Systematic review and/or Meta-analysis

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Effect of hyperthermic intraperitoneal chemotherapy on survival and recurrence rates in advanced gastric cancer: a systematic review and meta-analysis

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Background: Around 5–20% of patients who undergo surgery for advanced gastric cancer (AGC), which invades into the muscularis propria or beyond, have peritoneal carcinomatosis. The peritoneal recurrence rate is 10–54%, which is associated with a poor prognosis. The role of hyperthermic intraperitoneal chemotherapy (HIPEC) in AGC with and without peritoneal carcinomatosis is not clearly defined.

Methods: The authors conducted a meta-analysis, in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, of the clinical trials and high-quality nonrandomized studies evaluating the role of HIPEC in AGC over the last 10 years. The studies were searched in PubMed, EMBASE, MEDLINE, and Cochrane databases between January 2011 to December 2021. Clinical data including overall survival, recurrence free survival, overall recurrence rate, peritoneal recurrence rate, and complications analyzed using RevMan 5.4.

Results: Six randomized controlled trials and 10 nonrandomized studies, comprising a total of 1700 patients were included. HIPEC was associated with significantly improved OS at 3 [odd ratio (OR) 1.89, 95% CI: 1.17–3.05] and 5 years (OR 1.87, 95% CI: 1.29–2.71). HIPEC was associated with reduced overall recurrence (OR 0.49, 95% CI: 0.31–0.80) and peritoneal recurrence (OR 0.22, 95% CI: 0.11–0.47). HIPEC was not associated with increased complications. The occurrence of postoperative renal dysfunction was significantly higher in the HIPEC group (OR 3.94, 95% CI: 1.85–8.38).

Conclusion: The role of HIPEC in AGC has evolved over the past decade. HIPEC may improve survival rates and reduce recurrence rates in patients with AGC, without significant increase in complications and with a favorable impact on 3 and 5-year survival.

Keywords: complications, gastric cancer, HIPEC, recurrence, survival

Introduction

Gastric cancer (GC) accounts for the fifth most common neoplasia and the third most common cause of cancer death globally[1]. Approximately, 5–20% are associated with peritoneal carcinomatosis (PC)[2]. Involvement of the peritoneum is associated with a poor prognosis. There are limited therapeutic options like palliative chemotherapy or best supportive care, for this cohort of patients[3].

HIGHLIGHTS

- There are limited therapeutic options for patients with advanced gastric cancer, which includes gastric cancer which invades into muscularis propria and beyond.
- In this meta-analysis of randomised controlled trials and high-quality nonrandomised study, the effect of hyperthermic intraperitoneal chemotherapy on survival and recurrence rates was assessed.
- Hyperthermic intraperitoneal chemotherapy improved the overall survival and recurrence rates, without significant increase in complications.

Survival is affected by local tumor recurrence and the peritoneum is one of the most common sites of GC recurrence[4,5]. Even after radical surgery, the peritoneal recurrence rate is 10–54%[6,7]. Thus, removal of residual cancer cells from the peritoneal cavity should improve the survival of these patients. Assessing treatment strategies to treat peritoneal disease with the aim of improving survival and recurrence rates is under investigation. Hyperthermic intraperitoneal chemotherapy (HIPEC) has been effective to control PC from ovarian or mucinous appendiceal cancer[8,9]. A meta-analysis evaluating 10 studies which analyzed the implications of HIPEC in GC with serosal invasion indicated that HIPEC was associated with a better prognosis compared to

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standard treatment[10]. There have been multiple trials and reports, which have shown promising results with the use of HIPEC for advanced GC. However, the available data is heterogeneous and geographically skewed. Hence, the latest consensus guidelines, including the National Comprehensive Cancer Network (NCCN)[3], the European Society for Medical Oncology (ESMO)[11], and the Japanese guidelines[12] have not recommended HIPEC beyond the scope of clinical trials.

The use of HIPEC for advanced GC is not used as a treatment in the United Kingdom and remains a topic of debate. In order to assess the efficacy and safety of HIPEC in the treatment of advanced GC, we conducted a meta-analysis of the most recent clinical trials and high-quality comparative nonrandomised studies (NRCT) over the last 10 years.

Methods

The study protocol was registered with PROSPERO. The PROSPERO registration number is CRD42022310556. No ethical approval is needed as data from previously published studies has been analyzed.

Literature search strategy

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. The work has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the Methodological Quality of Systematic Reviews) Guidelines[13]. According to the guidelines, the PRISMA checklist was completed. An electronic literature search was performed using databases from PubMed, Embase, Medline, and the Cochrane Databases by two authors. The period of search performed was from January 2011 to December 2021. The search terms were: 'hyperthermic', 'intraperitoneal chemotherapy', 'gastric', 'cancer' combined with AND/OR. The search also included all MeSH terms. In order to avoid missing any relevant studies we included the search with the

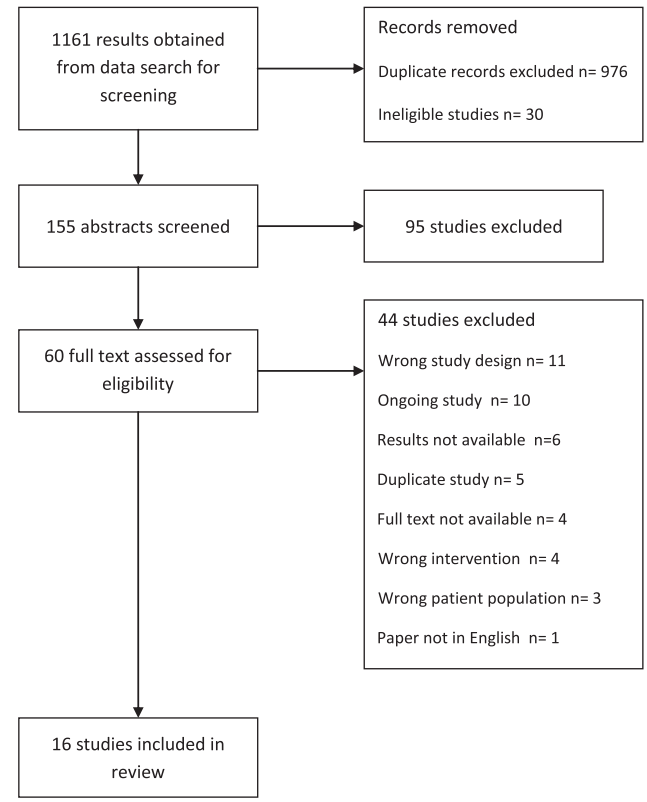


Figure 1. PRISMA flowchart.

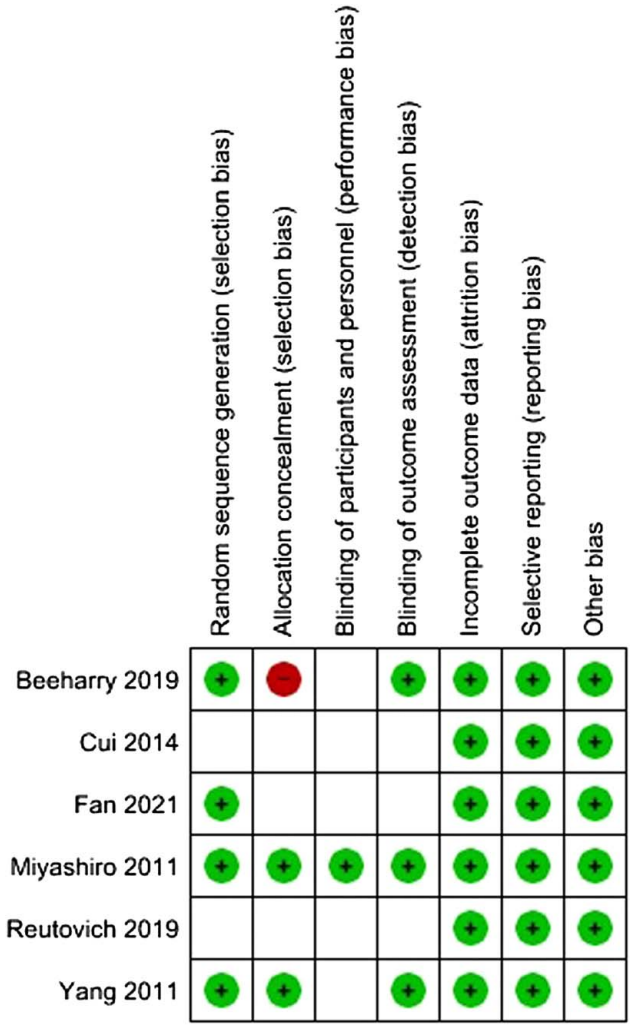


Figure 2. Summary of risk of bias of included RCTs. RCT: Randomised controlled trial.

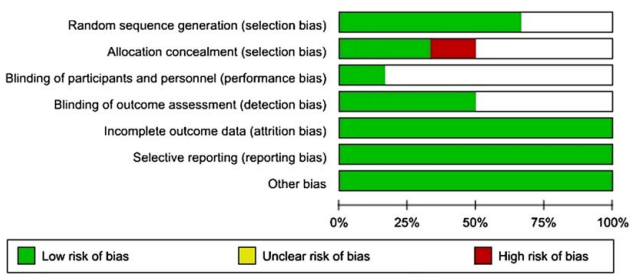


Figure 3. Risk of bias assessment for RCT. RCT: Randomised controlled trial.

Table 1

Modified MINORS score of NRCTs.

