OX compared to MMC.

3.6. Disease-free survival

Pooled proportions and heterogeneity of the outcomes within a cohort were calculated for the one-, three- and five-year DFS. One-year DFS proportions were 46% (3 studies) and 76% (2 studies) for MMC and OX, respectively. For the three-year DFS, these numbers were 28% (2 studies) and 34% (2 studies). Proportions for the five-year DFS were 21% for the MMC cohort (3 studies) and 22% for the OX cohort (3 studies) (Figs. 4 and 5).

Heterogeneity was high for the one-year outcomes in both cohorts, but low for the three- and five-year intervals.

The studies included in the meta-analysis of five-year DFS rates were assessed for comparability.

3.6.1. Synchronous / metachronous PMCRC

None of the three MMC articles that were included in meta-analysis for DFS rates reported on this characteristic. This information could be extracted from two out of three articles on OX. However, since no data was available for the MMC cohort, a comparison could not be made.

3.6.2. Administration of neo-adjuvant systemic chemotherapy

Data on the administration of neo-adjuvant systemic chemotherapy per study can be found in Table 2 for MMC studies

and in Table 3 for OX studies.

A higher percentage of the patients treated with OX received neo-adjuvant systemic chemotherapy than those treated with MMC. Neo-adjuvant therapy was administered in all three articles included in the

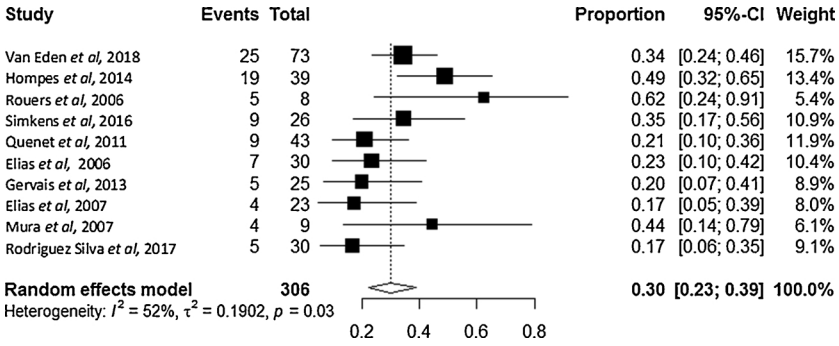

Fig. 3. Forest plot showing postoperative complications for the OX cohort.

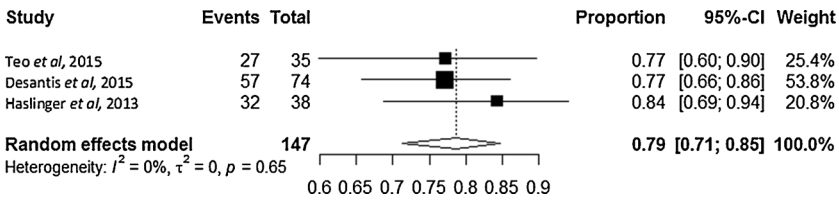

Fig. 4. Forest plot showing 5-year DFS for the MMC cohort.

analysis for OX, whereas it was not in any of the articles included in the MMC analysis. Moreover, rapid progression of PM under intravenous chemotherapy was considered a contraindication for undergoing HIPEC in several studies reporting on OX. This entails the exclusion of patients who are unlikely to benefit from HIPEC.

3.6.3. Extent of peritoneal metastases

Data on the extent of PM was extracted from two out of the three articles included for analysis for MMC and from all three included for analysis for OX. Comparison was again performed by educated observation and discussion between two reviewers. Ultimately, the MMC and OX cohorts were deemed comparable in terms of extensiveness of PM median PCI ranging from 9.4 to 12 and 9.6 to 12, respectively.

