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Systematic Review

Prognostic factors influencing survival in patients undergoing cytoreductive surgery with HIPEC for isolated colorectal peritoneal metastases: A systematic review and meta-analysis

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Abstract

Background and Aims

Peritoneal metastases from colorectal cancer confer the worst survival among all sites of metastases. The adoption of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) can offer selected patients with isolated colorectal peritoneal metastases (CRPM) a favourable long-term survival. There are numerous factors postulated to influence survival in patients undergoing CRS and HIPEC. The aim of this study was to identify key peri-operative prognostic factors that influence survival in patients undergoing CRS and HIPEC for isolated CRPM.

Methods

A systematic review and meta-analysis was conducted to evaluate prognostic factors influencing survival in patients undergoing CRS and HIPEC for isolated CRPM.

Results

Thirty-three studies fit the inclusion criteria for the systematic review, with twenty-five studies included in the meta-analysis. On pooled analysis, incomplete cytoreduction, increasing peritoneal carcinoma index and lymph node involvement were significantly associated with a worse survival. Additionally, a rectal primary (HR 1.93, 95% CI 1.10-3.37), adjuvant chemotherapy (HR 0.71, 95% CI 0.54-0.93) and peri-operative Grade III/IV morbidity (HR 1.59, 95% CI 1.17-2.16) were also found to significantly influence survival. Notably, tumour differentiation and signet ring cell histology did not influence survival on pooled analysis.

Conclusion:

This meta-analysis confirms that in patients undergoing CRS and HIPEC for isolated CRPM, incomplete cytoreduction, high PCI and lymph node involvement negatively influence survival. In addition, a rectal primary, adjuvant chemotherapy use and grade III/IV morbidity were important factors also found to significantly influence survival.

(Abstract word count 238)

What does this paper add to the literature?

This meta-analysis reaffirms the prognostic value of incomplete cytoreduction, high PCI and lymph node involvement. In addition, this is the first meta-analysis to demonstrate a significant prognostic impact of a rectal primary, adjuvant chemotherapy and major peri-operative morbidity. These new findings should be considered when patients with isolated CRPM are considered for CRS and HIPEC and by those involved in the development of new guidelines for this treatment

Introduction

The peritoneum confers the worst prognosis among all sites of colorectal cancer (CRC) metastases¹. Historically, patients with colorectal peritoneal metastases (CRPM) had a median survival of three to six months^{2,3}. Approximately eight to ten percent of patients present with peritoneal metastases at the time of diagnosis with up to 40 percent going on to develop metachronous peritoneal metastases³⁻⁵.

Over the last twenty years, CRPM has begun to be considered as loco-regional disease with cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) the appropriate treatment option. In a randomised trial, Verwaal et al demonstrated that CRS and HIPEC led to a significantly improved survival in patients with CRPM: 22.3 months with this treatment compared to 12.6 months with systemic therapy⁶. Further studies have since demonstrated that CRS and HIPEC can offer selected patients with low volume isolated CRPM a median survival of up to 62.7 months with a 22-51% five year survival⁷⁻¹¹. With increasing acceptance in recent years, CRS and HIPEC has been integrated into treatment pathways for CRPM in many countries¹²⁻¹⁴.

Prognostic factors such as completeness of cytoreduction (CC score) and peritoneal carcinoma index (PCI) have been shown to influence survival following CRS and HIPEC¹⁵⁻¹⁹. However, there remains significant variability in patient selection and prognostic factors reported by investigators. In this study, we aim to conduct a systematic review and meta-analysis to evaluate key peri-operative prognostic factors that influence survival in patients undergoing CRS and HIPEC for isolated CRPM.

Methods

Search strategy and inclusion/exclusion criteria

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive search was undertaken on Ovid MEDLINE, EMBASE database and the Cochrane collaboration library. The following keywords were used either alone or in combination: colorectal; peritoneum; cytoreductive surgery; hyperthermic intraperitoneal chemotherapy; prognostic factor. The search strategy is supplied as Supplementary Figure 1.