	Kang, [22]	Yarema, [23]	Coccolini, [24]	Diniz, [25]	Liu, [26]	Xie, [29]	Zhong, [27]	Zhang, [15]	Zhu, [28]	Rosa, [31]	Merboth, [30]
Inclusion of consecutive patients.	1	2	1	2	2	2	2	1	1	1	2
Prospective collection of data.	1	1	2	2	2	1	1	1	1	2	1
Endpoints appropriate to the aim of the study.	2	2	2	2	2	2	2	2	2	2	2
Unbiased assessment of the study endpoint.	2	2	2	2	1	1	2	1	2	2	2
Prospective calculation of study size.	2	1	0	1	2	1	1	2	2	0	0
Adequate control group.	2	2	2	2	2	2	2	1	2	2	2
Contemporary groups.	2	2	2	2	2	2	2	2	2	2	2
Baseline equivalence of groups.	2	1	1	1	0	1	2	1	2	1	1
Total score	14	13	12	14	13	12	14	11	14	12	12

NRCT, Non randomised studies.

most results. In the case of duplicate results from the same center, we utilized the most complete reports in the meta-analysis. Reference lists of all retrieved articles were reviewed for identification of relevant studies. Review articles were also checked to identify any additional studies. Only studies written in English were included. Papers without available abstracts or full texts were excluded. In the case of duplicate published studies with increased lengths of follow up or accumulating numbers of patients, only the most recent version of the study was included.

Study selection

Titles and abstracts were reviewed after deleting duplicates by two authors independently. The second stage of screening involved a full-text review of all included studies. The two researchers excluded studies at this stage which were different from the inclusion criteria, results unavailable and those that were only protocols.

Participants

Patients with advanced GC, with and without PC who underwent potentially curative resection were included.

All patients included should have gastric or type III gastro-esophageal junction adenocarcinoma proven on histology.

The included studies considered both locally advanced gastric cancers with macroscopic serosal involvement as well as PC that underwent surgery with curative intent.

Studies in which patients underwent HIPEC in addition to surgery were included.

Studies with patients having distant solid organ metastasis, palliative surgery, non chemotherapeutic intraperitoneal perfusion were excluded.

Types of interventions and comparison

Patients who underwent potentially curative surgery in combination with HIPEC formed the intervention group. The intervention group was compared with patients who received surgery alone with/without systemic chemotherapy.

Outcomes

The primary endpoint was overall survival at 1-, 3-, and 5 years.

The secondary endpoints were disease-free survival (DFS), postoperative morbidity: complications, that is, myelosuppression, anastomotic leak, intestinal obstruction, liver dysfunction, and renal dysfunction and 3-year mortality. The impact of HIPEC on overall and peritoneal recurrence was also evaluated.

Quality assessment: Two reviewers used RevMan 5.4 (Review Manager Version 5.4 Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2020), to assess the risk of bias in randomised controlled trials (RCTs). The risk of bias is presented as a percentage and that of individual studies is represented as low risk, high-risk, and unclear. The quality of NRCTs was assessed using the modified methodological index for non randomised studies (MINORS) score[14]. Studies with a score of less than 12 were excluded. In the case of a dispute, the third author resolved it.

Data extraction

Two investigators completed the data extraction independently. According to the MINORS score, the quality assessment table for NRCTs was completed. The characteristics of the included studies extracted included the following: author, country, year of publication, RCT/NRCT, age, sex distribution, stage of tumor, and characteristics of intervention. The patient outcomes and response to treatment are summarized in a separate table.

Statistical analysis

RevMan 5.4 (Review Manager Version 5.4 Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2020) was used to perform statistical analysis. The odds ratio (OR) was calculated for dichotomous data. Fixed and random effects models based on the Mantel-Haenszel method were built to assess the impact of heterogeneity on results. For heterogeneity, quantified by the I^2 statistic, with a value less than 50% the fixed effects model was used. While for I^2 greater than 50%, we chose the random effects model. In case of heterogeneity greater than 80%, we performed a sensitivity analysis and excluded studies with significant heterogeneity from the analysis.

Table 2

Summary of characteristics of interventions used.

Authors	Country	Tumor characteristics	M:F	Age	Number of participants		Surgery performed in both groups	Therapy regimen		Follow up
					HIPEC	SA		HIPEC	Control	
Miyashiro et al.[17]	Japan	cT3-4 with cN0-2	182:86	Sx + HIPEC = 59 (33–75) Control = 57 (23–73)	135	133	Radical gastrectomy with D2 lymoadenectomy.	Intraperitoneal Cisplatin (70 mg/m2) followed by intravenous cisplatin (70 mg/m2) on postoperative day 14; intravenous 5-FU (700 mg/m^2) daily on days 14–16 and oral 5-FU (267 mg/m^2) daily starting at 4 weeks postoperatively and continued till 12 months.	SA. No adjuvant chemotherapy.	6 years
Rosa et al[31]	Italy	Preoperative stage II–IV, with peritoneal carcinomatosis (stage IV), or at high-risk to develop them.	21::25	Mean = 55 years (28–76)	46	39	Cytoreductive surgery/Gastrectomy with D2 lymphadenectomy.	Surgery plus HIPEC with curative intent: AGC patients with apparent peritoneal dissemination who underwent cytoreductive surgery, including gastrectomy and partial peritonectomy of peritoneal sections affected by implants, followed by HIPEC – Surgery plus HIPEC with prophylactic intent: AGC patients with serosa invasion and consequent high-risk of intraperitoneal progression, who underwent gastrectomy followed by HIPECMitomycin C (15 mg/m^2) and Cisplatin (75 mg/m^2) at 41–42°C for 90 min.	Surgery	Median = 68 months
Yang et al.[16]	China	Gstric cancer + Peritoneal carcinomatosis.	35:33:00	24–75 (median 50 years)	34	34	Cytoreductive surgery.	120 mg cisplatin + 30 mg mitomycin in 6 l of saline. Temperature :43 + /- 0.5°C Time: 60–90 mins Technique: Open.	Cytoreductive surgery	32 months (7.5–83.5 months).
Kang et al.	Taiwan	Tumors with pathological serosal invasion were included.	NR	NR	29	83	Gastrectomy	3–4 l of RL solution containing cisplatin (30 mg/l), mitomycin (10 mg/l) + etoposide (20 mg/l) Temperature: 41–43°C Duration: 60 min.	Surgery	5 years
Cui et al.[18]	China	Stage IIIA and B	43::53	HIPEC = 53 (Mean) Control = 56 (Mean).	48	48	Radical gastrectomy.	60 mg/m^2 cisplatin in 3000 cc NS on days 1 and 4 and 0.75 gm fluorouracil in 3000 cc NS on days 2 and 3.Temperature : Both at 41–43° C Duration 90 mins.Adjuvant chemotherapy 1 months after surgery.	Surgery + ECF (50 mg/m^2 epirubicin and 60 mg/m^2 cisplatin administered via an intravenous drio on day 1 and 600 mg/m^2 fluorouracil administered via an intravenous drip on day 1and 3)	36 mo
Yarema et al[23]	Ukraine	Stage IIB-IIIC	65::33	22-74 (mean 56.6 + /- 10.2).	19	19	Gastrectomy with hand swen anastomosis.	Cisplatin (75 mg/m^2) and mitomycin C (12.5 mg /m^2) Teperature 42.3 + 1.3°C Duration 90 mins.	Surgery	Minimum 12 months.
Coccolini et al[24]	Italy	pT3-4	26::14	70.86 + /- 14.8	16	28	Radical gastrectomy with D2 lymphadenectomy.	Surgery + HIPEC with cisplatin (100 mg/m^2) and paclitaxel (75 mg/m^2) Temperature: 40–41°C Duration: 90 mins.	Surgery + ECF (50 mg/m^2 epirubicin and 60 mg/m^2 cisplatin administered via intravenous drip on day 1 and 600 mg/m^2 fluorouracil administered via an intravenous drip between day 1 and 3).	50 months
Beehary et al.[19]	China	c > T3	46::34	HIPEC = 59 + /-10 Control = 58 + /-10.	40	40	Radical gastrectomy with D2 lymphadenectomy.	Surgery + HIPEC with 50 mg/l of cisplatin at 42.0 + 1.0°C at 600–1000 ml/min for 60 mins. Adjuvant chemotherapy 6 regimens of standard dosage of the XELOX regimen starting within 1 months after surgery (Regimen: Oxaliplacin 130 mg/m^2 ivgtt d1 + Xeloda 1500 mg/m^2 bid po d1–15, Q3W).	Standard radical gastrectomy + D2 Lymphadenectomy Adjuvant chemotherapy 6 regimens of standard dosage of the XELOX regimen starting within 1 months after surgery (Regimen: Oxaliplacin 130 mg/m^2 ivgtt d1 + Xeloda 1500 mg/m^2 bid po d1–15, Q3W).	36 months
Reutovich et al.[20]	Belarus	pT4 N0-3	95::59	Sx + HIPEC = 56 + /-8 Control = 56 + /-9.	68	55	Radical gastrectomy with R0 resection and D2 lyph node dissection.	Cisplatin (50 mg/m^2) and doxorubicin (50 mg/m^2) in 5–6 l of RL Temperature 42°C.	Surgery	41 months (median)
Diniz et al[25]	Brazil	cT3-4 or cN +	159::110	HIPEC = 49.8 + /-10.8 Control = 59.3 + /-11.3.	28	241	Radical gastrectomy.	38 mg/m^2 Mitomycin C Temperature: 41–42°C Duration: 90 min. Other agents included cisplatin or oxaliplatin (200 mg/m^2) or cisplatin with docetaxel (30 mg/m^2 each).	Perioperative chemotherapy + Surgery (a) Platinum-based doublets (Carboplatin + Paclitaxel, Carboplatin + 5-FU, CDDP + 5-FU, FOLFOX, XELOX, FLOX); (b) Epirubicin-based triplets (ECF, ECX, EOX); or (c) Taxane-based triplets (DCF, DCX).	52 months (48.1–56.9).
Liu et al[26]	China	Stage IIIA and B	68::60	69.4 + /-5.3	64	64	Radical gastrectomy.	100 mg/m^2 oxaliplatin in 3000 cc NS on days 1 and 4 and 0.75 gm fluorouracil in 3000 cc NS on days 2 and 3. Temperature: 41–43°C Duration: 90 mins. Dexamethasone (10 mg) and 2% lidocaine (10 ml) were added into the perfusion solutions every day to relieve the peritoneal reactions of the patients.	Surgery + Systemic chemotherapy 2 week after surgery. Intravenous infusion of paclitaxel 135 mg/m^2 on the first day; intravenous drip of cisplatin 20 mg/m^2 and tegafur 1.0 g from the first day to the fifth day. The regimen was repeated for every 4 week, with a total of six cycles.	5 years
Xie et al[29]	China	cT4 N0-3	79::34	HIPEC = 60.9 + /-7.1 Control = 61.5 + /-8.6.	51	62	Laparoscopic assisted radical gastrectomy.	Cisplatin (50 mg/l of NS). Temperature: 42–43°C. Duration: 60 mins followed by oral and intravenous chemotherapy (capecitabine and oxaliplatin, XELOX) or tegafur gimeracil and oxaliplatin (SOX) combined oral–intravenous chemotherapy 6–8 week after surgery.	Surgery followed by adjuvant chemotherapy XELOX or SOX chemotherapy at 4–6 week after surgery and received a total of 6–8 cycles every 3 week. Oxaliplatin 130 mg/m^2 ivgtt d1 + xeloda 1500 mg/m^2 BID PO d1–15.	HIPEC = 27.3 + /-10.5 months Control = 25.5 + /-11.4 months.
Zhong et al[27]	China	cT3-4 N0-3	65::64	HIPEC = 52.4 + /-10.7 (28–72) Control = 53.1 + /-10.5 (25–70).	61	68	Laparoscopic assisted radical gastrectomy.	Lobaplatin (50 mg/m^2) in 3000 cc 5% glucose solution. Temperature: 43° C. Duration: 60 mins Rate: 500 ml/min.	Surgery	HIPEC = 33.1 + /-2.1 (20–42) months Control = 32.6 + /-5.1 (18–42) months.

