European Journal of Surgical Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Prognostic impact of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) in gastric cancer patients: A meta-analysis of randomized controlled trials

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ARTICLE INFO

Article history:
Accepted 7 May 2021
Available online xxx

Keywords:
Gastric cancer
Peritoneal metastases
Cytoreductive surgery
Hyperthermic intraperitoneal chemotherapy
Systematic review
Meta-analysis

ABSTRACT

Background: gastric cancer patients frequently develop peritoneal metastases (PM) with a poor long-term prognosis. A solid body of evidence underlines the beneficial role of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) on survival, but to date, there is a lack of consensus regarding the optimal strategy in the treatment of locally advanced primary tumors with or without peritoneal metastasis. The present meta-analysis aims to assess the impact of CRS + HIPEC on survival analyzing the results of randomized studies only.
Methods: A systematic review of articles was conducted according to PRISMA guidelines. Twelve studies were included in qualitative and quantitative analysis.
Results: A survival benefit for patients treated with CRS + HIPEC at all time points was highlighted. However, difference in survival was significant at all time points for patients treated for prophylaxis of PM, but no difference was found when considering resection with a curative intent. The 1, 2, 3 and 5-year survival rates (SR) for patients undergoing CRS + HIPEC were 86.9%, 70.5%, 63.7% and 55.7% respectively. CRS + HIPEC for the treatment rather than prophylaxis of PM was the only predictor of a reduced 3y SR.
Conclusions: CRS + HIPEC may lead to improved prognosis for patients suffering from locally advanced gastric cancer in both prophylactic and curative settings. However, due to far from negligible post-operative morbidity and mortality rates, a strict patient selection is crucial to achieve the best results. The presence of extraperitoneal disease strongly limits the indication of this kind of surgery.

Introduction

Gastric cancer (GC) is the fifth most frequent neoplasia and the second cause of death for cancer worldwide [1]. At surgical exploration, up to 50% (average 15%) of patients present with peritoneal metastasis (PM), especially in case of serosal involvement by the primary tumor [2,3], and about 60% of patients present with peritoneal disease at the time of death [4]. These patients have a poor prognosis with a median overall survival (OS) ranging from 8.8 to 13.8 months [5–7].

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https://doi.org/10.1016/j.ejso.2021.05.016
0748-7983/

In this setting, cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has progressively gained interest as a treatment option even for gastric cancer patients with peritoneal metastasis. In 2004, Glehen et al. highlighted the importance of a complete CRS (CC) reporting 21.3 months median survival time (MST) for patients receiving CC0-1 surgery compared with 6.1 months MST for those with CC > 1 resection [8]. The completeness of cytoreduction is one of the most important predictors of a favorable prognosis [9,10]. According to other valuable pieces of evidence available in the literature, the adjunct of HIPEC to CRS contributes to significant long-term survival improvement.

Currently, CRS + HIPEC has been proven mainly in the treatment of PM with curative intent and as adjuvant treatment for gastric tumors arising to the serosal layer in the absence of macroscopic carcinomatosis. According to the most recent NCCN and JGCA guidelines [11,12], peritoneal dissemination (including positive peritoneal cytology) is considered M1 disease and not to be resected. Therefore, these patients are proposed with palliative chemotherapy or best supportive care. On the other hand, ESMO guidelines [13] suggested less strict recommendations, supporting the concept that selected patients with peritoneal spread can achieve a significant survival benefit from complete CRS + HIPEC. Nevertheless, this approach is not recommended outside the context of clinical research.

There is a lack of consensus regarding the optimal strategy in the treatment of gastric cancer patients with locally advanced primary tumors with or without peritoneal metastasis. Therefore, the present systematic review and meta-analysis aims to provide an up-to-date overview of randomized studies only, to assess the impact of CRS with HIPEC on survival, and to identify prognostic factors related to survival outcomes.

Methods

Search strategy

A systematic review of the English-language literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines [14,15]. Moreover, the meta-analysis was conducted following the MOOSE recommendations.

Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42020220245.

The PubMed, Scopus, and Cochrane Library databases were screened without time restrictions up to November 16th, 2020 using the keywords “gastric” and “stomach” combined with “cancer/tumor/adenocarcinoma/neoplasm”, “peritoneal carcinomatosis/metastasis”, “HIPEC”, “IPHP”, “IHCP”, “CHPP”, “hyperthermic intraperitoneal chemotherapy”, “intraperitoneal hyperthermic perfusion”, “intraperitoneal hyperthermic chemoperfusion”, “continuous hyperthermic peritoneal perfusion”, “cytoreductive surgery”, “cytoreduction”, “CRS”, “prognosis”, “survival”, “survival rate”, and “risk ratio”. The research also included all the MeSH Terms. Articles without free full text available were searched through the University of Milan digital library and direct contact with authors. A hand-search of references of included studies and previous reviews on the topic was also performed to include additional relevant studies according to our selection criteria. Two investigators (SG, AC) carried out the literature search independently.

Inclusion criteria

We included only randomized controlled studies reporting survival outcomes of gastric cancer patients who developed peritoneal only metastases (included positive peritoneal cytology) treated with surgical resection of the primary tumor, complete cytoreduction of peritoneal disease with HIPEC. Patients suffering from locally advanced gastric cancer with serosal invasion of the primary tumor, for whom prophylactic HIPEC was performed, were selected as well.

A specific population (P), intervention (I), comparator (C), outcome (O), and study design (S) (PICOS) framework was specified to define study eligibility, as recommended. In particular, the following criteria were outlined:

- Population (P): patients suffering from histologically confirmed adenocarcinoma of the stomach with or without peritoneal only metastases/positive peritoneal cytology;
- Intervention (I): complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with curative intent;
- Comparison (C): patients undergoing surgery without curative intent or any other systemic palliative treatment;
- Outcomes (O): overall survival of patients treated with surgical resection;
- Study design (S): randomized-controlled trials only.

Studies with insufficient reporting of the PICOS criteria were excluded.

This meta-analysis aimed to investigate the effect of CRS + HIPEC on survival in gastric cancer patients and to identify variables with a prognostic impact on OS.

Exclusion criteria

All non-randomized controlled studies were excluded from the present review. Studies exploring the role of CRS with HIPEC for primary tumors other than gastric cancer were excluded as well. Similarly, composite studies enrolling gastric cancer patients and patients suffering from other malignancies without reporting separated results were deemed not eligible.

Systematic review process

Mendeley reference software (Mendeley Ltd, London, UK) was used to identify and remove duplicates among identified records. Overall, 1990 articles were preliminarily identified by the literature search. After exclusion of duplicates, two independent reviewers (AB, FB) screened titles and abstracts of 1971 records. An a priori developed screening form was created to guide study selection. Investigators were blinded to each other's' decisions. The disagreement was solved by a third party (SG), who supervised the systematic review process.

Fifty articles were assessed for eligibility. Finally, 12 studies fulfilling all inclusion criteria were selected for qualitative and quantitative analysis. The flow-chart depicting the overall review process according to PRISMA is reported in supplementary materials.

Assessment of risk of bias

The risk of bias was assessed for individual studies according to the RoB 2 tool provided by the Cochrane Collaboration [16] independently by two investigators (SF, SP). The following domains were explored: 1) bias arising from the randomization process; 2) bias due to deviations from intended interventions; 3) bias due to missing outcome data; 4) bias in measurement of the outcome; 5) bias in selection of the reported results.

Data were collected according to the methodology proposed by Higgins [16] in a computerized spreadsheet. Bar and traffic light plots were created to display the results of the risk of bias assessment graphically.