Inclusion criteria

Only full text English studies with over 30 patients, reporting on prognostic factors influencing overall survival following CRS and HIPEC for isolated CRPM published between 1 January 2008 to 30 November 2018 were included. Manual cross-referencing from bibliographies of papers

in the initial search was done to include additional papers that had not previously been identified. Two reviewers performed the search and data extraction. The senior author independently evaluated any discrepancies in study inclusion or exclusion.

Exclusion criteria

Studies reporting on outcomes from appendiceal or non-colorectal cancers were excluded. Similarly, studies reporting on multiple cancers were screened and excluded if data specific to CRPM could not be extracted. Also excluded were studies on patients with synchronous liver resections and those with inadequate or absent survival outcomes or prognostic factors.

Papers were excluded from the meta-analysis if hazard ratios with 95% confidence intervals were not reported or could not be extracted from the study results.

Data extraction and analysis

An electronic datasheet with pre-determined criteria was used to ensure all pertinent data was collected from each study. Data analysis was performed using general inverse variance statistical methods, with random effects model on Review Manager (RevMan) Version 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014). The parameters of interest were prognostic factors influencing survival, with the outcome of interest being overall survival. Hazard ratios with 95% CI were extracted from included papers. A minimum of three papers had to report the same variable for a pooled analysis to be performed. The in-built RevMan software reported pooled P values for overall effect and forest plots with 95% CI for each variable. P value <0.05 was considered significant. Heterogeneity was calculated by the I^2 test. Heterogeneity can be interpreted as: 0-30%: minimal; 30-60%: moderate; 60-90%: substantial and >90%: very high heterogeneity.

Results

Thirty-three studies were eligible and included in the systematic review, with 25 studies included in the meta-analysis (Figure 1).

The Systematic review was registered with Prospero (CRD42019138094).

Eight studies were excluded from the meta-analysis due to inadequate statistical data available (Supplementary Table 1).

Study Quality and Risk of Bias assessment

Study quality was assessed using the Newcastle Ottawa Score (Supplementary Table 2). There was one prospective Phase II trial⁸, with the remaining 32 being retrospective studies. There were no randomised trials published during the defined search period. Nine studies were multi-centre, with 24 being single institution studies. All studies had similar methodology and interventions and were of fair quality. Risk of bias assessment was performed using the Modified Cochrane Tool for cohort studies and EPOC data collection form (Supplementary Table 3).

Follow up and Assessment of Survival

Median follow up ranged from 13.3-88 months^{20, 21}. Median overall survival ranged from 16.0-51 months^{8, 22-24}, with a median disease free survival of 10.9-34.5 months^{22, 25}. One, three and five year survival ranged from 70.5-91%^{8, 20}, 22-65%^{8, 25} and 22-43.2%^{8, 15} respectively. Study characteristics and survival data are summarised in Table 1 and Table 2.

Prognostic factors influencing overall survival

Location of primary tumour

Three studies (254 patients) reported the impact of primary tumour location²⁵⁻²⁷. On pooled analysis, a rectal primary leading to peritoneal metastases was associated with a significantly worse survival than a colonic primary (HR 1.93, 95% CI 1.10-3.37, $p=0.02$), with no heterogeneity ($I^2=0\%$). (Figure 2).

Timing of onset of peritoneal metastases

Three studies (366 patients) evaluated the difference in survival between synchronous or metachronous presentation of peritoneal metastases²⁶⁻²⁸. On pooled analysis, there was no difference in survival based on timing of onset of peritoneal metastases (HR 1.02, 95% CI 0.59-1.73, $p=0.96$), with moderate heterogeneity ($I^2=50\%$). (Figure 2)

Grade III/IV morbidity

Four studies (717 patients) evaluated the effect of peri-operative Grade III/IV morbidity on overall survival^{15, 28-30}. On pooled analysis, the presence of Grade III/IV morbidity was independently associated with worse overall survival (HR 1.59, 95% CI 1.17-2.16, $p=0.003$), with low heterogeneity ($I^2=18\%$). (Figure 2)