Zhu et al[28]	China	Stage IIA to IIIC	29::14	HIPEC = 51 (38–69) Control = 55(43–68).	22	21	Gastrectomy	4–6 week after surgery intravenous 5-fluorouracil (500 mg/m^2) and LV (200 mg/m^2) on days 1–5 and Cisplatin (75 mg/m^2) on day 1 in 2000 cc NS Temperature: 45°C Duration: 30 mins.	Surgery followed by adjuvant chemotherapy 4–6 week after surgery intravenous 5-fluorouracil (500 mg/m^2) and LV (200 mg/m^2) on days 1 – 5, and intravenous cisplatin (25 mg/m^2) on days 1–3 (IV group).	60 months
Fan et al. [21]	China	cT3-4 N0-3	41::9	HIPEC = 61 Control = 60.	33	17	Radical gastrectomy.	Cisplatin (50 mg/l) Temperature: 42.5–43°C Duration: 30 min at a perfusion rate of 400–500 ml/min adjuvant chemotherapy with SOX regime (S-1, 40–60 mg (40 mg when BSA < 1.25m^2, 60 mg when BSA > 1.5m^2), twice per day, Day 1–14; Oxaliplatin (130 mg/m^2) was given intravenously at the first day of each cycle).	Surgery + postoperative adjuvant chemotherapy (a 3 week cycle SOX regime), S-1, 40–60 mg (40 mg when BSA < 1.25m^2, 60 mg when BSA > 1.5m^2), twice per day, Day –14; Oxaliplatin (130 mg/m^2) was given intravenously at the first day of each cycle.	36–48 months (median :37 months)
Merboth et al.	Germany	pT3-4, pN +	38::20	HIPEC = 59.4 (50.1–69.3) Control = 63.6 (57.6–74.8).	15	43	Cytoreductive surgery.	Intraperitoneal Oxaliplatin (350 mg/m^2) Temperature: 41.5°C (±0.5°C) Duration: 30 min and an IV injection of 5-FU (400 mg/m^2) and calciumfolinat (20 mg/m^2),1 case, she patient refused systemic chemotherapeutic treatment, and therefore doxorubicin (15 mg/m^2) and cisplatin (50 mg/m^2) were applied i.p. Duration: 60 min Temperature 1.0° C.	Surgery	5 years

Results

Literature search and findings

Two researchers searched using databases from PubMed, Embase, Medline, and Cochrane Databases. A total of 1161 results were obtained. After removing duplicate studies, 155 studies were included for abstract review, which was carried out by two researchers independently. Sixty full-text reviews were performed, and 44 studies were excluded. Sixteen studies fulfilled the inclusion criteria and were included in the meta-analysis. The literature search findings are represented in the PRISMA flow diagram (Fig. 1).

Risk of bias assessment and quality of study

Two investigators used RevMan 5.4 to assess the risk of bias for the six RCTs included. The evaluation is depicted in Figures 2 and 3. Most of the studies had methodological drawbacks, mainly difficulties in allocation concealment and the challenge of blinding between the groups. Table 1 summarized the modified MINORS score for the NRCTs. One study that scored less than 12 was excluded from analysis[15].

Study, patient, and intervention characteristics

These are summarized in Tables 2 and 3. A total of 16 studies; 6 RCTs[16–21] and 10 NRCTs[22–31] were included. This comprised of a total of 1700 patients. Most of the studies ($n = 10$) were conducted in Asia. The remaining six studies were from Italy, Brazil, Germany, Belarus, and Ukraine. All included studies reported the patient age, sex, and stage of tumor, except for one study. The characteristics of the intervention used in each study and outcomes are summarized in Tables 2 and 3, respectively. Cisplatin was the HIPEC chemotherapeutic drug used in 13 studies, either alone or in combination with other drugs like paclitaxel, 5-fluorouracil, mitomycin C, or etoposide. In two studies, oxaliplatin with 5-fluorouracil were used for HIPEC. The temperature of HIPEC ranged from 40–45°C, and the duration of the procedure was from 30 to 90 min. The surgery performed in both arms was a radical gastrectomy with D2 lymphadenectomy. In two studies, cytoreductive surgery (CRS) was performed.

Primary outcome

Overall 1-year survival (Fig. 4A).

Six studies reported 1-year survival (two RCTs and four NRTCs)[16,18,23,26,29,30]. Two hundred and thirty patients received surgery + HIPEC while 207 patients received standard treatment. Analyzing under the random effects model, overall heterogeneity was acceptable. On analysis of AGC with/ without carcinomatosis, the overall 1-year survival was not statistically significant (OR 2.10, 95% CI: 0.90–4.88). On analyzing RCTs versus NRCTs, the overall effect was not statistically significant as well (OR 1.52, 95% CI: 0.79–2.92).

Overall, 3-year survival (Fig. 4B)

Eight studies reported 3-year survival (four RCTS, four NRCTs)[16,18,20,21,26,27,29,30]. Three hundred and seventy-three patients received HIPEC while 388 received standard therapy. In the random effects model, on analysis of AGC with/ without PC the OR was 1.95, 95% CI: 1.40–2.72). Three year survival significantly favoured HIPEC (OR 1.89, 95% CI: 1.17–3.05), when RCTs and NRCTs were considered separately.

Table 3

Summary of patient outcomes in the included studies.