3.6.4. Optimal cytoreduction

Three articles for both chemotherapeutical agents reported on the completeness of cytoreduction. For two of the articles on MMC, this data concerned the entire cohort. This was the case for one of the articles on OX. One article did not differentiate between any cytoreduction scores from one onwards and was left out of the comparison. Optimal cytoreduction was reached in 94% and 97% for the MMC and OX studies, respectively.

Overall, MMC and OX studies were deemed comparable in terms of the ratio of synchronous to metachronous presentation, extent of PMCRC, and optimal cytoreduction. However, the MMC cohort appeared to be at a considerable disadvantage where the administration of neo-adjuvant therapy is concerned. For this reason, no formal statistical comparison was performed between the pooled proportions of the MMC and OX studies.

3.7. Overall survival

Pooled proportions and heterogeneity of the outcomes were calculated for the one-, three-, and five-year OS for both the MMC and OX studies. One-year OS proportions were 73% (11 studies) and 92% (4 studies) for MMC and OX, respectively. Two-year OS proportions were 38% for MMC (13 studies) and 54% for OX (3 studies). Proportions for the five-year OS were 25% for MMC (9 studies) and 47% for OX (5 studies) (Figs. 6 and 7).

Heterogeneity in OS outcomes was high (> 50%) in all plots concerning MMC and low (< 50%) for those of OX. Comparability between the MMC and OX studies that reported on 5-year OS was assessed for the predefined criteria.

3.7.1. Synchronous / metachronous PMCRC

Data on the ratio of synchronous to metachronous PMCRC could be extracted from only four out of nine articles on MMC which were included for meta-analysis. Out of the five articles on OX, only two reported on this characteristic. This concerned the entire cohort instead of our specific subgroup of colorectal patients in one of these two. The percentage of synchronous PM calculated from these articles amounted to 50% in the MMC studies versus 14% in the OX studies. Based on these numbers, the MMC studies seem to be at a great disadvantage.

Table 2
Characteristics of systemic chemotherapy, MMC studies reporting on 5-year DFS.

Study	Characteristics
Ching et al., 2015	**Neo-adjuvant therapy:** - not applied -
Desantis et al., 2014	**Neo-adjuvant therapy:** - not applied -
Haslinger et al., 2013	**Neo-adjuvant therapy:** - not applied -

3.7.2. Administration of neo-adjuvant systemic chemotherapy

Data on the administration of systemic chemotherapy per study included for analysis can be found in Table 4 for MMC and in Table 5 for OX.

It becomes obvious from the data collected that a higher percentage of the patient cohort treated with OX has received neo-adjuvant therapy than the cohort treated with MMC. Neo-adjuvant therapy was namely administered in all five articles included in OS analysis for OX.

Amongst the articles reporting on MMC, mention of a similar pre-procedure selection is only expressed in 'Tan et al., 2017'. Furthermore, neo-adjuvant systemic chemotherapy was not administered whatsoever in five out of the total of nine articles and the remaining four articles did not differentiate clearly between whether the systemic chemotherapy was given mere hours preoperatively or over the course of multiple weeks prior to HIPEC.

3.7.3. Extent of peritoneal metastases

Five out of the total of nine articles on MMC and five out of the total of 10 articles on OX reported data on this clinico-histopathological characteristic. Data extracted from two of the articles on MMC and from one on OX, referred to the entire study population consisting of multiple subgroups. Another article on MMC only reported on an incomplete amount of patients. The MMC and OX cohorts appeared to be comparable in terms of extensiveness of PM after comparison performed through observation and discussion between two reviewers. The reported median PCI scores ranged from 9.4 to 12 and 9.6 to 12, respectively.