Completeness of Cytoreduction (CC 0/1)

Eight studies (1675 patients) evaluated completeness of cytoreduction on survival after CRS and HIPEC^{8, 9, 15, 22, 31-34}. On pooled analysis, incomplete cytoreduction was associated with a significantly worse survival (HR 2.21, 95% CI 1.57-3.10, $p < 0.001$), with moderate heterogeneity ($I^2 = 46\%$). To evaluate heterogeneity further, the largest weighted study (Elias et al³¹) was removed and re-analysed, with a similar significant outcome, with low heterogeneity ($I^2 = 21\%$). (Figure 2)

Peritoneal Carcinoma Index (PCI)

PCI was evaluated as a continuous variable in eight studies (1279 patients)^{18, 21, 22, 25, 29, 31, 35, 36}. Increasing PCI was associated with worse survival, with each unit increase in PCI contributing to a 10% increased hazard of death (HR 1.10, 95% CI 1.05-1.15). Heterogeneity was high ($I^2 = 78\%$). (Figure 2)

Tumour differentiation

Three studies (452 patients) evaluated tumour differentiation as a prognostic factor^{9, 30, 34}. On pooled analysis, poor tumour differentiation did not appear to confer a worse survival (HR 1.91, 95% CI 0.72-5.07). Heterogeneity was substantial ($I^2 = 72\%$). (Figure 3)

Lymph node positivity

Nine studies (1675 patients) evaluated the effect of lymph node involvement of the primary tumour on overall survival after CRS and HIPEC^{9, 17, 27-31, 36, 37}. On pooled analysis, lymph node involvement was associated with a significantly worse overall survival (HR 1.33, 95% CI 1.04-1.72, $p = 0.03$). Heterogeneity was moderate ($I^2 = 31\%$). When Ung et al²⁹ was excluded, the overall outcome remained the same, with no heterogeneity ($I^2 = 0\%$). (Figure 3)

Signet ring cell histology

Three studies (643 patients) evaluated the role of signet ring cell histology on overall survival^{30, 38, 39}. Pooled analysis revealed no survival difference based on signet ring cell histology (HR 1.11, 95% CI 0.65-1.90, $p = 0.71$), with no heterogeneity ($I^2 = 0\%$). (Figure 3)

HIPEC drug

Four studies (1112 patients) evaluated the survival benefit based on HIPEC drug used^{28, 32, 40, 41}. On pooled analysis, there was no difference in survival based on HIPEC drug used (HR 1.00, 95% CI 0.65-1.53, $p = 0.99$). There was substantial heterogeneity ($I^2 = 70\%$). (Figure 3)

Adjuvant systemic chemotherapy

Six studies (1372 patients) evaluated the impact of adjuvant systemic chemotherapy following CRS and HIPEC^{26, 28-31, 33}. Use of adjuvant systemic chemotherapy was associated with an improved overall survival (HR 0.71, 95% CI 0.54-0.93, $p=0.01$), with moderate heterogeneity ($I^2=43\%$). (Figure 3)

Figure 4 summarises all evaluated prognostic factors and their influence on OS.

Other factors

Age and gender did not influence survival on pooled analysis (Supplementary figure 2)

Sensitivity Analysis

Sensitivity was evaluated on all variables using fixed effects model. The outcomes remained the same for all variables except tumour differentiation, where poorly differentiated tumours were associated with a significantly worse survival (HR 1.62, 95% CI 1.01-2.60, $p=0.01$), with substantial heterogeneity ($I^2=73\%$) (Supplementary figure 3-5).

Discussion

In addition to completeness of cytoreduction, increasing PCI and lymph node involvement, this meta-analysis demonstrates that primary tumour location, adjuvant chemotherapy and peri-operative grade III/IV morbidity are also key prognostic factors influencing survival in patients undergoing CRS and HIPEC for isolated CRPM.