References	RCT/ NRCT	Group	Number of participants	Overall and DF survival in months	Survival rate (%)			Recurrence (%)		Complications (*n*)					
					1-year	3 year	5 year	Overall	Peritoneal	Myelosuppression	Leak	Intestinal obstruction	Liver dysfunction	Renal dysfucntion	Mortality
Yang [16]	RCT	Surgery + HIPEC	34	11 (10–11.9)	41.2	5.9	NR	NR	79.40	NR	0	1	NR	NR	64.7
		Control	34	6.5 (4.8–8.2)	29.4	0	NR	NR	79.40	NR	1	0	NR	NR	100
Miyashiro [17]	RCT	Surgery + HIPEC	135	NR	NR	NR	62.00	48.90	14.1	NR	9	NR	21	43	54
		Control	133	NR	NR	NR	60.90	48.1	17.3	NR	3	NR	3	44	52
Yarema [23]	NRCT	Surgery + HIPEC	19	22.5	100	NR	NR	NR	10.53	NR	NR	NR	NR	NR	NR
		Control	19	12	52.63	NR	NR	NR	73.68	NR	NR	NR	NR	NR	NR
Cui [18]	RCT	Surgery + HIPEC	48	32	85.41	58.33	NR	16.67	NR	27	NR	NR	NR	NR	NR
		Control	48	27	79.16	35.41	NR	33.33	NR	26	NR	NR	NR	NR	NR
Kang [22]	NRCT	Surgery + HIPEC	29	NR	NR	44.83	NR	NR	NR	NR	NR	NR	NR	NR	NR
		Control	83	NR	NR	10.84	NR	NR	NR	NR	NR	NR	NR	NR	NR
Coccolini [24]	NRCT	Surgery + HIPEC	16	34.6 (DFS 34.5)	Prophylactic HIPEC: 34.6 months Therapeutic HIPEC: 10 months					(According to CTCAE, rate of grade 3–5 complications) Prophylactic HIPEC: 17% Therapeutic HIPEC: 60%.	Morbidity = 16.7%.				NR
		Control	28	27.7 (DFS 24.7)	SA for T3: 28.2 months SA for T4: 27.1 months.					SA for T3: 8% SA for T4: 25%.	Morbidity = 16.4%.				NR
Beehary [19]	RCT	Surgery + HIPEC	40	NR (DFS 93%).	NR	NR	NR	NR	2.5	1	0	0	0	1	5
		Control.	40	NR (DFS 65%).	NR	NR	NR	NR	22.5	2	1	1	2	1	5
Reutovich [20]	RCT	Surgery + HIPEC.	68	NR	NR	47.37	NR	52.9	12.8	Surgery related complications = 9.	Non surgical complications = 11.				NR
		Control	55	NR	NR	26.92	NR	76.4	27.6	Surgery related complications = 5.	Non surgery related complications = 7				NR
Diniz [25]	NRCT	Surgery + HIPEC	28	59.5% (DFS 49.5% 34.7 months)	NR	NR	NR	46.43	28.57	NR	NR	NR	NR	NR	NR
		Control	241	68.7% (DFS 65.8%)	NR	NR	NR	21.99	9.54	NR	NR	NR	NR	NR	NR
Liu [26]	NRCT	Surgery + HIPEC	64	NR	96.88	70.31	28.13	7.81	NR	NR	NR	NR	NR	NR	NR
		Control	64	NR	79.69	34.38	9.38	25	NR	NR	NR	NR	NR	NR	NR
Zhong [27]	NRCT	Surgery + HIPEC	61	3 years DFS 89.4%	NR	89.4	NR	NR	4.9	NR	3	2	0	0	NR
		Control	68	3 years DFS 73.9% ($P = 0.031$)	NR	84.3	NR	NR	17.6	NR	3	1	1	0	NR
Zhu [28]	NRCT	Surgery + HIPEC	22	Median OS - > 50 months DFS = 36.5 months	NR	NR	NR	63.64	4.55	NR	NR	NR	12	8	NR
		Control	21	OS = 33.1 months DFS = 24.5 months ($P = 0.044$)	NR	NR	NR	90.48	33.33	NR	NR	NR	7	4	NR
Xie [29]	NRCT	Surgery + HIPEC	51	3 years DFS = 63%	96.1	68.6	NR	21.57	3.92	7	0	4	NR	3	NR
		Control	62	3 years DFS = 60.4%	95.2	66.3	NR	46.77	17.74	7	0	3	NR	2	NR
Merboth 2021	NRCT	Surgery + HIPEC	14	NR	64.3	NR	NR	85.7	57.1	NR	1	NR	NR	NR	30 days mortality = 6.7%.
		Control	40	NR	72.5	NR	NR	65	37.5	NR	4	NR	NR	NR	30 days mortality = 4.7%.
Fan [21]	RCT	Surgery + HIPEC	33	NR	NR	87.9	NR	NR	NR	8	4	NR	23	NR	NR
		Control	17	NR	NR	100	NR	NR	NR	4	1	NR	13	NR	NR
Rosa [31]	NRCT	Surgery + curative HIPEC	23	5 years DFS = 20%	NR	NR	27	NR	28.2	NR	1	1	NR	NR	NR
		Surgery + Prophylactic HIPEC	23	5 years DFS = 30%	NR	NR	33	NR	21.74	NR	1	0	NR	NR	NR
		Control	39	5 years DFS = 9%	NR	NR	9	NR	65.4	NR	4	0	NR	NR	NR

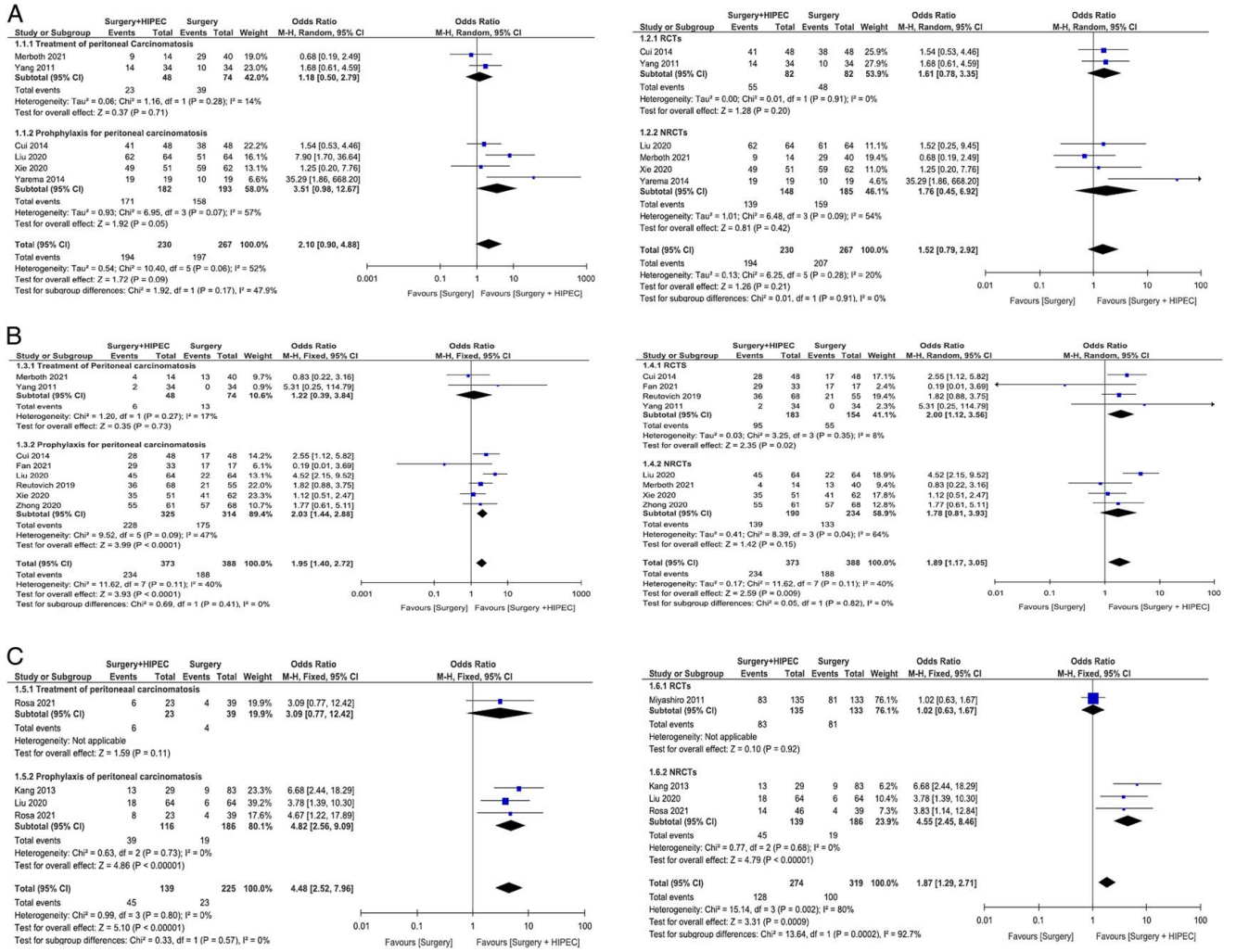


Figure 4. (A) Overall 1-year survival (B) 3-year survival (C) 5-year survival, PC versus Non PC and RCT versus NRCT. NRCT, nonrandomised studies; NPC, No peritoneal carcinomatosis; PC, Peritoneal carcinomatosis; RCT, Randomised controlled trial.

Overall 5-year survival (Fig. 4C)

Four studies reported 5-year survival (one RCT, three NRCTs)[17,22,26,31]. Two hundred and seventy-four patients received HIPEC while standard treatment was provided to 319 patients. On analysis for prophylaxis versus treatment for PC, using a random effects model, the heterogeneity was significant; hence, we conducted a sensitivity analysis, and eliminated the study[17] that caused significant heterogeneity. Four studies were then evaluated. Using the fixed effects model, there was no heterogeneity between studies ($I^2 = 0$). 5-year survival was significantly favorable to HIPEC (OR 4.48, 95% CI: 2.52–7.96). Using the fixed effects model, for analyzing RCTs and NRCTs, overall heterogeneity was 80%. The 5-year survival rate significantly favoured HIPEC (OR 1.87, 95% CI: 1.29–2.71).

Secondary outcomes

Recurrence rate

Overall recurrence rate (ORR) (Fig. 5). Eight studies evaluated overall recurrence (three RCTs, five NRCTs), with 448 patients undergoing HIPEC and 462 receiving standard treatment[17,18,20,26,28–31]. Studies were evaluated for treatment versus prophylaxis for PC. Using the fixed effects model, the ORR was significantly favorable to HIPEC (OR 0.57, 95% CI: 0.43–0.75).

When RCTs and NRCTs were considered separately for analysis, using the random effects model, the heterogeneity was 54%. The ORR was significantly favorable to surgery with HIPEC (OR 0.49, 95% CI: 0.31–0.80).

Peritoneal Recurrence (PR) rate (Fig. 6). PR rates were analyzed in nine studies (three RCTs, six NRCTs)[16,19,20,23,27–31]. Three hundred and fifty-five patients received HIPEC, while 417 patients were in the control group. Using the random effects model for analysis, the heterogeneity was 67%. The PR rate was significantly favorable to HIPEC (OR 0.22, 95% CI: 0.11–0.47). When RCTs and NRCTs were considered separately, the difference remained statistically significant (OR 0.232, 95% CI: 0.10–0.52).