Data extraction and assessment of included studies

Data were extracted independently by three authors (SG, AB, SF). Information about study design and methodology, participant demographics and baseline characteristics, CRS + HIPEC, and control groups treatment details, survival, and complication outcomes were gathered in a computerized spreadsheet (Microsoft Excel 2016; Microsoft Corporation, Redmond; WA).

In case of disagreement, two further investigators (MD, SK) helped resolve it through discussion.

Primary and secondary endpoints

Primary outcomes were represented by 1-, 2-, 3- and 5-year OS. Secondary outcomes were represented by 1-, 2-, and 3-year disease free survival (DFS), and median survival time (MST) and post-treatment morbidity/mortality rates and prognostic factors related to survival.

Statistical analysis

Primary outcome measures were expressed in terms of Risk Ratio (RR) and 95% Confidence Intervals (CI) for overall survival and disease-free survival. Meta-analyses of binary outcomes were developed. Moreover, meta-analyses of proportion were performed to explore cumulative survival rates of HIPEC patients at different time points. Secondary outcome measures were reported as RR and 95% CI. Meta-analyses of binary outcomes and medians were developed.

Fixed and random effects models based on the Mantel-Haenszel method were built to assess the impact of heterogeneity on results. In the presence of low heterogeneity (<25%), a fixed-effects model was chosen to compute the outcome. One-, 2-, 3- and 5-year survival rates were calculated as the proportion of patients alive at different time points. If not reported, the number of survivors was estimated by Kaplan-Meier curves. The presence of outliers was investigated, and their effect sizes were excluded.

Heterogeneity between studies was quantified by I^2 statistic and Cochran's Q test; cut-off values of 25%, 50%, and 75% were considered as low, moderate, and high, respectively [17]. Sensitivity analyses were conducted after inspecting patterns of effect sizes and heterogeneity of the included studies. To identify studies overly contributing to heterogeneity Graphic Display of Heterogeneity (GOSH) plots were developed, and sensitivity analysis was conducted excluding studies predominantly responsible for heterogeneity.

Mixed-effects meta-regression models were developed to investigate the association between potential predictors of survival at 3 years and effect size differences among patients undergoing CRS + HIPEC. Due to the insufficient number of included studies, the possibility to build multiple meta-regression was precluded. Therefore, the analysis was conducted exploring the moderators one by one.

Funnel plots were developed to explore publication bias, and Egger's test of the intercept was used to quantify funnel plots' asymmetry. Duval & Tweedie's trim-and-fill method was adopted to estimate and adjust the number and outcomes of missing studies each time Egger's test demonstrated significant asymmetry.

Statistical analysis was conducted with R statistical software (The Comprehensive R Archive Network – CRAN, ver. 4.0.0 × 64) [18], using "meta", "metafor", "metamedian", "robvis" and "dmetar" packages [19–22].

Results

Descriptive noncomparative analysis of included studies and primary endpoint

After the literature search, 12 randomized controlled studies [23–34] were included in the qualitative and quantitative analysis. Most of the excluded studies were deemed not eligible due to no English language, tumors other than gastric included without separated data, lack of randomization, normothermic intraperitoneal chemotherapy, overlapping series, absence of a CRS + HIPEC arm, or missing data.

In total, 1376 patients were included in the meta-analysis. All studies but the one published by Rudloff et al. [33] came from Eastern countries. The average male/female ratio was 1.6. Only five studies reported the median follow-up [24,30,31,34,35]: 35.4 months for patients receiving CRS + HIPEC and 34.2 months for the control group. Table 1 summarizes patients' characteristics.

Primary endpoint

Meta-analysis of binary outcomes: Overall survival

A survival benefit for patients treated with CRS + HIPEC at all time points was highlighted. However, difference in survival was significant only at 1 (RR = 0.6; 95% CI: 0.47–0.75; p < 0.0001; I^2: 22.9%), 2 (RR = 0.7; 95% CI: 0.57–0.87; p = 0.0009; I^2: 51%) and 3 (RR = 0.68; 95% CI: 0.57–0.81; p < 0.0001; I^2: 59.7%) years. The comparison between CRS + HIPEC and control groups on overall survival (forest plot) is shown in supplementary materials.

Sensitivity analysis. GOSH plots were computed to identify studies overly contributing to heterogeneity. An example is represented in Fig. 1. The other plots are reported in supplementary materials.

Afterward, sensitivity analysis was conducted. At 1-year follow-up, after excluding the studies by Fujimura and Ikeguchi [24,26], a significant overall effect was confirmed for the CRS + HIPEC group (Fig. 2A, RR = 0.61, 95% CI: 0.48–0.78; p = 0.0001). However, no difference was found between the two groups for patients with PM (RR = 0.75; 95% CI: 0.55–1.01).

At 2-year follow-up, after excluding the study by Fujimura [24], a significant overall effect was confirmed for the CRS + HIPEC group (Fig. 2B, RR = 0.71, 95% CI: 0.61–0.83; p < 0.0001). Nevertheless, no difference was found between the two groups for patients undergoing treatment for PM (RR = 0.83; 95% CI: 0.69–1.003).

At 3-year follow-up, after excluding the studies by Takahashi, Yu and Yang [27,30,31], a significant overall effect was confirmed for the CRS + HIPEC group (Fig. 2C, RR = 0.63, 95% CI: 0.52–0.76; p < 0.0001). Again, no difference was found between the two groups for patients undergoing treatment for PM (RR = 0.8; 95% CI: 0.54–1.19).

At 5-year follow-up, after excluding the studies by Yu and Yang, a significant overall effect was confirmed for the CRS + HIPEC group (Fig. 2D, RR = 0.77, 95% CI: 0.64–0.94; p = 0.01). This result is based

Table 1
Detailed characteristics of included studies.

Author	Year of publication	Years of enrollment	Indication	HIPEC group (n)	Control group (n)	T2 (%)	T3-T4 (%)	N0-1	N ≥ 2	HIPEC characteristics					Control characteristics		Median FUP HIPEC (months)	Median FUP Control (months)
										Technique	Drug 1	Drug 2	Temp (°C)	Time (mins)	Type of treatment	CT regimen		
Kaibara	1989	1983 −1985	Prophylaxis	42	40		100			close	MMC		44 −45	60	Surgery			
Fujimura	1994	1988 −1992	Prophylaxis	22	18	45	55	23	16	open	MMC	CDDP	41	60	Surgery		35	31
Hamazoe	1994	1983 −1986	Prophylaxis	42	40	19,5	80,5		26	close	MMC		48	60	Surgery			
Ikeguchi	1995	1980 −1989	Prophylaxis	78	96		100				MMC	IV MMC	44 −45	60	Surgery + Adjuvant CT	Oral UFT	72	
Takahashi	1995	1987 −1992	Prophylaxis	56	57					open	MMC			180	Surgery		42	40
Fujimoto	1999	1987 −1996	Prophylaxis	71	70	17	83	11	130	close	MMC		45	120	Surgery			
Yonemura	2001	1988 −1993	Prophylaxis	48	91	5	95	45*	94**	open	MMC	CDDP	42	60	Normothermic intraperitoneal chemoperfusion/Surgery alone			
Yu	2001	1990 −1995	Prophylaxis	125	123	30,6	69,4	165	83	close	MMC	5FU	37		Surgery		36	36
Yang	2011	2006 −2010	Treatment	34	34					open	CDDP	MMC	43	60−90	Surgery		32	32
Cui	2014	2006 −2010	Prophylaxis	96	96					close	CDDP	5FU	41 −43	90 (for 4 days)	Surgery/Neoadjuvant CT + Surgery	PTX + CDDP (neoadjuvant)/ECF (adjuvant)		
Rudloff	2014	2009 −2012	Treatment	9	7		100	4*	13**	close	OHP		41	30	Palliative CT	FOLFOXIRI		
Beeharry	2019	2014 −2015	Prophylaxis	40	40		100	27	53	open	CDDP		42	60	Surgery		32	32

Abbreviations: CT − chemotherapy; MMC − Mitomycin C; CDDP − Cisplatin; 5FU − 5 Fluorouracil; OHP − Oxaliplatin; UFT - tetrahydrofuryl-5FU; PTX − paclitaxel; FOLFOXIRI − 5FU + Folinic Acid + Oxaliplatin + Irinotecan; ECF - epirubicin + cisplatin + fluorouracil; IV − intravenous; * only N0; **N ≥ 1.