This is the first meta-analysis to demonstrate that a rectal primary leading to peritoneal metastases in patients undergoing CRS and HIPEC confer a significantly worse survival than patients with a colonic primary. Rectal cancers less commonly spread to the peritoneum than colonic cancers⁴². Rectal cancers metastasising to the peritoneum is a manifestation of more advanced disease, and possibly more aggressive tumour biology, with other possible sites of undetected micro-metastatic disease. This cohort of patients may benefit from more aggressive multi-modal treatment including incorporation of longer duration of peri-operative systemic treatment, an area for further research.

The timing of peritoneal metastases and its impact on survival has not been well described in the literature. While some consider the presence of synchronous metastases as a more aggressive disease manifestation, we found no difference in survival based on synchronous or metachronous presentation. Recently, a large multi-centre study also evaluated the impact of timing of metastases and found no difference in survival⁴³.

Along with completeness of cytoreduction, PCI has long been the backbone in evaluating the value of CRS and HIPEC. By stratifying tumour burden and potential resectability, it is both predictive and prognostic. While this meta-analysis confirms that increasing PCI is associated with a worse survival, it does not define a cut-off PCI above which CRS and HIPEC would offer no benefit. This is largely due to variability in studies reporting the effect of PCI. While a PCI >15 confers a worse prognosis, there remains significant variability in practice between institutions⁴⁴. The recent Prodigy 7 trial for example included patients with a PCI up to 25⁴⁵. Such variability in practice highlights the need for a consensus on a cut off PCI for offering CRS and HIPEC. Furthermore, PCI does not take into account important factors such as tumour biology¹⁸, histologic subtype³⁰ or small bowel involvement²², all of which are known to influence survival. In contrast, composite tools such as the peritoneal surface disease severity score (PSDSS) incorporate some of these factors and may help stratify patients better than PCI⁵. The development of a multi-faceted prognostic tool incorporating patient and tumour related factors, with imaging findings that help predict resectability is an area of research that would greatly help this field.

The favourable results achieved with CRS and HIPEC have been obtained in studies utilising peri-operative systemic chemotherapy^{6,45}. A recent study reported that in patients suffering recurrence after CRS and HIPEC, 31% recur at distant sites⁴⁶. Adjuvant chemotherapy use may help reduce this distant failure rate. Additionally, adjuvant chemotherapy treats residual micro-metastatic disease, helping reduce loco-regional or distant failure. However, the use of systemic chemotherapy in conjunction with CRS and HIPEC varies according to country. In France, centres use peri-operative systemic chemotherapy routinely while in the Netherlands upfront CRS and HIPEC is offered without systemic therapy⁴⁷. To date, there have been no prospective studies that have evaluated outcomes with CRS and HIPEC without use of peri-operative systemic chemotherapy. The CAIRO 6 RCT, which is currently recruiting, aims to evaluate the role of peri-operative systemic chemotherapy with CRS and HIPEC versus upfront

CRS and HIPEC alone⁴⁸. Hopefully, results will better guide the future use of systemic chemotherapy.

Lymph node involvement of the primary tumour was found to significantly influence survival. Predictive nomograms have previously described nodal status as an independent risk factor for peritoneal recurrence⁴⁹. Some studies have also suggested that evidence of lymph node metastases, along with other poor prognostic factors should be a contraindication to offering CRS and HIPEC³¹. This is possibly because lymph node metastases are a portal to haematogenous spread of tumour cells to other sites such as the lung or liver^{15, 50}.