Recurrence free survival (RFS) (Fig. 7). RFS was reported in only two studies[17,25]. One hundred and sixty-three patients received HIPEC while 374 patients received standard treatment. There was no significant heterogeneity between the studies. Using the random effects, the RFS was not statistically significant

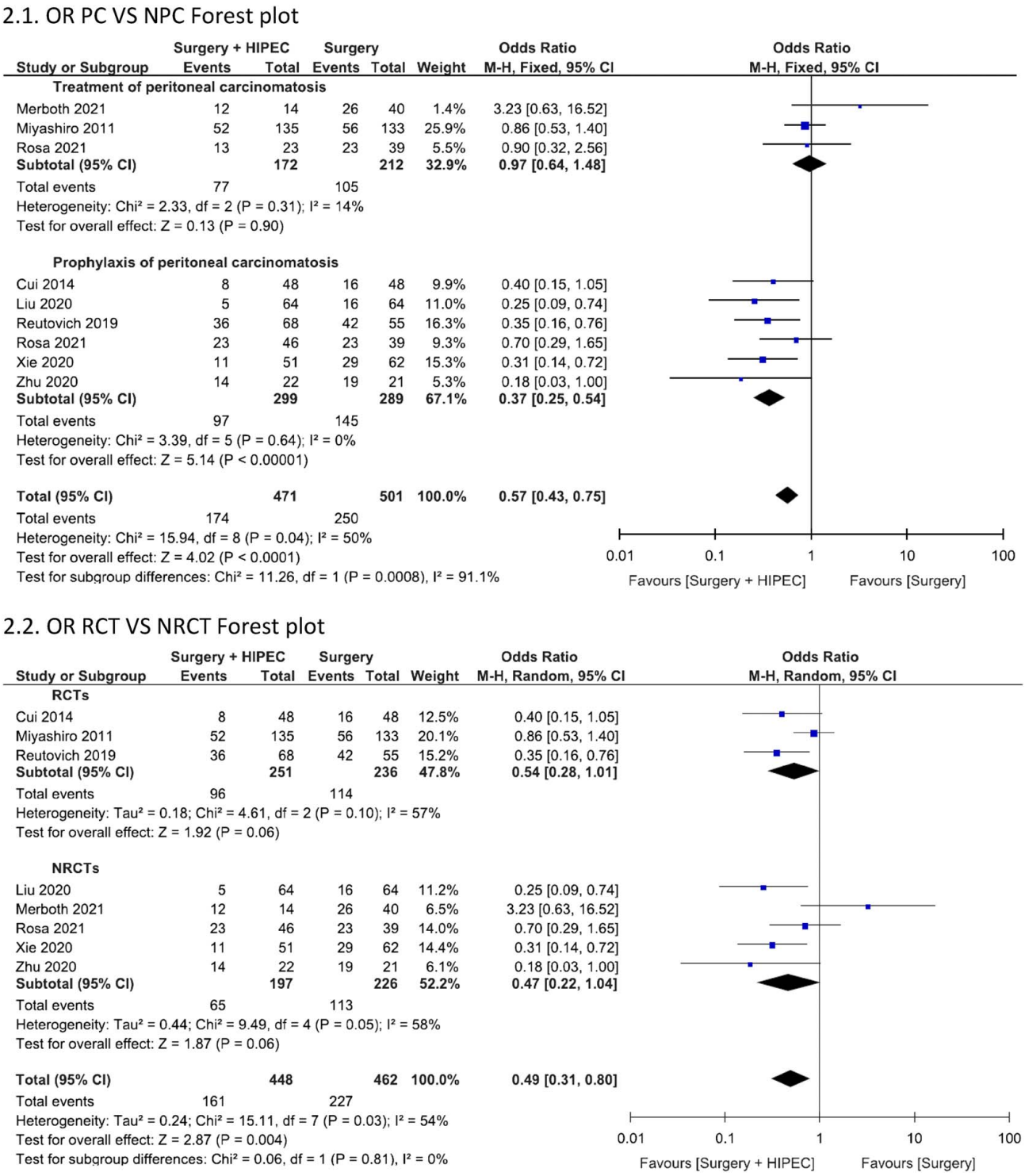


Figure 5. Overall recurrence rate (OR) 2.1 PC versus NPC 2.2. RCT versus NRCT. NRCT, nonrandomised studies; NPC, No peritoneal carcinomatosis; PC, Peritoneal carcinomatosis; RCT, Randomised controlled trial.

(OR 0.80, 95% CI: 0.39–1.65). As the number of studies were only two, subgroup analysis was not done.

Complications

Myelosuppression (Fig. 8). In four studies, myelosuppression was evaluated (three RCTs, one NRCTs)[18,19,21,29]. One hundred and seventy-two patients underwent Surgery + HIPEC, 167 patients underwent surgery alone. There were no studies evaluating the effect in patients with PC. Hence, subgroup analysis of AGC with and without PC was not done. There was no statistical heterogeneity between the studies. The overall effect was not statistically different (OR1.07, 95% CI: 0.60–1.89).

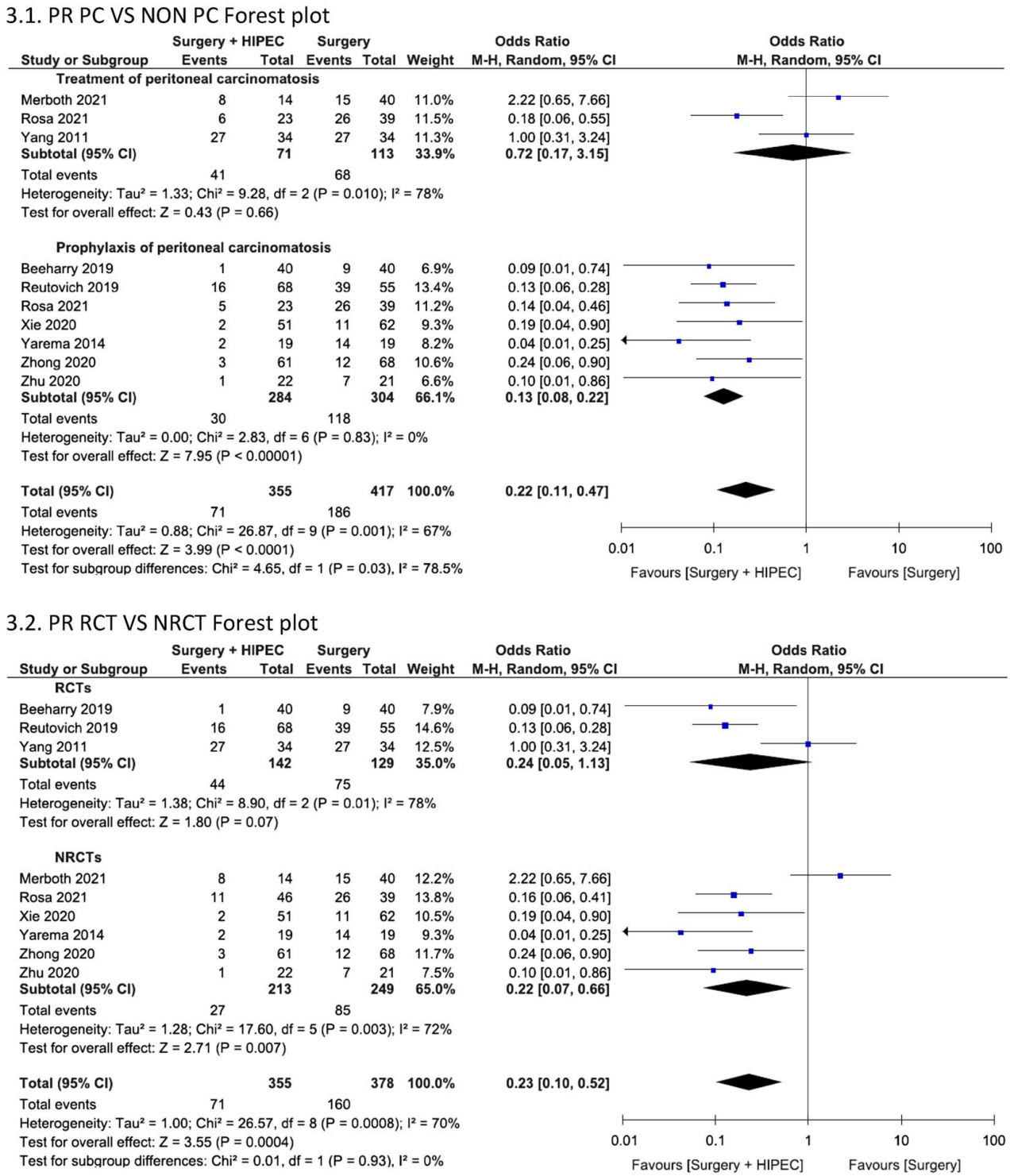


Figure 6. Peritoneal recurrence rate 3.1 PC versus Non PC 3.2. RCT versus NRCT. NRCT, nonrandomised studies; NPC, No peritoneal carcinomatosis; PC, Peritoneal carcinomatosis; RCT, Randomised controlled trial.

Liver dysfunction (Fig. 8). Five studies (three RCTs, two NRCTs) evaluated the incidence of postoperative liver dysfunction[17,19,21,27,28], which included 291 patients receiving HIPEC and 279 patients in control group. Analyzing using fixed effects model, there was no statistical heterogeneity between studies. The overall effect was not significantly different (OR 0.96, 95% CI: 0.63–1.48). Only one study[17] evaluated the effect in patients with PC; hence, subgroup analysis comparing PC versus non PC was not done.