3.7.4. Optimal cytoreduction

All nine articles on MMC reported on the completeness of cytoreduction. One of these articles did not differentiate between any scores higher than zero and could therefore not be used for this particular

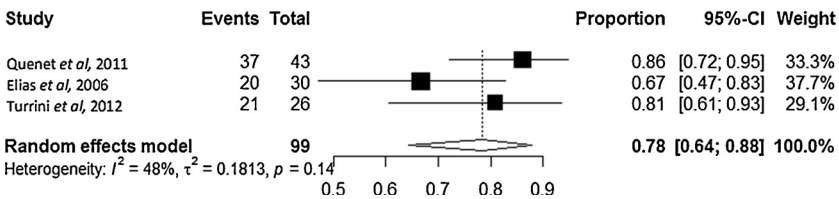

Fig. 5. Forest plot showing 5-year DFS for the OX cohort.

Table 3
Characteristics of systemic chemotherapy, OX studies reporting on 5-year DFS.

Study	Characteristics
Quenet et al., 2011	**Neo-adjuvant therapy:** At least 1 regimen for a minimum period of 2 months, agent not further specified* Rapid progression of PM under IV CT was considered a contraindication
Elias et al., 2006b	**Neo-adjuvant therapy:** LOHP / Irinotecan for a minimum period of 3 months Rapid progression of PM under IV CT was considered a contraindication Patients who achieved an objective response received the same regimen postoperatively over 4 - 6 months
Turrini et al., 2012	**Neo-adjuvant therapy:** 88% of patients A mean number of 1.5 (SD 0.9) lines of CT prior to HIPEC A mean number of 7.6 (SD 4.9) cycles of CT prior to HIPEC, agent not further specified

* This article does however refer to 'Elias, D., Delperro, J.-R., Sideris, L., Benhamou, E., Pocard, M., Baton, O., … Lasser, P. (2004). Treatment of Peritoneal Carcinomatosis From Colorectal Cancer: Impact of Complete Cytoreductive Surgery and Difficulties in Conducting Randomized Trials. Annals of Surgical Oncology, 11(5), 518–521. doi:10.1245/aso.2004.09.008′ in which 5-FU + Leucovorin-based chemotherapy and occasionally Oxaliplatin or Irinotecan was used.

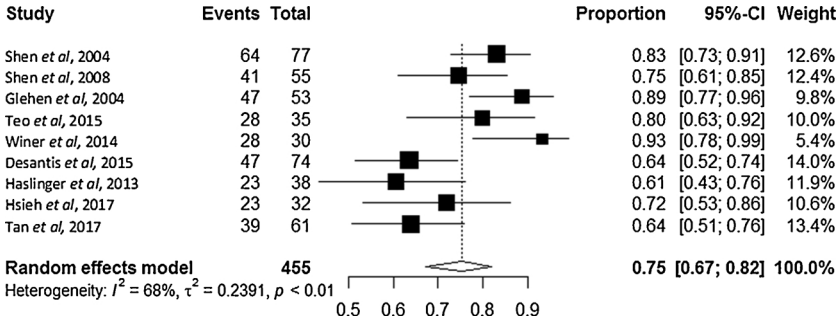

Fig. 6. Forest plot showing 5-year OS for the MMC cohort.

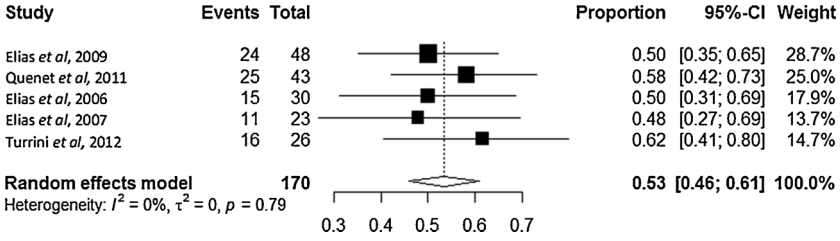

Fig. 7. Forest plot showing 5-year OS for the OX cohort.

Table 4
Characteristics of systemic chemotherapy, MMC studies reporting on 5-year OS.

