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The Thirty-Year Experience - A Meta-analysis of Randomized and High Quality Non-Randomized Studies of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in the Treatment of Gastric Cancer

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Abstract

Importance—Hyperthermic intraperitoneal chemotherapy (HIPEC) has been employed within various multimodality strategies for the prevention and treatment of gastric cancer peritoneal carcinomatosis.

Objective—To systematically evaluate the role of HIPEC in gastric cancer and clarify its effectiveness at different stages of peritoneal disease progression.

Data Sources—Medline and Embase databases between January 1, 1985, and June 1, 2016.

Study Selection—Randomized control trials (RTC) and high-quality nonrandomized control trials (NRCTs) selected on a validated tool (Methodological Index for Nonrandomized Studies) comparing HIPEC and standard oncological management for the treatment of advanced stage gastric cancer with and without peritoneal carcinomatosis were considered.

Data Extraction and Synthesis—A random-effects network meta-analysis.

Main Outcomes and Measures—The primary outcomes were overall survival and disease recurrence. Secondary outcomes were overall complications, type of complications, and sites of recurrence.

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Specific authors' contributions:

Jacopo Desiderio, Yanghee Woo were involved in conception of the study.

Jacopo Desiderio, Yanghee Woo were involved in designing the study.

Jacopo Desiderio, Yanghee Woo were involved in analysing the literature and references searching.

Jacopo Desiderio, Yanghee Woo were involved in drafting the rationale and methods.

Joseph Chao, Laleh Melstrom, Susanne Warner, Federico Tozzi, Yuman Fong and Amilcare Parisi, were involved in critical revision and drafting of the final manuscript.

Results—A total of 11 RCTs and 21 NRCTs (2520 patients) were included. For patients without the presence of peritoneal carcinomatosis (PC), the overall survival rates between the HIPEC and control groups at 3 or 5 years resulted in favor of the HIPEC group (RR=0.82, P=0.01). No difference in the 3-year overall survival (RR=0.99, P=0.85) in but a prolonged median survival of 4 months in favor of the HIPEC group (WMD=4.04, P<0.001) was seen in patients with PC. HIPEC was associated with significantly higher risk of complications for both patients with PC (RR=2.15, P<0.01) and without (RR=2.17, P<0.01). This increased risk in the HIPEC group was related to systemic drugs toxicity. Anastomotic leakage rates were found to be similar between groups.

Conclusions and Relevance—Our study demonstrates a survival advantage of the use of HIPEC as a prophylactic strategy and suggests that patients whose disease burden is limited to positive cytology and limited nodal involvement may benefit the most from HIPEC. For patients with extensive carcinomatosis, the completeness of cytoreductive surgery is a critical prognostic factor for survival. Future RCTs should better define patient selection criteria.

Introduction

Gastric cancer is the third leading cause of cancer death worldwide and is uniformly fatal in the advanced stages.(1) Like other primary gastrointestinal cancers, the peritoneum becomes a common site of treatment failure for gastric cancer and at time of death, 60% of gastric cancer patients will have peritoneal dissemination.(2, 3) Whether found at initial diagnosis, progression, or recurrence, peritoneal disease has a dismal prognosis. Moreover, it leads to significant quality of life impairment from complications such as tense ascites, malignant bowel obstruction, malnutrition, and cachexia.

Chemotherapy and immunotherapy alone have limited efficacy against peritoneal carcinomatosis. Thus, multimodality strategies including various combinations of systemic chemotherapy and hyperthermic intraperitoneal chemotherapy (HIPEC) with or without cytoreductive surgery have been studied to improve survival and prevent morbid complications. Cytoreductive surgery and HIPEC have demonstrated improved survival in ovarian and colorectal cancers with benefit attributed to the chemosensitivity of these malignancies.(4, 5) For gastric cancer, however, the use of HIPEC remains controversial.

Initially, cytoreductive surgery and HIPEC for gastric cancer were performed in Japan as experimental treatments based on the rationale for the prevention of the intraperitoneal spread of serosa positive disease at greatest risk for peritoneal recurrence and poor prognosis.(6) Later the focus shifted to investigating the possible role of cytoreductive surgery and HIPEC in the treatment of gross peritoneal carcinomatosis with the goal of improved survival.(3) Unfortunately, many questions remain unanswered: What is the most effective use of HIPEC in gastric cancer patients? Do the currently available studies provide a clear strategy in employing HIPEC to improve the outcome of gastric cancer patients? As novel approaches for patient-specific treatment are being developed to improve the outcome of gastric cancer patients with advanced stage diseases, the impact these interventions require closer and more sophisticated evaluation.