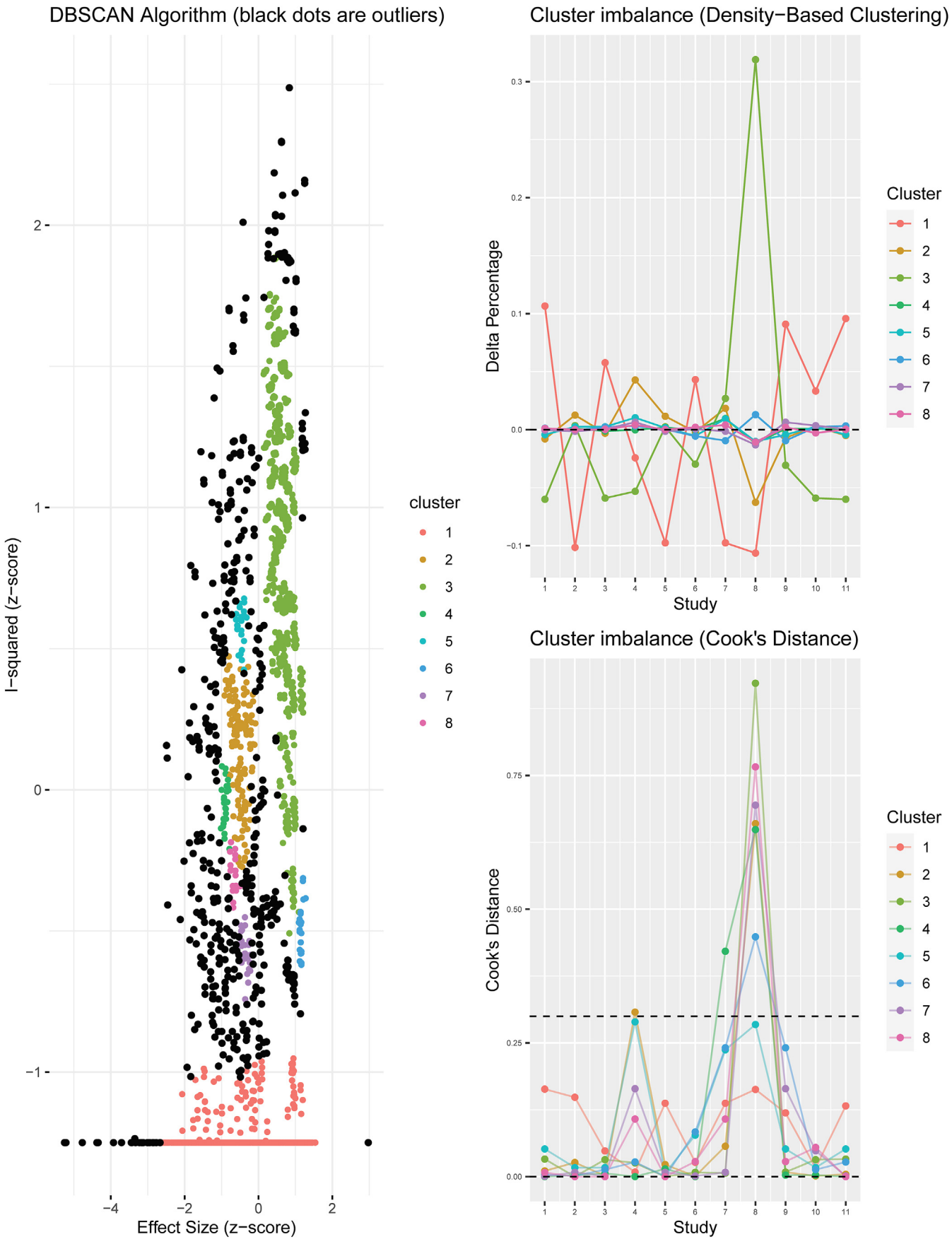

Fig. 1. 3-year survival: GOSH plot analysis.

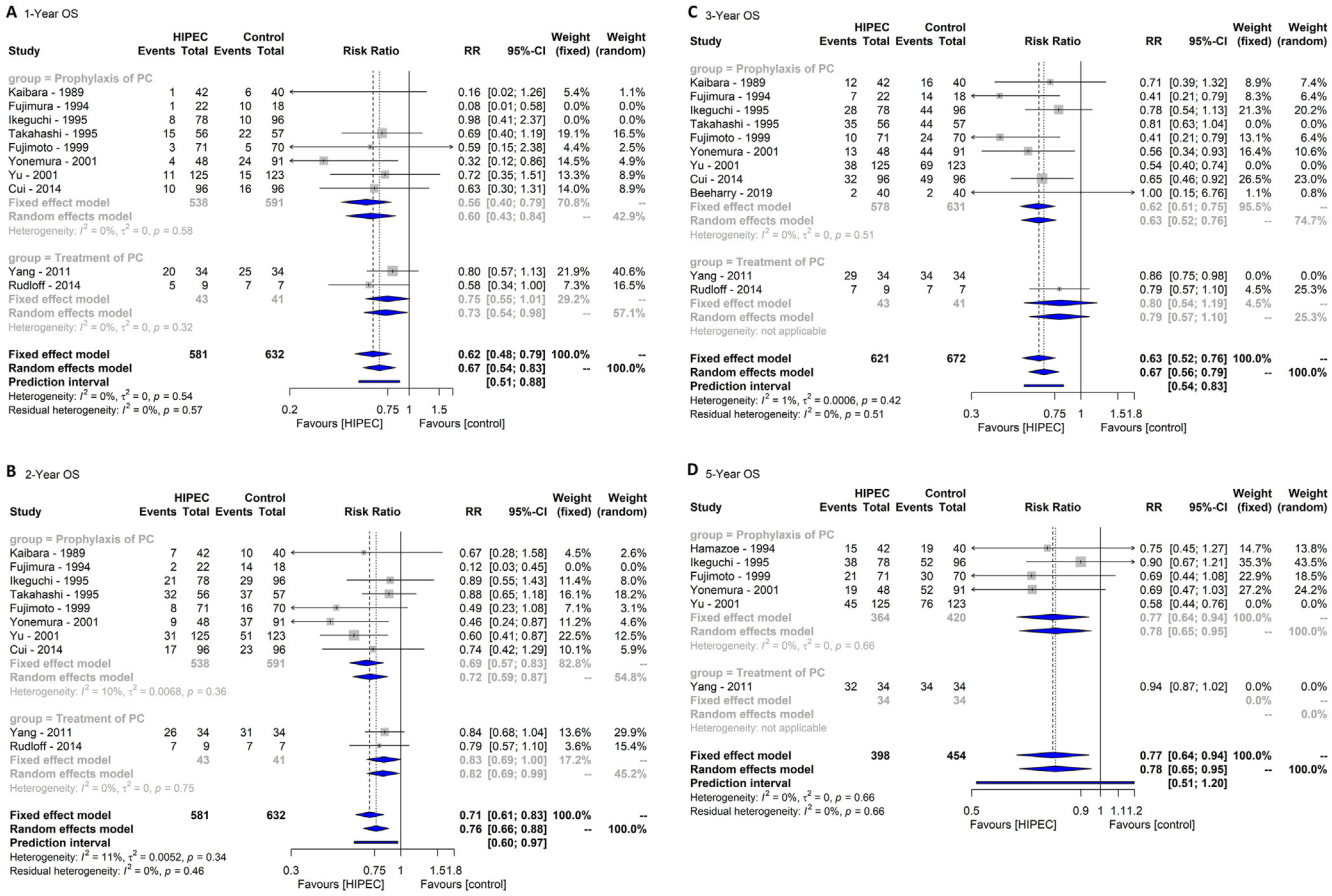

Fig. 2. Forest plots CRS + HIPEC vs Control – A) 1y-survival, B) 2y-survival, C) 3y-survival, D) 5y-survival.