Renal dysfunction (Fig. 8). Four studies (two RCTs, two NRCTs), reported the incidence of postoperative renal dysfunction[17,19,28,29]. Two hundred and forty-eight patients received HIPEC and 256

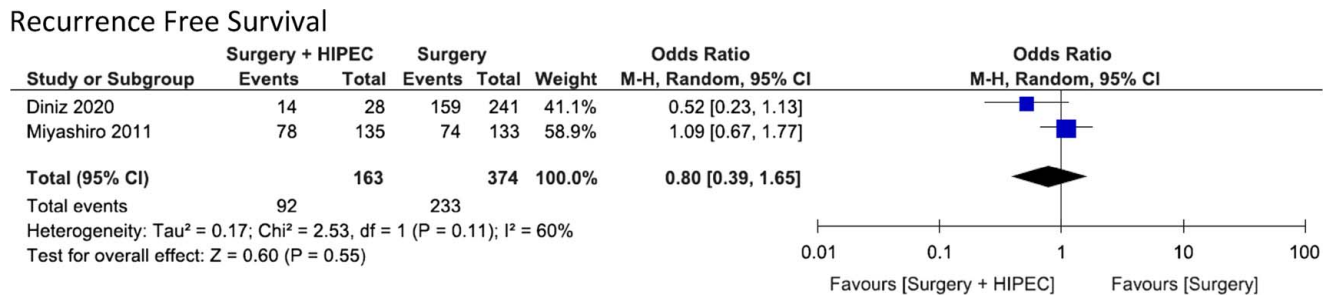


Figure 7. Recurrence free survival rate.

patients were in the control group. The overall heterogeneity was not significant (I^2 =8%). Using the fixed effects model, the occurrence of post operative renal dysfunction was significantly favorable to the control group (OR 3.94, 95% CI: 1.85–8.38). As the effect in patients with PC was evaluated in only one study[17]; hence, subgroup analysis comparing PC versus non PC was not done.

Anastomotic leak (Fig. 9). In eight studies, anastomotic leak rate was assessed (four RCTs, four NRCTs)[16,17,19,21,27,29–31], which included 415 patients who received HIPEC and 438 patients in the control group. There was no statistical heterogeneity between the studies. In the fixed effects model, the bowel leak did not significantly differ (OR 1.10, 95% CI: 0.57–2.11) while assessing PC versus non PC. On assessing RCTs and NRCTs separately, the difference remained insignificant (OR 1.17, 95% CI: 0.60–2.29).

Bowel obstruction (Fig. 10). Six studies reported post operative bowel obstruction rate (three RCTs, three NRCTs), which included 265 patients who received HIPEC, and 260 patients in the control group[16,19,21,27,29,30]. There was no statistical heterogeneity between studies. Using the fixed effects model, the overall effect was not statistically significant (OR 1.76, 95% CI: 0.64–4.84) when assessing PC versus non PC. When RCTs and NRCTs were considered separately, the difference remained statistically insignificant (OR 1.62, 95% CI: 0.59–4.50).

3-year mortality (Fig. 11). Three studies reported the post operative mortality at 3 years (two RCTs, one NRCT)[16,19,29]. One hundred and twenty-five patients received HIPEC, while 136 patients received standard treatment. There was no statistical heterogeneity between studies. In the fixed effects model, 3-year mortality was significantly favorable to surgery + HIPEC (OR 0.38, 95% CI: 0.18–0.82). As only one study[16] assessed effect in patients with PC, subgroup analysis was not performed to compare effects in PC versus non PC.

Discussion

In this meta-analysis, we evaluated the efficacy of HIPEC in the treatment of AGC with or without PC, but without solid organ metastasis, in terms of survival and recurrence. We also assessed its safety with regards to perioperative complications.

This review highlighted the beneficial effect of HIPEC on survival and recurrence rates. Our results show that HIPEC offers a significant advantage over standard treatment for 3-year and 5-year overall survival. The rate of renal dysfunction is more common in patients receiving HIPEC. Survival has been reported in many studies, with a survival advantage conferred by the use of HIPEC. A survival advantage of prophylactic HIPEC at 3 years (RR 0.71, CI: 0.53–0.96) and 5 years (RR 0.82, CI: 0.70–0.96) without a difference in 1-year survival was found in a recent meta-analysis by Desiderio *et al.*[32]. However, the survival rate was favorable at 1-year in patients where HIPEC was used for treatment of PC, but failed to have an advantage on 2-year and 3-year survival. HIPEC offered a significant advantage on 3-year mortality analysis in our study. A meta-analysis by Sun *et al.*[10] and Feingold *et al.*[33] similarly found a significant reduction in mortality and recurrence rates. In the last decade, there has been extensive research to include CRS + HIPEC as part of integrated therapy for AGC with PC. Individual studies have reported that achieving complete cytoreduction for low-volume PC provides beneficial outcomes from CRS + HIPEC[16,23]. CRS + HIPEC have been shown to result in a median survival of up to 13 months, which is twice as compared to conventional palliative therapy.

PC and the presence of loco-regional nodal infiltration influences the recurrence rate of patients with AGC. HIPEC does not have an effect on cancer cells that have penetrated deeply into the sub peritoneal layers[34] or in the presence of extensive lymph node metastasis[35]. Yonemura *et al.*[36] found an improved survival with HIPEC in node positive GC patients, but no statistically significant difference in the node negative group. Ikeguchi *et al.*[37] evaluated survival on the basis of the number of retrieved metastatic lymph nodes, and found a greater effect of HIPEC on survival in patients with 1–9 metastatic lymph nodes, whilst involvement of more than 10 lymph nodes favoured the control group[37]. These findings have supported that patients with positive cytology and limited lymph node involvement may benefit the most from HIPEC.

In this review, we report the advantage of HIPEC in improving overall recurrence and PR rates in AGC. The results from a meta-analysis by Coccolini *et al.*[7] have similarly reported significantly favorable results with surgery + HIPEC for advanced gastric cancers. The PERISCOPE I trial[38] results have raised concerns about frequent recurrence rates. One reason could be that 64% of the patients in the study had diffuse-type cancer. They did obtain a median survival of 15 months, and a DFS of 12 months. This trial gave information that the underlying gastric tumors exhibit a number of unfavorable features (high T stage, diffuse-type histology, and limited response to systemic chemotherapy).

HIPEC can cause high post operative morbidity. Our review evaluated the common complications associated with gastrectomy with HIPEC. The results were encouraging as there was no significant difference in the post operative rates of myelosuppression, anastomotic leak, bowel obstruction, or liver dysfunction. However, renal dysfunction was higher in the HIPEC group. Similar results were reported by Desiderio *et al.*[32]. Reutovich *et al.*[20]

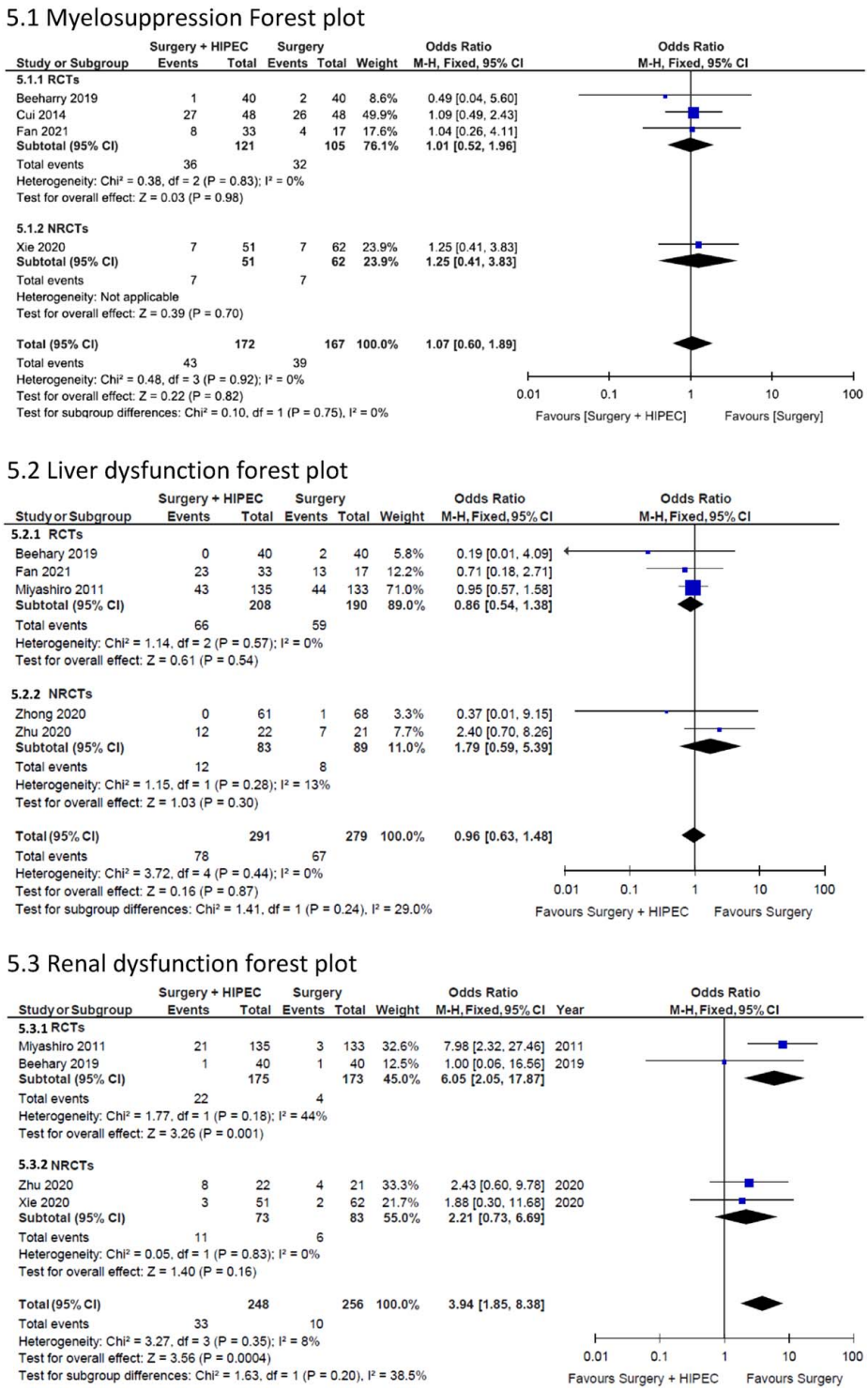


Figure 8. Complication : myelosuppression (5.1), liver dysfunction. (5.2), renal dysfunction (5.3).