While CRS and HIPEC as a combined treatment has been demonstrated to be superior to systemic chemotherapy in CRPM, very few studies have evaluated the role of CRS alone without HIPEC⁶. In an RCT, Elias et al compared the use of EPIC plus systemic chemotherapy versus systemic chemotherapy alone, in patients undergoing complete cytoreduction⁵¹. While this trial closed early due to patient dissatisfaction with the inclusion criteria, it did report a 60% two-year survival in both groups, with no survival benefit evident with the use of EPIC. In a single centre study, Desolneux et al evaluated outcomes following CRS alone with peri-operative systemic chemotherapy, and reported a favourable median survival of 32.4 months if a CC 0/1 resection was achieved⁵². More recently, the PRODIGE 7 RCT evaluated the role of Oxaliplatin based HIPEC by comparing CRS and HIPEC versus CRS alone in patients undergoing complete cytoreduction⁴⁵. Median survival was 41.2 months for patients undergoing CRS alone, with no survival advantage seen with the addition of Oxaliplatin based HIPEC. Additionally, the HIPEC group had a significantly higher complication rate. Sub-group analysis however, did demonstrate a survival advantage with HIPEC in those with a PCI 11-15. This trial has contributed to international debate as to the actual benefit of HIPEC, with one publication proposing that HIPEC be dropped altogether⁵³. While yet unpublished, PRODIGE 7 has reaffirmed the value of high quality cytoreductive surgery, but has raised doubts amongst the international community about the efficacy of oxaliplatin based HIPEC.

While cytoreductive procedures are relatively standardised around the world⁵⁴, there remains variability in HIPEC drugs used, with the choice of Mitomycin C or Oxaliplatin largely based on country and institutional preference, rather than efficacy of the drug^{32, 40}. Additionally, comparative retrospective studies have not clearly determined either to be superior, a finding

confirmed in this meta-analysis. Importantly, there are no prospective trials to date that have compared outcomes between the two agents. With results from PRODIGE 7 demonstrating no overall benefit from Oxaliplatin HIPEC, it would be a logical step to stop using Oxaliplatin and consider preferentially use Mitomycin C, especially as the sentinel RCT that demonstrated a survival benefit with CRS and HIPEC over systemic chemotherapy utilised Mitomycin C⁶. The negative findings of PRODIGE 7 suggests that prospective studies are urgently required to compare the efficacy of other HIPEC agents with CRS alone to establish if any HIPEC agent offers a survival advantage over CRS alone.

Peri-operative complications are associated with a worse survival in a number of studies^{55, 56}. Complications such as anastomotic leaks lead to an immunosuppressive effect on the host immune system, coupled with an inflammatory cascade and release of cytokines and pro-inflammatory mediators that contribute to tumour cell dissemination^{15, 57}. This emphasises the importance of careful patient selection, along with meticulous operative technique and safe decision-making.

It is plausible that studies evaluating CRS and HIPEC have an inherent degree of selection bias with regard to age, with only younger patients with favorable functional status being offered this treatment. This is a reasonable assumption, given CRS and HIPEC carries a 12.5-35% and 1.0-8.3% risk of major morbidity and mortality, respectively^{33, 58, 60}. Gender has not been shown to influence survival in previous studies. Apart from ovarian metastases, there is no difference in sites of peritoneal metastases in either sex.

While the lack of RCTs is a limitation in our study, it reflects the existing literature, with only one RCT completed successfully⁶. Despite careful study selection, differences in the quality of the underlying included studies contributed to an overall moderate degree of heterogeneity. Studies had different prognostic factors evaluated, with discordance in how factors such as PCI were reported. Contributing to further heterogeneity were variable sample sizes, with heterogeneous populations, and selection bias within each study owing to individual institutional policies for offering CRS and HIPEC.

Important prognostic factors, such as tumour biology and histologic subtypes were not reported in many studies. Tumour biology is an important prognostic factor, with Ras/Raf mutations and high-grade tumours recently shown to be independently associated with worse

cancer specific survival in patients undergoing CRS and HIPEC⁵⁹. The presence of Ras/Raf mutations render anti-EGFR antibodies ineffective, thereby limiting treatment options for these patients. Similarly, aggressive histologic subtypes such as mucinous and signet ring cell histology have also previously been shown to confer a worse prognosis^{60, 61}. However, these are relatively rare, with signet ring cell histology for instance accounting for less than 1-2% of all CRCs⁶². With limited studies reporting on tumour biology, small study populations, patient selection bias in study samples and low incidence of features such as signet ring cell histology, it is plausible that we were unable to accumulate an adequate sample size to demonstrate a survival difference. Chemotherapy protocols similarly, were variable, and not fully reported in many studies, along with different HIPEC agents, delivery techniques (open or closed) and drug dosages.