on the analysis of studies including only patients undergoing CRS + HIPEC with a prophylactic intent.

Meta-analysis of proportion

Meta-analysis of proportions of patients undergoing CRS + HIPEC pointed out 86.9% 1-year survival rate (SR) (95% CI:74.2–93.1; I^2: 86.9%). Compared to those undergoing prophylactic CRS + HIPEC, patients treated with curative intent showed a remarkably lower survival (41.9%; 95% CI: 28.2–56.9). At 2-year follow-up 70.5% SR (95% CI: 56.1–81.7; I^2: 88.5%) was observed. Patients undergoing treatment for PM showed a 3-fold lower SR (23.3%; 95% CI: 13–38.1). The 3-year cumulative SR was 63.7% (95% CI: 51.1–74.7; I^2: 86.1%), with patients suffering from PM showing an even lower survival (16.5%; 95% CI: 8.1–30.8). At 5-year follow-up the SR dropped to 55.7% (95% CI: 42.8–67.8; I^2: 80.6%). Only 5.9% (95% CI: 1.5–20.7) of patients undergoing treatment for PM were alive at this time point.

Sensitivity analysis. After GOSH plots assessment, sensitivity analysis was conducted. At 1-year follow-up, after excluding the studies by Takahashi, Yang, and Rudloff [27,31,33], the cumulative SR was 91.6% (95% CI: 88.6–93.8; I^2: 0%). At 2-year follow-up, after excluding the studies by Takahashi and Yung, the cumulative SR was 79.2% (95% CI: 71.5–85.2). Patients undergoing treatment for PM had a significantly reduced survival (22.2%; 95% CI: 5.6–57.9). Moderate heterogeneity was detected (I^2: 64.8%). The 3-year SR, after excluding the studies by Takahashi, Fujimoto, Yang, Rudloff, and Beharry [27,28,31,33,34], was 68.3% (95% CI: 63.6–72.6; I^2: 0%). At 5-year follow-up, after removal of the studies by Ikeguchi and Yang [26,31], the SR was 64% (95% CI: 42.8–67.8; I^2: 80.6%). Results are shown in Fig. 3.

Secondary endpoint

Meta-analysis of binary outcomes: Disease-free survival

Disease free survival analysis showed a significant benefit in favor of patients undergoing CRS + HIPEC at 1- (RR = 0.33; 95% CI: 0.13–0.82; p = 0.017; I^2: 0%), 2- (RR = 0.43; 95% CI: 0.28–0.66; p = 0.0001; I^2: 0%) and 3- (RR = 0.44; 95% CI: 0.24–0.78; p = 0.005; I^2: 54.6%) year follow-up. Only 3 studies [28,32,34], for a total of 413 patients, reported data about DFS, all of them including patients undergoing CRS + HIPEC for prophylaxis of PM. Forest plots are reported in supplementary materials. Due to the limited number of studies included, sensitivity analysis was not performed.

Meta-analysis of binary outcomes: completeness of cytoreduction

The median PCI score in the studies published by Yang and Rudloff was 15 (range 2–36) and 5 (range 0–21) respectively. The comparison between complete (CC0-1) and incomplete (CC > 1) cytoreduction in patients treated with a curative intent highlighted a significant survival benefit for the former group at 1- (RR = 0.69; 95% CI: 0.5–0.96; p = 0.029; I^2: 0%), 2- (RR = 0.8; 95% CI: 0.67–0.96; p = 0.019; I^2: 0%), and 3- (RR = 0.83; 95% CI: 0.69–0.99; p = 0.038; I^2: 0%) year follow-up. Forest plots are reported in supplementary materials.

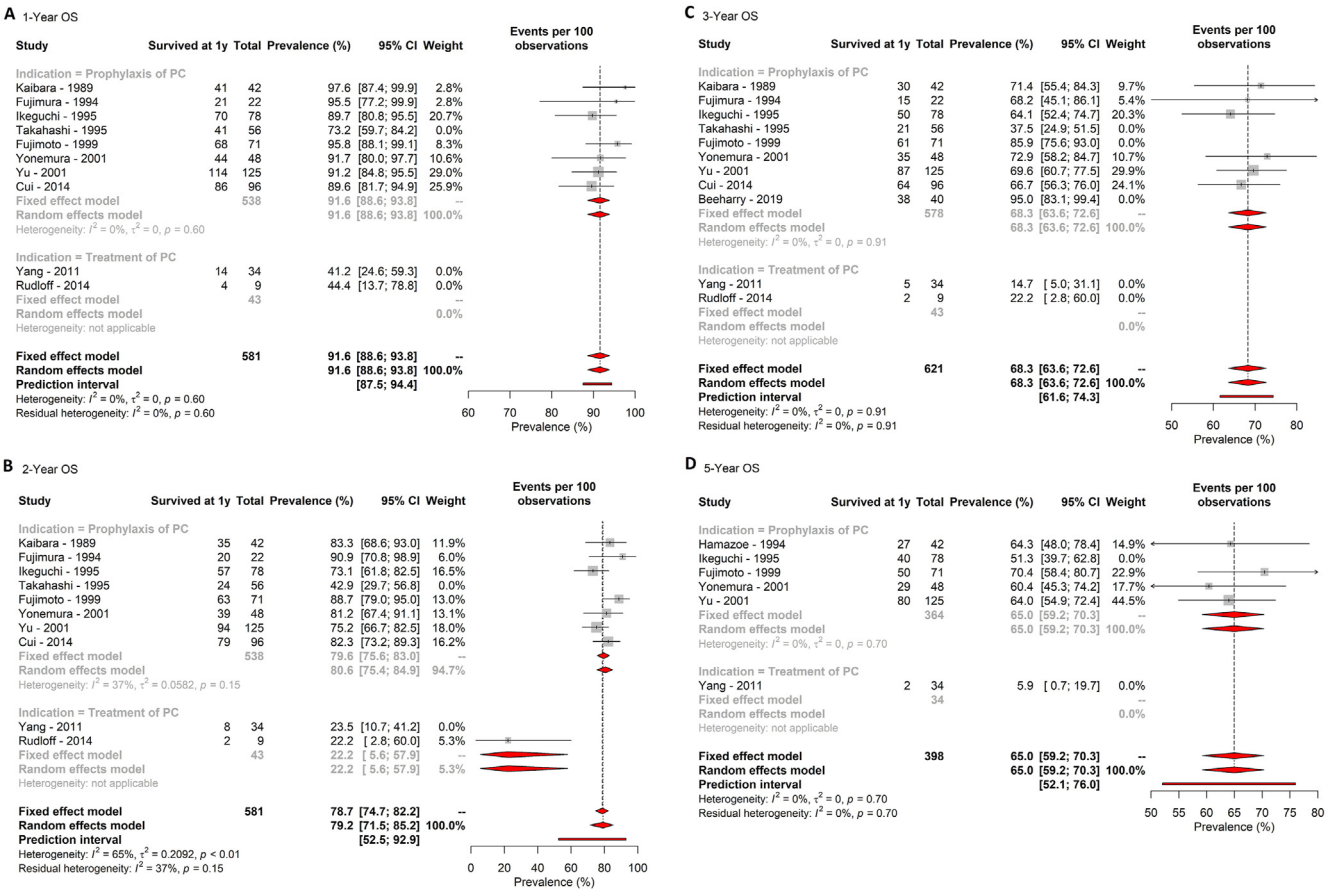

Fig. 3. Meta-analysis of proportion - patients undergoing CRS + HIPEC. A) 1y-survival, B) 2y-survival, C) 3y-survival, D) 5y-survival.