reported two mortalities associated with oesophagojejunal anastomotic leak (2.6%) in the HIPEC group. Although not statistically significant, this is worth noting. Due to the differences in research aims, we evaluated different adverse events. However, more comprehensive evidence is warranted. Delivering a sufficiently high intraperitoneal drug concentration to provide an adequate concentration gradient between the peritoneal cavity and tumor tissue is one of the challenges of intraperitoneal chemotherapy. Several drug-delivery systems, such as nano-particles, microspheres, and hydrogels are under development to maximize peritoneal concentration

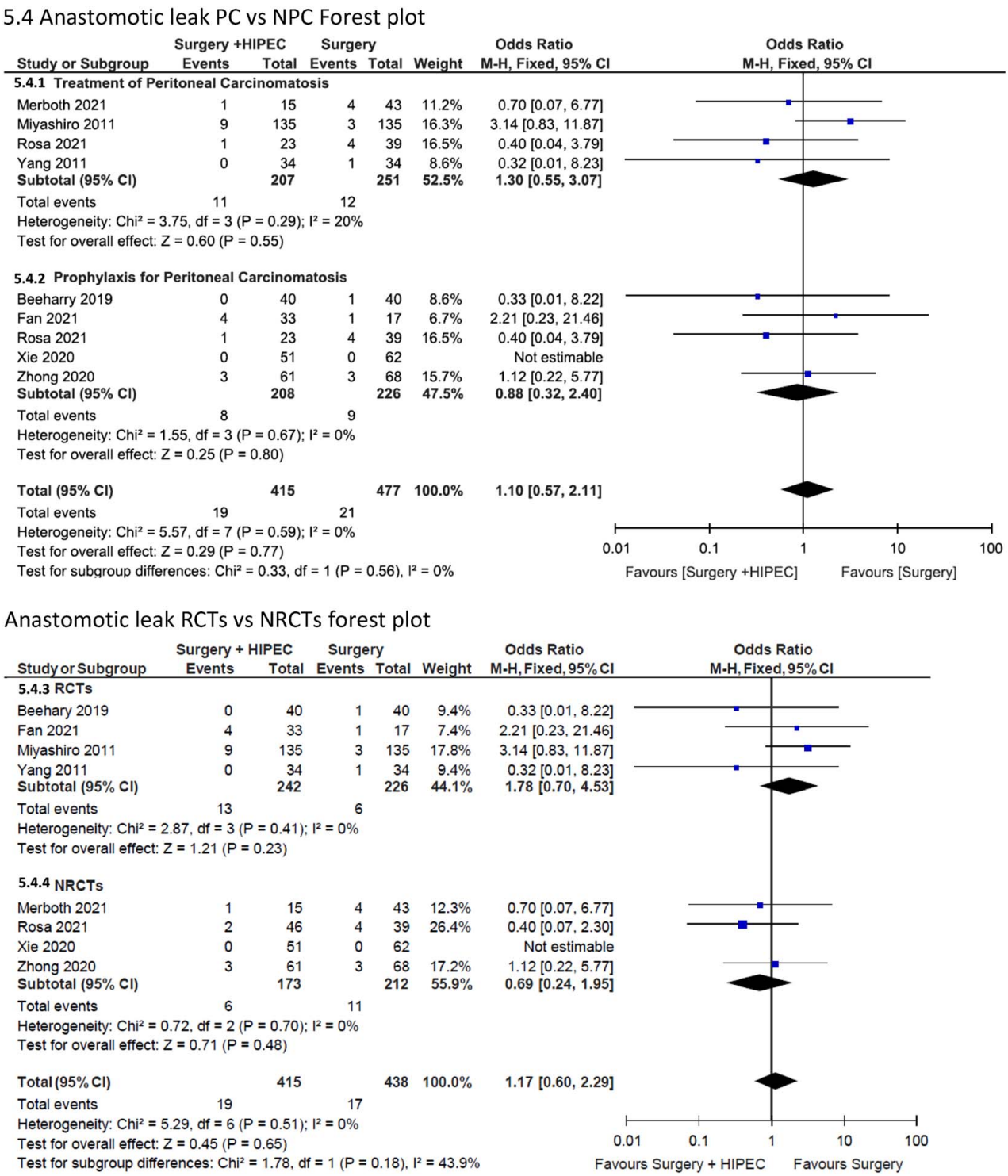
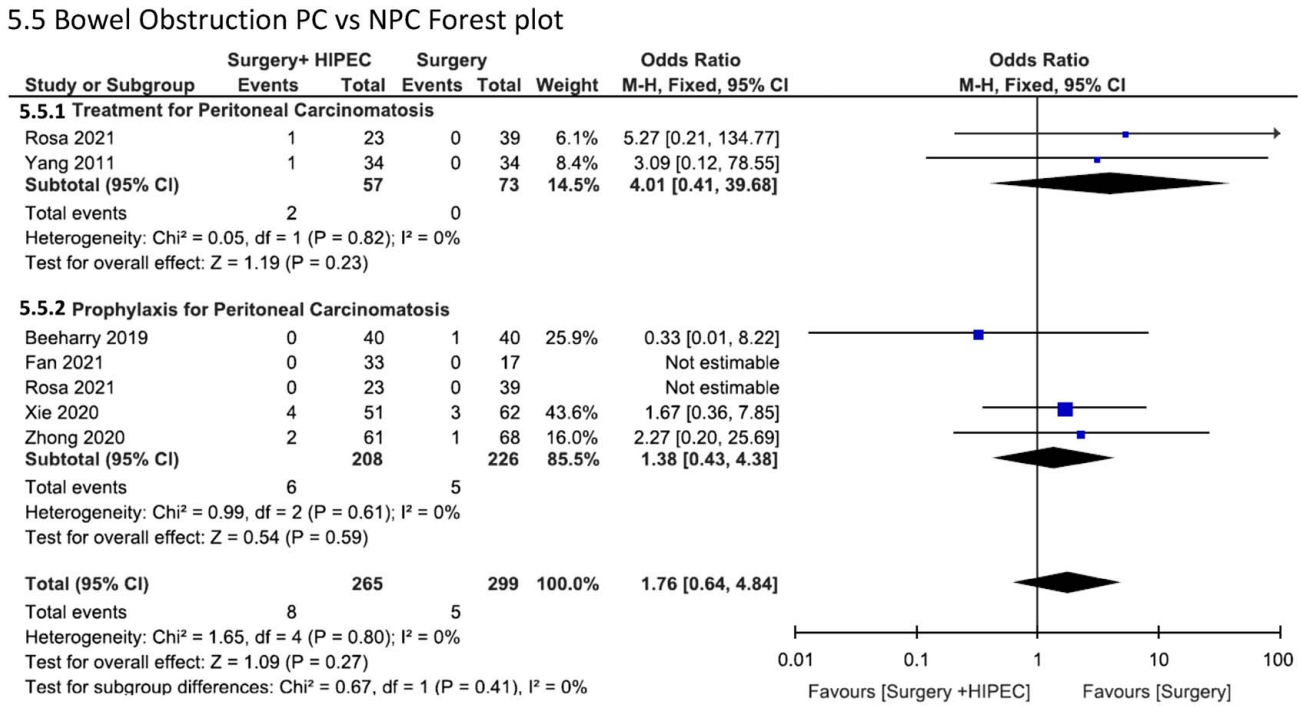


Figure 9. Complication: anastomotic leak rate PC versus Non PC, RCT versus NRCT. NRCT, nonrandomised studies; NPC, No peritoneal carcinomatosis; PC, Peritoneal carcinomatosis; RCT, Randomised controlled trial.

while aiming to reduce systemic toxicity[39]. The development of technology may help minimize the adverse effects of HIPEC. The choice of different chemotherapeutic drugs and its efficacy has been evaluated in previous studies. However, a difference in doses and the small number of studies limits its practical application. As there were a relatively small number of studies and varied drug combinations used, we did not assess the effects.