Furthermore, studies were over different time frames, with variable follow up, with possibly different levels of experience among surgeons. Eight studies were excluded for having inadequate survival data and this may have contributed to study inclusion bias. In addition, non-reporting of negative or poor results may be an issue, with this data remaining unpublished. With wider acceptance of CRS and HIPEC in recent years, we felt it more representative to evaluate recent evidence in the last decade and to limit our study to isolated CRPM with the advantage that papers could be more easily compared. . Liver metastases are a notable exclusion in our study, as they are already known to influence survival in patients with CRPM⁶³.

Conclusion

Apart from completeness of cytoreduction, PCI and lymph node involvement, this meta-analysis demonstrates that adjuvant chemotherapy use, rectal primary and peri-operative grade III/IV morbidity are important prognostic factors influencing survival in patients undergoing CRS and HIPEC for CRPM.

Table 1. Study Characteristics

No.	Author (year)	No. of Sites (country)	Study Period	Study type	No. of Patients	Intraperitoneal Chemotherapy Used	Systemic Chemotherapy (dosage)		Median Follow-up (months)
							NAC	AC	
1	Yan (2008) ³⁴	1 (Australia)	1997-2007	Cohort	50	MMC (HIPEC) and 5-FU (EPIC)	NR	NR	14
2	Shen (2009) ²⁰	1 (USA)	1991-2005	Cohort	121	NR	NR	NR	86
3	Chua (2010) ¹⁰	2 (multiple countries)	1997-2008	Cohort	56	MMC (HIPEC)	NR	NR	20**
4	Franko (2010) ²⁶	1 (USA)	2001-2007	Case control	105	5-FU + IRI or OXL (HIPEC)	NR	NR	NR
5	Elias (2010) ³¹	23 (France)	1990-2007	Cohort	523	MMC ± CIS or OXL ± IRI (HIPEC) and MMC + 5-FU (EPIC)	NR	NR	45
6	Cavaliere (2011) ¹⁶	5 (Italy)	1995-2007	Cohort	146	CIS ± MMC or OXL (HIPEC)	NR	NR	19
7	Quenet (2011) ¹⁷	2 (France)	1998-2007	Cohort	146	OXL ± IRI (HIPEC)	NR	NR	48.5
8	Benizri (2012) ²²	1 (France)	2000-2007	Cohort	49	MMC (HIPEC)	NR	NR	27**
9	Cashin (2012) ³⁸	1 (Sweden)	2005-2008	Cohort	107	NR	NR	NR	NR
10	Passot (2012) ¹⁹	1 (France)	1991-2010	Cohort	120	MMC ± IRI or MMC ± OXL (HIPEC)	Various *	NR	58.5
11	Gervais (2013) ¹¹	1 (Canada)	2004-2011	Cohort	40	OXL (HIPEC)	NR	NR	22.8

12	Ung (2013) ²⁹	1 (Australia)	2000-2012	Cohort	125	MMC (HIPEC) and 5-FU (EPIC)	NR	NR	23.3
13	Votanopoulos (2013) ²⁴	1 (USA)	1993-2011	Cohort	217	NR	NR	NR	88.1 (colon); 40.1 (rectal)
14	Yonemura (2013) ⁹	1 (USA)	1993-2011	Cohort	142	MMC + CIS (HIPEC)	Various +	NR	NR
15	Baratti (2014) ¹⁵	1 (Italy)	2004-2012	Cohort	101	CIS + MMC (HIPEC)	NR	NR	44.9
16	Ceelen (2014) ³³	1 (Belgium)	2002-2012	Cohort	166	MMC or OXL (HIPEC)	FOLFOX or FOLFIRI or FOLFIRI + BEVA	NR	18
17	Elias (2014) ⁶⁴	1 (France)	2000-2009	Cohort	139	OXL ± IRI (HIPEC)	5-FU and LV	NR	NR
18	Hompes (2014) ⁴⁰	2 (Netherlands and Belgium)	2004-2010	Cohort	95	MMC or OXL (HIPEC)	NR	NR	5.1 (MMC) 2.8 (OXL)
19	Huang (2014) ⁸	1 (Japan)	2005-2013	Prospective	60	MMC (HIPEC) and 5-FU (EPIC)	NR	FOLFOX or FOLFIRI + Carboplatin	29.9
20	Passot (2014) ³⁷	1 (France)	2005- 2012	Cohort	115	OXL (HIPEC)	Various #	NR	18.6
21	Prada-Villaverde (2014) ³²	15 (multiple countries)	2000-2012	Cohort	584	MMC or OXL (HIPEC)	NR	NR	NR
22	Rivard (2014) ²⁷	1 (Canada)	2003-2011	Cohort	68	NR	NR	NR	30.3