The purpose of this meta-analysis is to analyze the existing body of clinical trials which evaluated the use of HIPEC for gastric cancer both in the case of preventing peritoneal dissemination and for the treatment of peritoneal carcinomatosis. For comprehensive review, this meta-analysis considered both randomized controlled trials (RCTs) and relevant high quality comparative non-randomized controlled trials (NRCTs).

Methods

Types of Studies

The present meta-analysis evaluated published randomized controlled trials (RCTs) and nonrandomized controlled trials (NRCTs) comparing surgery associated with hyperthermic intraperitoneal chemotherapy (HIPEC) and standard surgical management for the treatment of advanced stage gastric cancer with and without peritoneal carcinomatosis. We considered the extent of peritoneal involvement and identified two investigational fields: 1) HIPEC in patients at high risk of developing peritoneal recurrence based on preoperative assessments treated with “prophylactic intent”; and 2) HIPEC in the treatment of patients with evidence of gastric cancer peritoneal carcinomatosis (GCPC). This work excluded articles if the study population included primary malignancies other than gastric cancer, unless the study presented those data separately. In the case of identifying two studies from the same institution, the evaluation included only the most recent or the most informative. Exceptions were made if the reports came from different time periods or if the data of overlapping patients could be subtracted.

Types of Interventions

Studies clearly defining the experiential use of HIPEC following standard gastrectomy or cytoreduction surgery (CRS) were included and the inclusion required a complete description of the technique used in HIPEC delivery. We analyzed information on the type and extension of the surgery performed, the drugs used, and the perfusion technique adopted for each article suitable for inclusion. We excluded from this analysis studies that reported generic terminology such as “intraperitoneal chemotherapy” without a specific description or other kind of treatment, such as “normothermic intraperitoneal chemotherapy (NIC)” or “early postoperative intraperitoneal chemotherapy (EPIC).” As control groups, we considered procedures described as “standard gastrectomies” for advanced gastric cancer without carcinomatosis and “cytoreduction surgery” or “systemic chemotherapy” for GCPC.

Types of Outcome Measures

The outcomes we measured include the following:

1. Primary: overall survival rate, median survival, survival rate by type of drug administered, overall survival rate by extent of carcinomatosis, overall recurrence rate.
2. Secondary: overall complications rate, rate of complications by type, recurrence rate by site.

Search

We performed a Medline and Embase database search using the following MeSH search terms: “hyperthermic intraperitoneal chemotherapy,” “stomach,” “gastric cancer,” “carcinosis,” “randomized trial,” “meta-analysis,” “prospective study,” and “comparative study.” We also used these terms, and their combinations, as key words, as we did with “gastric cancer,” “hyperthermic intraperitoneal chemotherapy,” and “carcinomatosis.” We used special database functions, such as “related articles” and “explosion,” to maximize the search. We searched references from relevant articles and reviews manually. We set the search to start from January 1, 1985, because to our knowledge, the first HIPEC for gastric cancer was reported in 1988(6). The last search was performed on June 1, 2016.

Data Collection Process

Two reviewers extracted relevant data independently from all studies. The data included study features, population characteristics, data needed for quality assessment, and the different outcome measures. Population characteristics include the number and type of procedures received, age, gender, and tumor pathologic variables.

Quality Assessment

We evaluated RCTs by individual components based on the Cochrane risk of bias tool.(7) We included all RCTs judged to be of adequate design at the full text assessment. The appropriate method to evaluate quality in NRCTs is controversial. For the purposes of this review, we decided to use the modified Methodological Index for Nonrandomized Studies (MINORS).(8, 9) Among the evaluated items, we adapted the “sample of the experimental group” to assess the proficiency of the surgical teams and the power given by the actual number of HIPEC cases. We assigned scoring for this item as follows: 0 points for fewer than 15 cases, 1 point for more than 15 but fewer than 30 cases, and 2 points for 30 or more HIPEC cases. In total, the 8 items we evaluated allowed a maximum score of 16 points. We considered studies with 12 or more points as high quality and included them in the present meta-analysis. We excluded those with fewer than 12 points.