Meta-analysis of medians

The median of median survival times for patients treated with a prophylactic intent was 34 months (95% CI: 11–77) for CRS + HIPEC group and 22.5 months (95% CI: 6.5–66) for control group. For those treated with a curative intent it was 11 months (95% CI: 11–11.3) for CRS + HIPEC patients and 6.5 months (95% CI: 4.3–6.5) for control patients.

Meta-analysis of binary outcomes: post-treatment mortality and morbidity

Eleven studies reported data about post-treatment mortality. A 2-fold increased risk was noticed for patients undergoing CRS + HIPEC; nevertheless, the difference between the two groups was not significant (RR = 2.25; 95% CI: 0.82–6.19; I^2: 0%). Only eight studies recorded information about post-treatment morbidity. After identifying outliers [28], the comparison between the two groups failed to show any significant difference in the incidence of post-treatment complications (RR = 1.08; 95% CI: 0.85–1.41; I^2: 13.5%) (Fig. 4). A table summarizing the details of post-treatment complications are shown in supplementary materials.

Meta-analysis of prognostic factors

Eleven out of 12 studies reported SR at 3 years. Meta-regression analysis showed that performing CRS + HIPEC for the treatment rather than prophylaxis of PM is the only variable significantly associated with a reduced 3y SR (RR: 1.28; 95% CI: 1.03–1.59; p = 0.024).

Higher HIPEC temperatures, and not administering adjuvant chemotherapy were moderators associated with a trend towards a worse survival outcome at 3 years. Conversely, the "close" technique showed a trend towards better prognosis. Focusing on HIPEC regimens, regression analysis failed to identify any CT scheme significantly related to improved prognosis, although the combination of Mitomycin-C and 5-Fluorouracil was the one related to the greatest reduction in the risk of death. Detailed results are displayed in Table 2. Bubble plots of meta-regression analysis are available in supplementary materials.

Risk of bias assessment

Fig. 4 summarizes the risk of bias evaluation according to the latest version of the Cochrane Collaboration handbook [16]. No high risk of bias was detected. Most of the bias was due to deviations from intended interventions, randomization process, and selection of reported results (Fig. 5).

Assessment of publication bias

Egger's test of 1-, 2-, 3- and 5-year survival meta-analyses pointed out significant asymmetry (p = 0.017, 0.0036, 0.008, and 0.0045 respectively). Duwal & Tweedie trim-and-fill method was applied and relative funnel plots of publication bias generated (available in supplementary materials).

Discussion

The present study was designed to evaluate the efficacy of CRS + HIPEC in both patients suffering from localized or locally

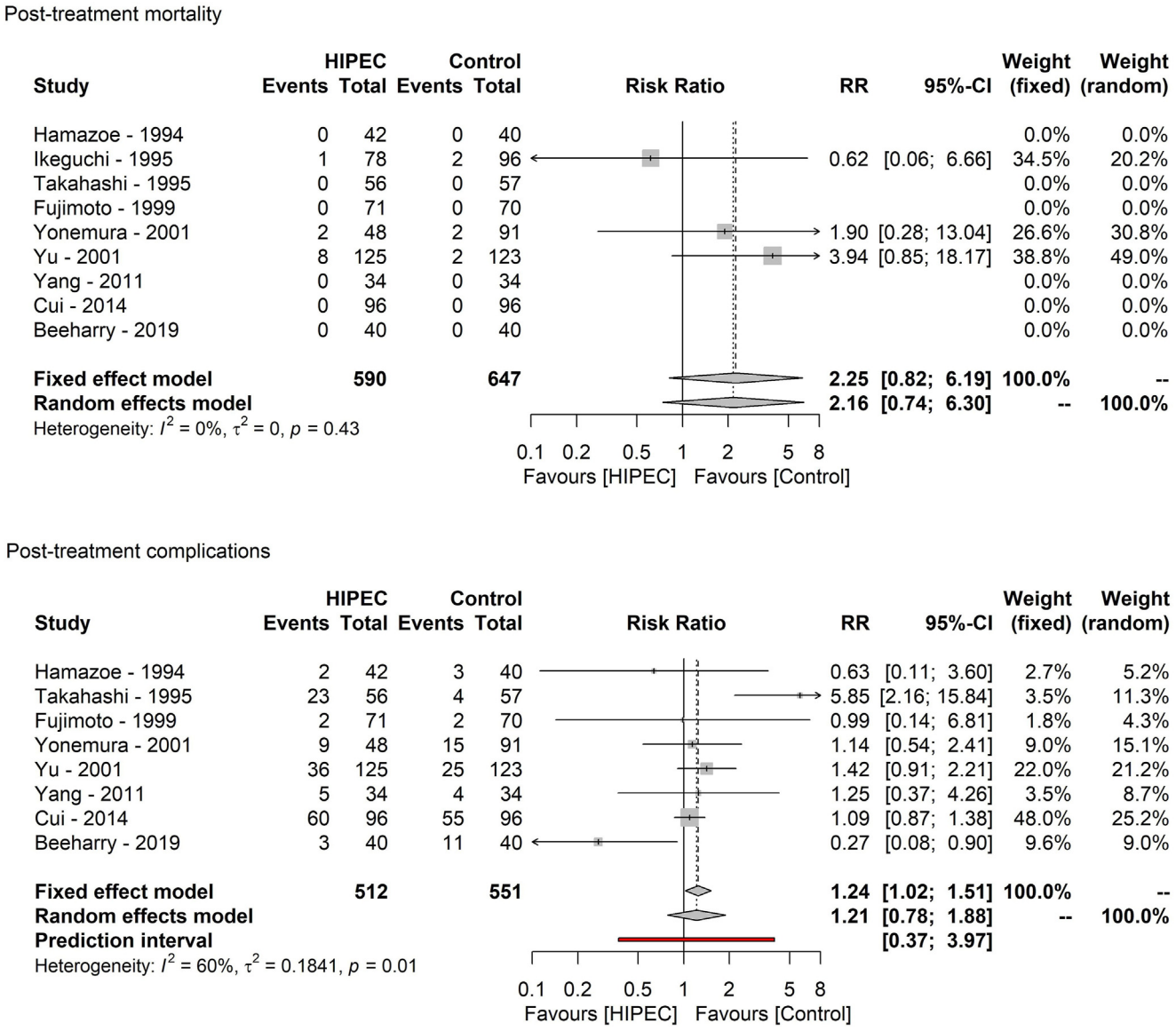

Fig. 4. Post-treatment mortality and complications.

Table 2
Results of meta-regression analysis - predictors of 3y survival.