23	Faron (2016) ³⁵	1 (France)	2003-2012	Cohort	173	OXL + IRI (HIPEC)	5-FU and LV	NR	48.5
24	Frøysnes (2016) ²⁵	1 (Norway)	2004-2013	Cohort	119	MMC (HIPEC)	NR	NR	45
25	Maillet (2016) ²⁸	4 (France)	2004-2012	Cohort	231	MMC or OXL (HIPEC)	NR	Various §	NR
26	Ng (2016) ^{24, 29}	1 (Singapore)	2003-2014	Cohort	50	MMC or OXL (HIPEC)	NR	NR	13.3
27	Sluiter (2016) ³⁶	2 (Netherlands)	2007-2010	Cohort	65	MMC (HIPEC)	NR	NR	21
28	Ihemelandu (2017) ³⁹	1 (USA)	1990-2015	Cohort	318	MMC (HIPEC) and 5-FU (EPIC)	NR	NR	15
29	Leung (2017) ⁴¹	1 (Australia)	1996-2015	Cohort	202	MMC or OXL (HIPEC)	NR	NR	NR
30	Massalou (2017) ²³	1 (France)	1999-2013	Cohort	84	MMC (HIPEC)	NR	NR	NR
31	Kozman (2018) ³⁰	1 (Australia)	1996-2016	Cohort	260	MMC or OXL (HIPEC)	NR	NR	NR
32	Sluiter (2018) ¹⁸	2 (Netherlands)	2008-2016	Cohort	175	MMC or OXL (HIPEC)	NR	OXL or Capecitabine or CAPOX or FOLFOX	NR
33	Tonello (2018) ⁶⁵	1 (Spain)	2004-2015	Cohort	36	MMC or OXL (HIPEC)	NR	NR	NR

HIPEC: hyperthermic intraperitoneal chemotherapy; EPIC: early post-operative intraperitoneal chemotherapy; NAC: neo-adjuvant chemotherapy; AC: adjuvant chemotherapy; NR: not reported; MMC: mitomycin-C; OXL: oxaliplatin; CIS: cisplatin; IRI: irinotecan; 5-FU: 5-fluorouracil; LV: leucovorin; BEVA: bevacizumab; CTX: cetuximab; NA: Neoadjuvant chemotherapy; **: mean value

* : 5-FU, LV, OXL, IRI, BEVA or CTX

† : FOLFOX + BEVA or FOLFIRI + BEVA or CTX or Xeloda + OXL or BEVA or S1 + Paclitaxel or IRI + Paclitaxel or Taxol + CBDCA or S1 + OXL

: FOLFOX or FOLFIRI or FOLFIRI + BEVA or FOLFIRI + CTX or FOLFOX + BEVA or FOLFOX + CTX

§ : FOLFOX or FOLFIRI or FOLFIRI + BEVA or FOLFIRI + CTX or FOLFOX + BEVA or FOLFOX + CTX or 5-FU + BEVA or LV5FU2 or FOLFIRINOX

Table 2. Survival data from all included studies

No.	Author (year)	Survival Rates (%)			Median DFS (months)	Median OS (months)	Overall Mortality (%)	Grade III/IV Morbidity (%)
		1-year	3-year	5-year				