Statistical Analysis

This study was performed in line with the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) Statement(10). RCT and NCRT were first analyzed separately using a random-effects model(11, 12) and then combined using a stratified analysis.

This presentation allowed us to see the contrasts between the results of RCTs with those of NCRTs. It also made possible the combination of the RCTs and NCRTs to obtain a single meta-analytic estimate.

Review Manager (RevMan) (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to perform the statistical analysis. Pooled odds ratios (OR) or risk ratio (RR) were calculated for discrete variables.

The fixed-effects and random-effects models were used to calculate the outcomes. In case of significant statistical heterogeneity, only the results of the random-effects model were reported. Heterogeneity amongst the trials was determined by means of the Cochran Q value and quantified using the I^2 inconsistency test. Estimated effect measures were weighted mean differences (WMDs) for continuous data. If authors did not report the standard deviations in continuous variables, and instead reported some other measure of variability (e.g., standard error of the mean, 95% confidence interval of the difference in means), measures were converted using the Cochran Calculator tool in order to enter data into RevMan. The P value threshold for statistical significance was set at 0.05 for effect sizes.

Results

Studies Selected

We identified 40 studies that met the eligibility criteria: 11 RCTs(6, 13–22) and 29 NRCTs. (6, 23–43) We excluded 8 NRCTs(37–43) after a quality assessment. Ultimately, we included 11 RCTs(6, 13–22) and 21 NRCTs(6, 23–36) in the present analysis. The flow diagram in Figure 1 details the selection process. We divided studies into two groups of analysis: treatment of AGC without carcinomatosis (nine RCTs(6, 13–20) and nine NRCTs(6, 23–30)) and treatment of GCPC (two RCTs(21, 22) and twelve NRCTs(24–26, 28–36)). Six authors(24–26, 28–30) of NRCTs reported in the same article both categories with separate analysis. One author(6) reported in the same article, but in different sections, results from a RCT and a NRCT.

We included a total of 2520 patients in the meta-analysis. In the analysis of AGC without carcinomatosis, we included a total of 1810 patients, 731 undergoing gastrectomy+HIPEC and 1079 standard gastrectomy alone. The nine RCTs(6, 13–20) contributed 970 cases, 404 of them allocated in the HIPEC group. In the GCPC analysis, we included a total of 620 patients, 289 undergoing CRS+HIPEC, while 331 patients served as control cases (244 received cytoreduction surgery and 87 systemic chemotherapy). The two RCTs(21, 22) contributed 85 cases, 43 of them in the HIPEC group.

Quality Assessment

Figure 2 presents the assessment of RCTs. In general, they suffer from methodologic drawbacks frequently seen in surgical RCTs, mainly difficulties in concealing the allocation of patients and the inherent complexity of blinding between groups. Table 1 shows the assessment of all NRCTs. The median score of the included studies was 14 points. The detailed characteristics of studies, including stage and tumor findings, can be accessed online (Table SDC1).

Study Characteristics

Table 2 summarizes the major features regarding all studies included. Matching of patient and tumor factors was almost complete throughout the studies. Particularly, 26 studies(6, 13–29, 32, 34, 36) adequately matched all factors reviewed. However, among NRCTs, three studies were not matched according to age(25, 30), one according to gender(35), one

according to the histological findings(31), and two according to the disease extension(33, 35).

In AGC without carcinomatosis, the authors reported the main inclusion criterion as cT4 stage in all studies, except four that considered cT3-cT4 stages.(13, 20, 28) All studies adopted similar exclusion criteria.

The authors described a similar method of HIPEC administration. One RCT(19) reported a four arm subgroup analysis comprising the effect obtained in patients undergoing or not undergoing neoadjuvant chemotherapy. Two studies(13, 17) reported a third group in which patients underwent gastrectomy+NIC. We did not analyze this group because it met the exclusion criteria for the meta-analysis. Eight studies(6, 14–16, 18, 26, 30) reported the use of Mitomycin C (MMC), eight studies(9, 16, 27, 30, 33, 42–44) a combination of MMC with cisplatin^{8,12,18,23} or etoposide(25) or cisplatin+etoposide(24, 27, 29), one study(20) cisplatin alone, and another study(19) cisplatin combined with fluorouracil. The studies provided limited data regarding administration of neoadjuvant and adjuvant treatments.