Meta-regression analysis							
Variable	Number of studies	RR	95% C.I.		p		R^2 (%)
			LB	UB		I^2 (%)	
Year of publication	11	1.01	0.99	1.02	0.38	37.6	0
HIPEC technique (close)	11	0.8	0.49	1.31	0.38	29.3	28.1
Temperature	10	1.04	0.97	1.11	0.26	33.4	32.7
Indication for CRS + HIPEC (treatment of PC)	11	1.28	1.03	1.59	0.024*	8.89	81.1
HIPEC regimen	11	0.65	0.085	5	0.68	51.8	0
Cisplatin + 5FU		0.71	0.097	5.14	0.73		
Mitomycin C		0.54	0.07	4.13	0.55		
Mitomycin C + 5FU		0.69	0.091	4.88	0.69		
Mitomycin C + Cisplatin		0.79	0.1	6.03	0.82		
Oxaliplatin							
HIPEC length	10	1	0.99	1.003	0.84	32.7	0
Adjuvant CT (not administered)	11	1.01	0.68	1.89	0.93	60.2	0

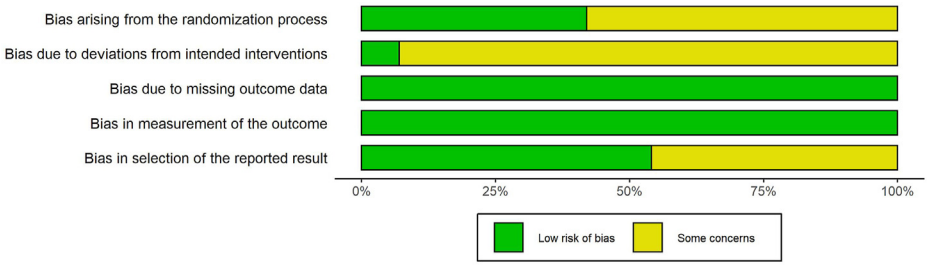

Fig. 5. Risk of bias assessment through barplot.

advanced gastric cancer without evidence of macroscopic PM (prophylaxis) and patients with gross evidence of PM (treatment). Our analysis extensively evaluated the survival outcome of these patients both in terms of overall and disease-free survival. Moreover, we explored the morbidity/mortality rates associated with this type of treatment and investigated the role of CRS + HIPEC characteristics.

Our results highlighted a beneficial role of HIPEC for patients suffering from gastric cancer with or without macroscopic PM. Nevertheless, some aspects need to be examined more in detail.

Although it may appear an obvious consideration, our findings reinforce the concept that patients with PM have a poorer prognosis compared with those who have not, regardless of the treatment they are exposed to. Patients undergoing gastric resection + HIPEC with a prophylactic intent showed a more favorable prognosis. On the other hand, patients undergoing CRS + HIPEC for PM treatment had an exponentially lower survival trend for increasing follow-up times. This should not be considered as a failure of CRS + HIPEC when adopted with a curative intent, but as a wider effect size of this procedure in a prophylactic setting.

This can be explained considering the greater load of the disease in the latter group. Moreover, in patients without gross PM, 13% had T2 neoplasms, and about 1/3 showed N0–N1 nodal involvement. The inclusion of patients with a more limited disease can have contributed to an improved survival outcome. Some of the most beneficial effects of HIPEC may occur in the presence of a reduced burden of nodal involvement. Ikeguchi et al. observed a greater benefit of HIPEC when applied in patients with less than 10 lymph nodes involved [26]. On the other hand, patients who already present with PM have a higher risk of developing more aggressive and CT resistant cellular clones.

Second, considering the subset of patients treated with curative intent, our analysis demonstrated how the completeness of cytoreduction represents a crucial step to achieve a survival benefit. Indeed, patients with a low CC score (0–1) showed a significant survival advantage at all time points when compared to their counterparts (CC > 1). Yet, granted the critical role of a total or near total cytoreduction, the adjunct of HIPEC to CRS represents an independent predictor of better prognosis, with a 2.6-fold increase in survival outcome [36]. Nevertheless, the tumor burden should always be considered when planning cytoreductive surgery in patients with PM: even though our results can not overtly support this consideration, it is well known that in peritoneal oncology lower PCI values are related to better survival outcomes due to the higher probability to achieve complete cytoreduction.

Though, this type of surgery is overloaded by non-negligible drawbacks. In our meta-analysis, the comparison between gastrectomy/CRS + HIPEC and control groups highlighted an increased risk for the former regarding postoperative morbidity and mortality, although not significant. This is a still more conspicuous result if one considers that all the studies included were conducted in tertiary referral centers. Besides other types of advanced surgeries, this underlines the well-consolidated need to perform such procedures in high-volume hubs.

Currently, the Italian Association of Medical Oncology (AIOM) guidelines for primitive and metastatic peritoneal tumors [37] strongly advise against CRS + HIPEC in patients with PM, mainly due to the lack of large RCTs in the western world. On the other hand, the Peritoneal Surface Oncology Group International (PSOGI) states that patients suffering from gastric cancer PM may profit from CRS + HIPEC, but additional evidence to support this strategy is needed [38].

At this regard it is worth noticing that, even though our analysis supports a potentially beneficial role of CRS + HIPEC with a curative intent when compared with other non-curative treatments, it should be borne in mind that the MST of stage IV gastric cancer patients is about 11 months (range 9–14 months). In our analysis the MST of CRS + HIPEC patients was exactly the same, but this procedure was burdened a more than doubled risk of significant morbidity.

Further results from various international randomized multicenter phase III clinical trials are awaited to define better this technique's efficacy and safety, both with a prophylactic and curative intent.

Regarding the former, HIPEC – 01 (NCT0235676) represents the largest ongoing clinical trial. This Chinese protocol aims to recruit 584 patients from May 2015 to January 2022. T3–T4 gastric adenocarcinoma patients, without evidence of distance metastasis, are randomly assigned to the HIPEC group (radical gastrectomy with D2 lymphadenectomy, followed by prophylactic postoperative HIPEC and adjuvant chemotherapy) or control group (same surgical procedure followed by adjuvant chemotherapy only). The primary outcome is the overall survival at 5-year follow-up; secondary outcomes are 5-year progression-free survival, liver metastatic rate, local recurrence rate, and adverse events rate.

The GASTRICHIP trial (NCT01882933) explores the HIPEC prophylactic efficacy testing the applicability of the results obtained by Asian research in western countries [39]. This French protocol started enrolling participants in June 2013, and the estimated study completion date is May 2026, with an estimated sample size of 306 patients. Inclusion criteria encompass gastric cancer diagnosis arising to the serosa with or without lymph node involvement and positive cytology at peritoneal washing. Curative gastrectomy is planned for all patients, but in the experimental arm of the study, intraoperative HIPEC is performed. The primary endpoint is the overall survival at 5-year-follow up and the secondary endpoints look at the recurrence-free survival, morbidity and the postoperative quality-of-life.

Regarding the therapeutic role of HIPEC in gastric cancer patients with gross PM, it is worth to mention an important ongoing western trial whose results are eagerly awaited.

The PERISCOPE II (NCT03348150) is a Dutch RCT aiming to explore HIPEC's therapeutical efficacy by the end of October 2022 [40]. More than 100 patients are currently enrolled and randomized

into CRS + HIPEC and palliative systemic chemotherapy arms. Eligible inclusion criteria are a primary T3-T4 gastric tumor, including lymph nodes, limited peritoneal dissemination, and/or positive peritoneal cytology. This protocol focuses on 5-year OS as the primary endpoint; secondary endpoints are represented by progression-free survival, treatment-related toxicity, and cost-effectiveness analysis. PERISCOPE II study design differentiates from the other RCTs cited above because it will evaluate the impact of surgery combined with HIPEC on survival rather than exploring the sole role of HIPEC.