Study	Characteristics
Winer et al., 2014	Only mentions the following: "A preponderance of patients received neoadjuvant chemotherapy in both groups." Hence, distinction unclear. Agent not further specified.
Glehen et al., 2004	**Neo-adjuvant therapy:** - not applied -
Ching et al., 2015	**Neo-adjuvant therapy:** - not applied -
Desantis et al., 2014	**Neo-adjuvant therapy:** - not applied -
Tan et al., 2017	**Neo-adjuvant therapy:** Mentions that recently the decision was made "to administer 'pseudo-neoadjuvant' CT for selected colorectal patients with PM, in an attempt to sieve out the patients who are likely to fail distally." Agent or duration not further specified
Hsieh et al., 2017	**Neo-adjuvant therapy:** - not applied -
Haslinger et al., 2013	**Neo-adjuvant therapy:** - not applied -
Shen et al., 2008	Only mentions the fact that 79.3% of patients had received systemic CT prior to HIPEC. Hence, distinction unclear.
Shen et al., 2004	Only mentions the fact that 58/77 patients (75%) had received systemic CT prior to HIPEC. Hence, distinction unclear.

Table 5
Characteristics of systemic chemotherapy, OX studies reporting on 5-year OS.

Study	Characteristics
Quenet et al., 2011	**Neo-adjuvant therapy:** At least 1 regimen for a minimum period of 2 months, agent not further specified* Rapid progression of PM under IV CT was considered a contraindication
Elias et al., 2006b	**Neo-adjuvant therapy:** Specifically mentions that data on systemic pre- and postoperative CT which most of the patients received is not shown
Elias et al., 2006a	**Neo-adjuvant therapy:** LOHP / Irinotecan for a minimum period of 3 months Rapid progression of PM under IV CT was considered a contraindication Patients who achieved an objective response received the same regimen postoperatively over 4 - 6 months
Elias et al., 2009	**Neo-adjuvant therapy:** LOHP / Irinotecan for a minimum period of 2 months, appears to have been delivered intra-peritoneally
Turrini et al., 2012	**Neo-adjuvant therapy:** 88% of patients A mean number of 1.5 (SD 0.9) lines of CT prior to HIPEC A mean number of 7.6 (SD 4.9) cycles of CT prior to HIPEC, agent not further specified

* This article does however refer to 'Elias, D., Delperro, J.-R., Sideris, L., Benhamou, E., Pocard, M., Baton, O., … Lasser, P. (2004). Treatment of Peritoneal Carcinomatosis From Colorectal Cancer: Impact of Complete Cytoreductive Surgery and Difficulties in Conducting Randomized Trials. Annals of Surgical Oncology, 11(5), 518–521. doi:10.1245/aso.2004.09.008' in which 5-FU + Leucovorin-based chemotherapy and occasionally Oxaliplatin or Irinotecan was used.

comparison. Data from three of the remaining eight articles concerned the total study population rather than the specific subgroup we aimed to compare. Likewise, all five articles on OX reported this characteristic. One study did not report data for our specific subgroup of colorectal patients separately. Pooled proportions of optimal cytoreduction were 84% of patients in the MMC studies versus 98% of patients in the OX studies. Hence, the MMC cohort appears to be at a slight disadvantage.

Overall, the MMC cohort appeared to be at a disadvantage compared to the OX cohort when looking at the comparisons of prognostic factors above. For this reason, it was concluded that MMC and OX studies were not comparable regarding the endpoint OS, and no statistical comparison was performed.

4. Discussion

This systematic review based on a total of 46 studies evaluated published literature on CRS/HIPEC for PMCRC using either MMC- or OX-based regimens. MMC and OX studies were comparable regarding extent of PMCRC, but differed substantially regarding synchronous versus metachronous presentation of PMCRC, application of neo-adjuvant systemic chemotherapy, completeness of cytoreduction and duration of HIPEC. Pooled proportions of five-year DFS and OS were 21% and 25% for MMC studies and 22% and 47% for OX studies, but formal statistical comparison was not performed because of the significant differences among the studies that could have influenced survival. MMC and OX cohorts were considered comparable for postoperative complications, and this resulted in a significantly higher pooled proportion for OX (30% vs. 21%, P = 0.046).