Studies on GCPC reported similar inclusion and exclusion criteria and method of HIPEC administration. Four studies reported the use of MMC(26, 30, 31, 33), seven studies(22, 24, 25, 28, 29, 34, 35) a combination of MMC with cisplatin(22, 28, 35) or etoposide(25) or cisplatin+etoposide(24, 29, 34), two studies(21, 36) cisplatin or oxaliplatin alone, and another study(32) cisplatin combined with doxorubicin.

The quantitative assessments of carcinomatosis, reported in the selected studies, were the Japanese gastric cancer P score, peritoneal cancer index (PCI), Gilly staging. Most studies(24–26, 28–31, 33–36) described the extent of the disease considering the Japanese system, while four studies(21, 22, 26, 32) have specified the PCI score, and two(21, 35) have used the Gilly assessment. The preoperative evaluation of the peritoneal involvement was performed in all studies with CT and MRI, before a final assessment at the time of laparotomy. Four studies(21, 26, 32, 33), in their methods, highlighted they have added routine exploratory laparoscopy in their assessment. Among the studies, seven articles(21, 22, 26, 28, 31, 34, 35) have also reported data on survival based on the extension of carcinomatosis, thus allowing us to identify two subgroups of analysis: limited (P1) and extensive carcinomatosis (>P1).

Primary Outcomes

For prevention of peritoneal carcinomatosis—The overall survival analysis (Figure 3) in AGC without carcinomatosis showed no significant differences in survival rates between the two groups at 1 year follow-up (Figure 3A, RR=0.55, 95%CI 0.23–1.30), while a statistical significant overall effect was found at the 3-year (Figure 3B, RR=0.71, 95%CI 0.53–0.96, P=0.03) and 5-year (Figure 3C, RR=0.82, 95%CI 0.70–0.96, P=0.01) endpoint favouring the HIPEC procedure. However, when RCTs or NRCTs were considered separately in the analysis for the same endpoints, this difference was not statistically significant.

Moreover, in the 5-year overall survival by type of drug administrated during HIPEC (Figure SDC1), both the two sections of the analysis (MMC alone, combination of drugs) didn't show a significant difference in the HIPEC versus the control group, with completely overlapping results between the use of MMC alone (RR=0.81, 95%CI 0.66–1.00, P=0.05) and the combination of drugs (RR=0.83, 95%CI 0.63–1.08, P=0.07).

The overall disease recurrence (Figure SDC3), evaluated in patients with AGC without carcinomatosis, showed a significant advantage versus the control group for the HIPEC procedure (RR=0.73, 95%CI 0.59–0.89, P=0.002).

For treatment of peritoneal carcinomatosis—The overall survival analysis in GCPC is shown in Figure 4. An advantage in the survival rate was found in favour of the HIPEC group at 1 year follow-up (Figure 4A, RR=0.67, 95%CI 0.52–0.86), while the same overall effect between HIPEC and control group resulted at the 2-year (Figure 4B, RR=0.87, 95%CI 0.73–1.04, P=0.12) and 3-year (Figure 4C, RR=0.99, 95%CI 0.93–1.06, P=0.85) endpoint.

Data allowed assessment of the median survival for GCPC (Figure SDC2) and showed a benefit in favour of the HIPEC group with a median survival of 11.1 months versus 7.06 months in the control group (WMD=4.04, 95%CI 2.40–5.67, P<0.001). This result is consistent in RCTs and NRCTs analyzed separately. However, when comparing HIPEC versus systemic chemotherapy alone, this analysis did not show a statistical significant difference between groups (WMD=2.95, 95%CI 0.92–6.83, P=0.14).

The analysis based on the extent of carcinomatosis showed, for the limited peritoneal dissemination (Figure SDC7), no statistically significant differences in the survival rates at the 1-year (RR=0.62, 95%CI 0.35–1.12, P=0.11), 2-year (RR=0.75, 95%CI 0.50–1.14, P=0.18), and 3-year follow-up (RR=0.78, 95%CI 0.57–1.06, P=0.11) assessment. Even the analysis of studies reporting data on the extensive peritoneal dissemination (Figure SDC8), didn't show differences in survival rates at 1-year (RR=0.84, 95%CI 0.64–1.11, P=0.22) and 2 years (RR=0.94, 95%CI 0.77–1.13, P=0.51) between groups. Only two studies(22, 26) can be considered to specifically evaluate the impact of the PCI index on survival. In the “low PCI” group (< 20 points), the median survival was not significant different between the two arms (11.57 months in the HIPEC group vs 8.6 months in the Control group, WMD=2.97, 95%CI 0.62–6.57, P=0.11), while the effect in the “high PCI” group (> 20 points) is shown only in Yang's study(22) (13.5 months in the HIPEC group vs 3 months in the control group, P=0.012).