Strengths and limitations

Our results rely on robust statistics. Identifying studies responsible for high heterogeneity through GOSH plot analysis, allowed us to select only those truly contributing to the effect estimate. Compared to previous similar meta-analyses [41,42], our research is based on a strict methodology ruling out overlapping series and considering RCTs only. Besides, to the best of our knowledge, this is the first meta-analysis about this topic that conducted a rigorous and advanced sensitivity analysis, contributing to the high-quality results obtained.

However, the present study has several limitations. First, the small number of studies included, especially when considering the ones exploring the role of CRS + HIPEC for the treatment of PM arising from gastric cancer. Nevertheless, to select high-quality evidence, we considered only studies with a randomized design.

Another major drawback is represented by the unblinding: this represents one of the most common limitations that burden surgical RCTs; nonetheless, it is hard to suppose that it could influence the survival outcome.

A further question that remains unanswered is which role has neoadjuvant chemotherapy on survival. In this regard, following the lead of Yonemura et al. who originally proposed the strategy more than a decade ago [43], the DRAGON II (ChiCTR1900024552) [44], a multicenter phase III RCT, aims to investigate the role of neoadjuvant laparoscopic HIPEC + chemotherapy, in combination with D2 curative gastrectomy and intraoperative prophylactic HIPEC. Trial's enrollment started prospectively in July 2019 and 326 patients with T4 gastric cancer, after laparoscopic confirmation of serosal involvement and absence of peritoneal carcinomatosis, will be randomly allocated in a 1:1 study protocol with two arms: experimental group, undergoing laparoscopic preoperative neoadjuvant HIPEC + neoadjuvant chemotherapy + R0 curative surgery + intraoperative prophylactic HIPEC + adjuvant chemotherapy, versus control group, undergoing only R0 gastrectomy and 8 cycles of adjuvant chemotherapy. The primary outcome is progression-free survival and secondary outcomes look at overall survival, peritoneal metastasis rate, radical resection rate, and postoperative complications. A significant and innovative contribution is expected from this study because it is the first to investigate the role of neoadjuvant intraperitoneal and systemic chemotherapy.

Conclusion

In light of the considerations above, a strict selection remains a major goal in the treatment of advanced gastric cancer patients. In our opinion, the optimal surgical candidate should have an excellent performance status, a limited nodal spread of the disease, and, if present, limited peritoneal dissemination without other distant metastases. The presence of extraperitoneal disease is a contraindication of such a demanding surgical approach, already burdened by far from negligible postoperative complications and mortality. The role of neoadjuvant chemotherapy is nowadays well established for locally advanced gastric cancer patients, whereas its effect on PM patients still represents a point to be addressed. The results of the aforementioned ongoing trials are eagerly awaited to better describe the role of CRS + HIPEC, especially with curative intent, and to identify the most favorable prognostic features for surgical candidates.

Furthermore, they could help to understand the reproducibility of Asian studies more thoroughly in the western world. Future perspectives should bear into consideration the biological behavior of the tumor. In this regard, liquid biopsies could help identify patients with favorable mutational arrangements that would profit the most from such an aggressive multimodal treatment.

CRediT authorship contribution statement

Stefano Granieri: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Supervision, Visualization, Project administration. **Alessandro Bonomi:** Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Simone Frassini:** Investigation, Data curation, Writing – original draft, Visualization. **Andrea Piero Chierici:** Investigation, Data curation, Writing – original draft, Visualization. **Federica Bruno:** Investigation, Data curation, Writing – original draft, Visualization. **Sissi Paleino:** Investigation, Data curation, Writing – original draft, Visualization. **Shigeki Kusamura:** Writing – original draft, Writing – review & editing. **Alessandro Germini:** Supervision. **Antonio Facciorusso:** Supervision. **Marcello Deraco:** Supervision. **Christian Cotsoglou:** Supervision.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Acknowledgments

None

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2021.05.016.

References

[1] Globocan Observatory W. Cancer today - world. Int Agency Res Cancer 2019;876:2018. 9.
[2] Sugarbaker PH, Yonemura Y. Clinical pathway for the management of resectable gastric cancer with peritoneal seeding: best palliation with a ray of hope for cure. Oncology 2000. https://doi.org/10.1159/000012086.
[3] Bozzetti F, Yu W, Baratti D, Kusamura S, Deraco M. Locoregional treatment of peritoneal carcinomatosis from gastric cancer. J Surg Oncol 2008. https://doi.org/10.1002/jso.21052.
[4] Montori G, Coccolini F, Ceresoli M, Catena F, Colaianni N, Poletti E, et al. The treatment of peritoneal carcinomatosis in advanced gastric cancer: state of the art. Int J Surg Oncol 2014. https://doi.org/10.1155/2014/912418.
[5] Al-Batran S-E, Hartmann JT, Probst S, Schmalenberg H, Hollerbach S, Hofheinz R, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either Oxaliplatin or cisplatin: a study of the arbeitsgemeinschaft internistische onkologie. J Clin Oncol 2008;26:1435–42. https://doi.org/10.1200/JCO.2007.13.9378.
[6] Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010. https://doi.org/10.1016/S0140-6736(10)61121-X.
[7] Starling N, Rao S, Cunningham D, Iveson T, Nicolson M, Coxon F, et al. Thromboembolism in patients with advanced gastroesophageal cancer treated with anthracycline, platinum, and fluoropyrimidine combination chemotherapy: a report from the UK National Cancer Research Institute Upper Gastrointestinal Clinical Studies Group. J Clin Oncol 2009. https://doi.org/