To date, there is no randomized controlled trial comparing MMC and OX as chemotherapeutic agents in CRS/HIPEC for patients with PMCRC and there has not been a similar systematic review or meta-analysis aiming for this comparison. Six comparative cohort studies were identified through the literature search of which four report survival outcomes. However, these articles could not be included in meta-analysis due to the fact they only reported median survival outcomes, which cannot be pooled. Of these four studies, 'Hompes et al., 2014' and 'Van Eden et al., 2017' show no significant differences in survival outcomes between the MMC and OX cohort. Patients receiving OX in 'Leung et al. (2016) had significantly greater median survival than those receiving MMC. 'Prada-Villaverde et al., 2014' reports no significant difference in survival outcomes between the MMC and OX cohort in patients in whom complete cytoreduction had been achieved. However, when stratified by Peritoneal Surface Disease Severity Score (PSDSS), treatment with MMC merited higher median OS rates in patients with a low burden of disease (PSDSS I/II).

One of the strengths of this systematic review is the assessment of the studies on predefined prognostic factors (the ratio of synchronous / metachronous presentation, use of neo-adjuvant systemic therapy, extent of PMCRC, and completeness of cytoreduction). 'Kerscher et al., 2013' reported a five-year OS rate of 8.1% in patients with synchronous PM, compared to 25.4% in those with metachronous PM (Kerscher et al., 2013). Neo-adjuvant systemic therapy enables for testing of biological behaviour and excludes patients with rapid disease progressing from CRS/HIPEC. This might explain the commonly reported favorable outcomes of studies using this sequential treatment approach (Rovers et al., 2017). Finally, extent of PMCRC and completeness of cytoreduction are consistently reported to be important prognostic factors (Simkens et al., 2017).

There are even more clinico-pathological parameters with relevance for prognosis that could have been used for comparability of the MMC and OX studies. These include lymph node status, histology (mucinous, signet ring cell), tumor differentiation and ECOG score (Kwakman et al., 2016). However, these were only limitedly reported.

Several other limitations have to be mentioned. As several large comparative studies could not be included in meta-analysis because only median survival was reported, the results in this review might not be representative of all conducted studies that met in- and exclusion criteria. Because of the variety in reported oncological outcome measures, only a limited number of studies could be used for pooled analysis of specific survival probabilities, and this may have increased the effect of chance on the outcome. Moreover, heterogeneity was high in one-, three- and five-year OS outcomes in the MMC cohort, indicating a large variability in results between studies. This could be explained by differences in baseline characteristics, national referral patterns and strategies between the studies. Some studies implemented strict exclusion criteria, thereby restricting the study population to those with favorable conditions. Moreover, comparability was limited for many of the predefined criteria, due to the large amount of incomplete or unrepresentative data. Due to the large variety in reporting of these characteristics, data could only be compared on the basis of educated observation. The majority of studies were retrospective cohort studies, often not following the STROBE rules (STrengthening the Reporting of OBservational studies in Epidemiology), especially providing insight in selection from an original cohort.

In conclusion, this systematic review showed a higher proportion of severe complications following OX based CRS/HIPEC. No meaningful comparison, however, could be made regarding DFS and OS, especially because induction systemic therapy was mostly given in OX studies,

while studies on MMC mainly included patients who underwent upfront CRS/HIPEC. In Prodige 7, 30 min OX based HIPEC did not improve survival in comparison with CRS alone in patients after months of oxaliplatin-based neoadjuvant chemotherapy. In our view this regimen should be discouraged in the latter patient category. For upfront CRS/HIPEC, the data are insufficient to abandon OX based HIPEC, but caution is warranted because of a potentially higher complication rate.

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Declaration of Competing Interest

None declared by any of the authors.

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