1	Yan (2008) ³⁴	79	39	NR	NR	29	NR	NR
2	Shen (2009) ²⁰	91	48	26	NR	34	5.5	NR
3	Chua (2010) ¹⁰	85	48	NR	NR	38	NR	NR
4	Franko (2010) ²⁶	90*	49*	25*	NR	34.7	NR	NR
5	Elias (2010) ³¹	81	41	27	NR	30.1	3.3	31
6	Cavaliere (2011) ¹⁶	80*	30*	NR	NR	21	2.7	NR
7	Quenet (2011) ¹⁷	95*	53*	41.8	NR	41	4.1	NR
8	Benizri (2012) ²²	82*	52*	40	34.5	51	0	20.5
9	Cashin (2012) ³⁸	NR	NR	NR	NR	NR	NR	NR
10	Passot (2012) ¹⁹	77	NR	33	NR	36.2	NR	NR
11	Gervais (2013) ¹¹	88	61	36	NR	NR	4	NR
12	Ung (2013) ²⁹	84 (colon)*; 80 (rectal)	53 (colon)*; 42 (rectum)*	33 (colon); 20 (rectal)	12.6 (colon); 19.0 (rectal)	37.1 (colon); 29.6 (rectal)	NR	48.8 (colon); 6.8 (rectal)
13	Votanopoulos (2013) ²⁴	63 (colon); 83 (rectal)	25.1 (colon); 28.2 (rectal)	NR	NR	17.3 (colon); 14.6 (rectal)	5.7 (colon); 0 (rectal)	18 (colon); 15 (rectal)
14	Yonemura (2013) ⁹	68*	25*	23.4	NR	24.4	0.7	17.6
15	Baratti (2014) ¹⁵	NR	NR	43.2	NR	32	3	NR
16	Ceelen (2014) ³³	95*	70*	NR	NR	27	2.4	35
17	Elias (2014) ⁶⁴	NR	NR	39	NR	39	5.5	21.5
18	Hompes (2014) ⁴⁰	NR	NR	NR	NR	26.5 (MMC); 37.1 (OXL)	0	41.1
19	Huang (2014) ⁸	70.5	22	22	NR	16	0	NR
20	Passot (2014) ³⁷	NR	NR	NR	NR	36	4	NR
21	Prada-Villaverde (2014) ³²	NR	NR	NR	NR	32.6	NR	NR
22	Rivard (2014) ²⁷	NR	30.8	NR	10.9	30.8	NR	23.5
23	Faron (2016) ³⁵	NR	NR	42	NR	41	4.6	NR
24	Frøysnes (2016) ²⁵	93*	65	36	14	47	0	15.1
25	Maillet (2016) ²⁸	NR	58	34	NR	43.3	4	NR
26	Ng (2016) ²¹	87.6	NR	NR	NR	28.8	NR	NR
27	Sluiter (2016) ³⁶	NR	NR	NR	NR	34.4**	NR	NR

28	Ihemelandu (2017) ³⁹	NR	35	25	NR	21.5	NR	NR
29	Leung (2017) ⁴¹	NR	NR	NR	20 (MMC); 19 (OXL)	26 (MMC); 56 (OXL)	NR	NR
30	Massalou (2017) ²³	NR	NR	NR	NR	39.7	NR	13
31	Kozman (2018) ³⁰	NR	NR	30.3	NR	35	0.77	35
32	Sluiter (2018) ¹⁸	NR	NR	NR	12	27	NR	25.7
33	Tonello (2018) ⁶⁵	NR	60	34	15.7	40.5	8.3	19.4

DFS: disease-free survival; OS: overall survival; NR: not reported; *: estimated based on survival curve; **: mean value

Identification

Screening

Eligibility

Included

Figure 2 (a-e) Forest plot demonstrating prognostic factors significantly influencing survival following CRS and HIPEC

Figure 3 (a-e) Forest plot demonstrating prognostic factors influencing survival following CRS and HIPEC

Figure 4 Summary forest plot with all evaluated prognostic factors influencing survival in patients undergoing CRS and HIPEC

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