10.1200/JCO.2008.19.4274.
[8] Glehen O, Schreiber V, Cotte E, Sayag-Beaujard AC, Osinsky D, Freyer G, et al. Cytoreductive surgery and intraperitoneal chemohyperthermia for peritoneal carcinomatosis arising from gastric cancer. Arch Surg 2004. https://doi.org/10.1001/archsurg.139.1.20.
[9] Glehen O, Gilly FN, Arvieux C, Cotte E, Boutitie F, Mansvelt B, et al. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. Ann Surg Oncol 2010. https://doi.org/10.1245/s10434-010-1039-7.
[10] Yonemura Y, Kawamura T, Bandou E, Takahashi S, Sawa T, Matsuki N. Treatment of peritoneal dissemination from gastric cancer by peritonectomy and chemohyperthermic peritoneal perfusion. Br J Surg 2005. https://doi.org/10.1002/bjs.4695.
[11] Ajani J, D'Amico T, Bentrem D, Chao J, Corvera C, Das P, et al. NCCN clinical practice guidelines in oncology gastric cancer. 2020.
[12] Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018. In: Gastric cancer. fifth ed. 2020. https://doi.org/10.1007/s10120-020-01042-y.
[13] Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v38–49. https://doi.org/10.1093/annonc/mdw350.
[14] Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009. https://doi.org/10.1371/journal.pmed.1000097.
[15] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. Amstar 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017. https://doi.org/10.1136/bmj.j4008.
[16] Chapter 8: assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJWV, editors. Cochrane handbook for systematic reviews of interventions version. 6.1; 2020 (updated September 2020).
[17] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Br Med J 2003. https://doi.org/10.1136/bmj.327.7414.557.
[18] Team RCR. A language and environment for statistical computing. 2019. Vienna, Austria, http://www.R-project.org/.
[19] Schwarzer G, Carpenter JR, Rücker G. An introduction to meta-analysis in R. 2015. https://doi.org/10.1007/978-3-319-21416-0_1.
[20] Viechtbauer W. Conducting meta-analyses in R with the metafor. J Stat Software 2010;36(3). https://www.jstatsoft.org/v36/i03.
[21] McGrath S, Sohn H, Steele R, Benedetti A. Meta-analysis of the difference of medians. Biom J 2020. https://doi.org/10.1002/bimj.201900036.
[22] Harrer M, Cuijpers P, Furukawa T, Ebert DD. Doing meta-analysis in R: a hands-on guide. Prot Lab 2019. https://doi.org/10.5281/zenodo.2551803.
[23] Kaibara N, Hamazoe R, Iitsuka Y, Maeta M, Koga S. Hyperthermic peritoneal perfusion combined with anticancer chemotherapy as prophylactic treatment of peritoneal recurrence of gastric cancer. Hepatogastroenterology 1989 Apr;36(2):75–8. PMID: 2499527.
[24] Fujimura T, Yonemura Y, Muraoka K, Takamura H, Hirono Y, Sahara H, et al. Continuous hyperthermic peritoneal perfusion for the prevention of peritoneal recurrence of gastric cancer: randomized controlled study. World J Surg 1994. https://doi.org/10.1007/BF00348209.
[25] Hamazoe R, Maeta M, Kaibara N. Intraperitoneal thermochemotherapy for prevention of peritoneal recurrence of gastric cancer. Final results of a randomized controlled study. Cancer 1994. https://doi.org/10.1002/1097-0142(19940415)73:8<2048::AID-CNCR2820730806>3.0.CO;2-Q.
[26] Ikeguchi M, Kondou A, Oka A, Tsujitani S, Maeta M, Kaibara N. Effects of continuous hyperthermic peritoneal perfusion on prognosis of gastric cancer with serosal invasion. Eur J Surg. 1995 Aug;161(8):581–6. PMID: 8519874.
[27] Takahashi T, Hagiwara A, Shimotsuma M, Sawai K, Yamaguchi T. Prophylaxis and treatment of peritoneal carcinomatosis: intraperitoneal chemotherapy with mitomycin C bound to activated carbon particles. World J Surg 1995. https://doi.org/10.1007/BF00294724.
[28] Fujimoto S, Takahashi M, Mutou T, Kobayashi K, Toyosawa T. Successful intraperitoneal hyperthermic chemoperfusion for the prevention of postoperative peritoneal recurrence in patients with advanced gastric carcinoma. Cancer 1999. https://doi.org/10.1002/(SICI)1097-0142(19990201)85:3<529::AID-CNCR3>3.0.CO;2-9.
[29] Yonemura Y, De Aretxabala X, Fujimura T, Fushida S, Katayama K, Bandou E, et al. Intraoperative chemohyperthermic peritoneal perfusion as an adjuvant to gastric cancer: Final results of a randomized controlled study. Hepatogastroenterology 2001 Nov-Dec;48(2):177–1782. PMID: 11813623.
[30] Yu W, Whang I, Chung HY, Averbach A, Sugarbaker PH. Indications for early postoperative intraperitoneal chemotherapy of advanced gastric cancer: results of a prospective randomized trial. World J Surg 2001. https://doi.org/10.1007/s00268-001-0067-7.
[31] Yang XJ, Huang CQ, Suo T, Mei LJ, Yang GL, Cheng FL, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: Final results of a phase III randomized clinical trial. Ann Surg Oncol 2011. https://doi.org/10.1245/s10434-011-1631-5.
[32] Cui H-B, Ge H-E, Bai X-Y, Zhang W, Zhang Y-Y, Wang J, et al. Effect of neoadjuvant chemotherapy combined with hyperthermic intraperitoneal perfusion chemotherapy on advanced gastric cancer. Exp Ther Med 2014:1083. https://doi.org/10.3892/etm.2014.1599. 8.
[33] Rudloff U, Langan RC, Mullinax JE, Beane JD, Steinberg SM, Beresnev T, et al. Impact of maximal cytoreductive surgery plus regional heated intraperitoneal chemotherapy (HIPEC) on outcome of patients with peritoneal carcinomatosis of gastric origin: results of the GYMSSA trial. J Surg Oncol 2014. https://doi.org/10.1002/jso.23633.
[34] Beeharry MK, Zhu Z, Liu W, Yao X, Yan M, Zhu Z. Prophylactic HIPEC with radical D2 gastrectomy improves survival and peritoneal recurrence rates for locally advanced gastric cancer : personal experience from a randomized case control study. BMC Canc 2019:1–9. https://doi.org/10.1186/s12885-019-6125-z.
[35] Takahashi M, Mutou T, Kobayashi K, Toyosawa T. Prophylaxis and treatment of peritoneal carcinomatosis: intraperitoneal chemotherapy with mitomycin C bound to activated carbon particles. World J Surg 1999:529–34.
[36] Yang X, Huang C, Suo T, Mei L, Yang G. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric Cancer : Final results of a phase III randomized clinical trial. 2011. https://doi.org/10.1245/s10434-011-1631-5. 1575–81.
[37] Associazione Italiana di Oncologia Medica. Linee guida TUMORI PERITONEALI PRIMITIVI E SECONDARI. 2019.
[38] PSOGI. International. Recommendations for the management of peritoneal metastases. n.d. http://www.psogi.com/psogi/international-recommendations-for-the-management-of-peritoneal-metastases/.
[39] Glehen O, Passot G, Villeneuve L, Vaudoyer D, Bin-Dorel S, Boschetti G, et al. GASTRICHIP: D2 resection and hyperthermic intraperitoneal chemotherapy in locally advanced gastric carcinoma: a randomized and multicenter phase III study. BMC Canc 2014. https://doi.org/10.1186/1471-2407-14-183.
[40] Koemans WJ, Van Der Kaaij RT, Boot H, Buffart T, Veenhof AAFA, Hartemink KJ, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy versus palliative systemic chemotherapy in stomach cancer patients with peritoneal dissemination, the study protocol of a multicentre randomised controlled trial (PERISCOPE II). BMC Canc 2019. https://doi.org/10.1186/s12885-019-5640-2.
[41] Desiderio J, Chao J, Melstrom L, Warner S, Tozzi F, Fong Y, et al. The 30-year experience—a meta-analysis of randomised and high-quality non-randomised studies of hyperthermic intraperitoneal chemotherapy in the treatment of gastric cancer. Eur J Canc 2017;79:1–14. https://doi.org/10.1016/j.ejca.2017.03.030.
[42] Coccolini F, Cotte E, Glehen O, Lotti M, Poiasina E, Catena F, et al. Intraperitoneal chemotherapy in advanced gastric cancer. Meta-analysis of randomized trials. Eur J Surg Oncol 2014;40:12–26. https://doi.org/10.1016/j.ejso.2013.10.019.
[43] Yonemura Y, Bandou E, Sawa T, Yoshimitsu Y, Endou Y, Sasaki T, et al. Neoadjuvant treatment of gastric cancer with peritoneal dissemination. Eur J Surg Oncol 2006;32:661–5. https://doi.org/10.1016/j.ejso.2006.03.007.
[44] Beeharry MK, Ni ZT, Yang ZY, Zheng YN, Feng RH, Liu WT, et al. Study protocol of a multicenter phase III randomized controlled trial investigating the efficiency of the combination of neoadjuvant chemotherapy (NAC) and neoadjuvant laparoscopic intraperitoneal hyperthermic chemotherapy (NLHIPEC) followed by R0 gastrec. BMC Canc 2020. https://doi.org/10.1186/s12885-020-6701-2.