At present, there are no clear guidelines regarding the chemotherapeutic regime for HIPEC. High-quality studies evaluating the efficacy of individual chemotherapeutic regimes will



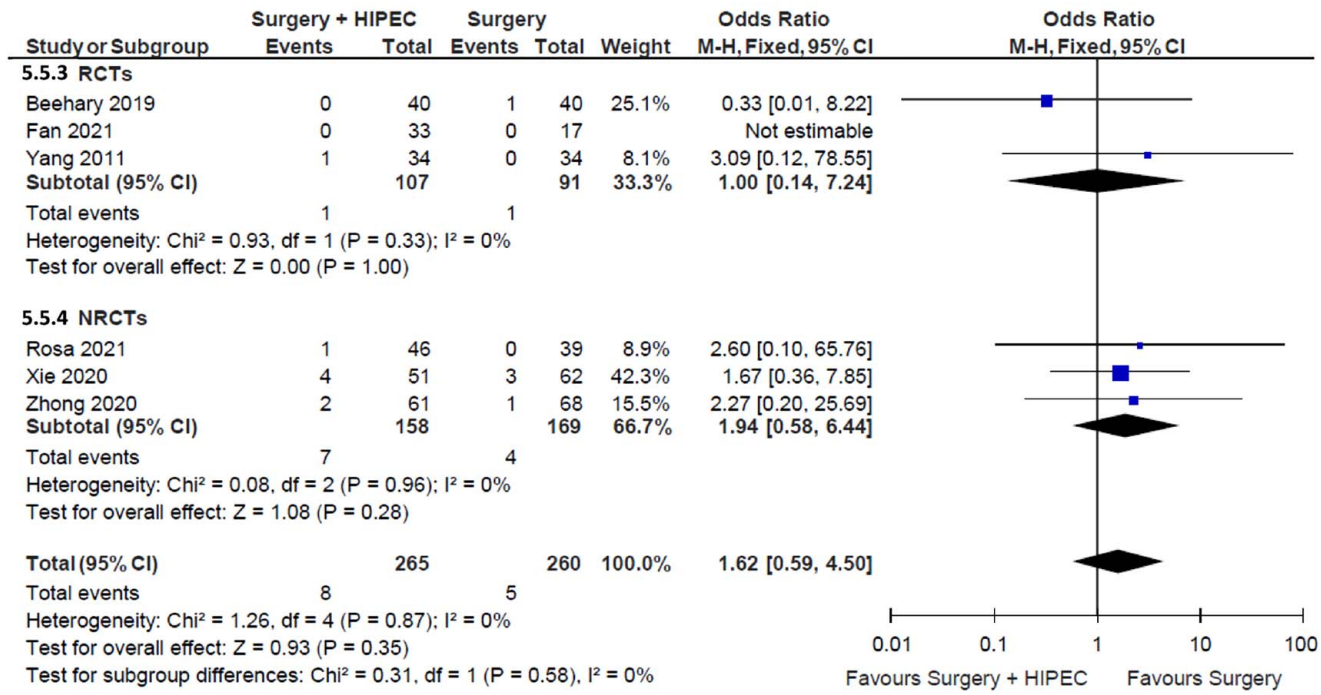


Figure 10. Complication: bowel obstruction, PC versus NPC , RCT versus NRCT. NRCT, nonrandomised studies; NPC, No peritoneal carcinomatosis; PC, Peritoneal carcinomatosis; RCT, Randomised controlled trial.

guide treatment strategy[40]. Additionally, there is no consensus with respect to the technical aspects of HIPEC, including drug dosages, optimal temperature, and duration. Most centers prefer an open HIPEC technique using mitomycin C and cisplatin based drug regimens for 60–90 min at 40–43°C with a flow rate of 500 ml/min (Table 2). Selecting the patients who are most likely to benefit from these therapies will depend on developing personalized approaches, which will be better guided by the ongoing studies to identify ways to detect molecular sequencing of alterations in tumor tissue. Cell-free circulating tumor DNA in patients with peritoneal metastases can potentially help in the prognostic assessment of disease and identify optimal therapeutic strategies[41].

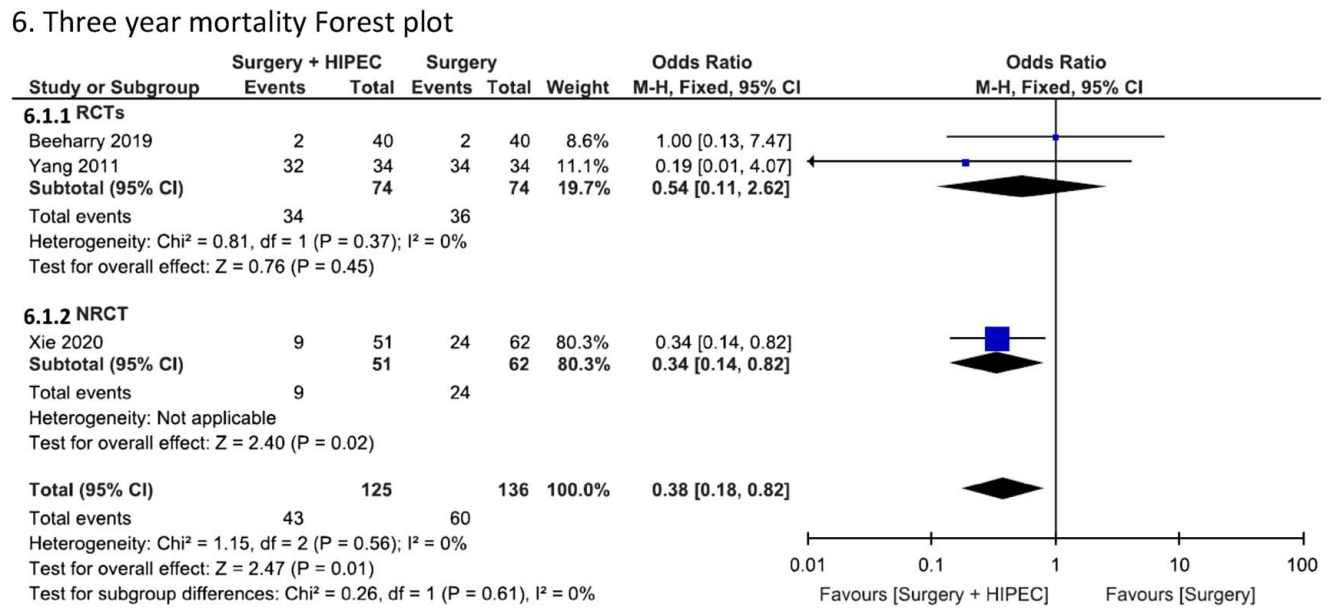


Figure 11. 3-year mortality.

There are limitations to the present meta-analysis. We have included 10 NRCTs, which may skew the results. We performed subgroup analysis to assess outcomes considering both separately, in order to guide the reader. Although similar findings have been reported previously, we have analyzed both, GC with and without PC where possible, separately to make the differences clearer. Additionally, we have included only the studies conducted within the last 10 years, which makes them more relevant to the current practice, considering the advances in management and treatment of GC. One major drawback that remains is the problem with blinding in the studies. However, it should not have an impact on the survival outcomes. Additionally, most of the studies are from Asian institutions, which might limit its suitability in Western centers. Furthermore, stage III and IV GC cases have not been assessed separately, as the outcomes of stage IV disease may be considerably worse than stage III. One important factor remains the peritoneal cancer index (PCI). PCI values in the studies included in our analysis are heterogeneous. Hence, this makes it difficult to define the PCI when considering HIPEC for these patients.

There remains a paucity of multicentre trials and international collaborations. At present, there are two ongoing European multicentre trials: GASTRIPEC and GASTRICHIP. The GASTRIPEC trial (NCT02158988) will assess CRS with and without HIPEC in patients with GC with PC. This study began recruiting in March 2014, and the final enrollment was completed in October 2020. They aim to assess the overall survival at 2.5 years follow up. 30-day post operative complication rate, time to progression, distant metastasis, and quality of life are the secondary outcomes being assessed[42]. The GASTRICHIP trial (NCT01882933) aims to assess the effect of HIPEC in T3/T4 resectable gastric adenocarcinoma with/ without lymph node metastasis or positive peritoneal cytology sampled during preoperative laparoscopy. The primary outcome to be assessed is overall survival at 5 years of follow up. The secondary outcomes they will investigate are RFS at 3 and 5 years, treatment related morbidity and mortality during 60 days postoperatively. They will also assess the quality of life with the EORTC questionnaire QLQ-C30. This trial started in June 2013 and has enrolled 367 patients. The study is planned to be completed by May 2026[43].

A German trial, PREVENT (NCT04447352), is a multicentre controlled, open-label study including a total of 200 patients with localized and locally advanced diffuse or mixed type (Laurens's classification) adenocarcinoma of the stomach and Type II/III Gastro Esophageal Junction[44]. The trial started in December 2020 and is estimated to be completed by November 2026. Only patients without PC will be included in this study (excluded on laparoscopy). The primary endpoint is progression free survival/DFS, major secondary endpoints are OS, rate of patients with peritoneal relapse at 2 and 3 years, perioperative morbidity/mortality and quality of life. This trial could guide the use of prophylactic HIPEC.

Conclusion

Our results suggest that HIPEC may improve survival rates and reduce recurrence rates in selected patients with AGC, without significant increase in complications. It showed a favorable impact on 3-year survival. The prognosis depends on patient selection like good performance status and fitness and also GC related factors. High-quality, multinational, randomized studies will guide patient selection and developing standardized protocols for the management of this cohort of patients.

Ethical approval

No ethical approval is needed as data from previously published studies has been analyzed.

Sources of funding

This study did not receive any funding.

Author contribution

M.P.: conceptualization, methodology, data collection, investigation, data interpretation, formal analysis, writing original draft ; A. A.: data collection, investigation, formal analysis; S.M., D.M.: conceptualization, validation, supervision, writing - review and editing, project administration.

Conflicts of interest disclosurse

There are no conflicts of interest to declare.

Research registration unique identifying number (UIN)

1. Name of the registry: PROSPERO.
2. Unique Identifying number or registration ID: CRD42022310556.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=310556.

Guarantor

Samrat Mukherjee.

Data availability statement

The data analyzed is available from the corresponding author on reasonable request.

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