Secondary Outcomes

For prevention of peritoneal carcinomatosis—In the analysis of recurrence by site (Figure SDC6) for patients without carcinomatosis, HIPEC obtained advantages in preventing peritoneal metastases (RR=0.63, 95%CI 0.45–0.88, P<0.01), even if a significant difference was not obtained either in RCTs (P=0.05) or NRCTs (P=0.08) when considered separately. No differences appeared in local or lymphnodal recurrence (RR=1.04, 95%CI=0.64–1.69, P=0.88). Liver recurrence was similar (RR=1.19, 95%CI 0.55–2.57, P=0.65), as well as distant recurrence (RR=0.81, 95%CI 0.50–1.30, P=0.38).

HIPEC was associated with a significant higher risk of post-operative overall complications (Figure SDC4) in AGC without carcinomatosis (RR=2.17, 95%CI 1.49–3.14, $P<0.01$). This finding is also consistent among RCTs (RR=1.74, 95%CI 1.04–2.91, $P=0.03$) and NRCTs (RR=2.80, 95%CI 1.62–4.84, $P<0.01$). Particularly, the HIPEC group showed higher renal dysfunction (RR=2.23, 95%CI 1.21–4.11, $P=0.01$).

For treatment of peritoneal carcinomatosis—A significant higher risk for the HIPEC group of developing postoperative complications (RR=2.15, 95%CI 1.29–3.58, $P<0.01$) was found in the analysis performed for GCPC (Figure SDC5), and consistent among RCTs (RR=2.88, 95%CI 1.04–7.97, $P=0.04$) and NRCTs (RR=1.86, 95%CI 1.04–3.33, $P=0.04$). In this category, HIPEC is related to a high risk of developing respiratory failure (RR=3.67, 95%CI 2.02–6.67, $P<0.001$) and renal dysfunction (RR=4.46, 95%CI 1.42–13.99, $P=0.01$). The anastomotic leakage analysis didn't reach a statistical significance in AGC without carcinomatosis ($P=0.63$) or GCPC ($P=0.42$).

In this category, a sensitive issue is also the patients' quality of life, but unfortunately, few data are available. Among the analyzed articles, only Hultman's study offered an indirect assessment of the impact of the disease measured in quality-adjusted life-years (QALY) calculated as survived years multiplied with health utility weights (HUWs). The total difference in HUW for the two groups was small. Mean HUW in the HIPEC group was calculated to 0.84 and for systemic chemotherapy alone to 0.82. The mean difference in QALY was 0.49. This study reported a gain in survival of 0.56 years in favor of HIPEC, but authors considered this a too slightly prolonged survival if related to the gained QALY.

Discussion

This meta-analysis examined the strategies studying the efficacy of HIPEC in different stages of peritoneal disease in gastric cancer. Two goals were found: to prevent the peritoneal disease progression or recurrence in patients who were assumed to have undergone curative gastrectomy; and to treat patients with gross evidence of carcinomatosis within a multimodality strategy. Both positive and negative points related to HIPEC use were revealed highlighting some research challenges which may help direct future investigations. A decreased 3- and 5-years overall survival and overall recurrence rates in patients without carcinomatosis, and an increased median survival of 4.04 months in GCPC, were in favor of the HIPEC group. However, the HIPEC group experienced a higher risk of severe complications. Moreover, the choice of combining RCTs and NRCTs allows the reader to evaluate the results in a multidimensional way. A single meta-analytic estimate was provided together with the effect obtained from RCTs and NRCTs.

For prevention of peritoneal carcinomatosis

First, the population considered in the studies (patients with serosal invasion/cT4) intrinsically includes large pathological variability as witnessed by the reported histopathologic characteristics in the trials: a total of 12.83% had a stage less than III and a differentiated to undifferentiated ratio of 0.56. Moreover, not all patients with serosal invasion experienced the same disease progression. In fact, in patients with serosal invasion, studies(45, 46) have shown that positive cytology correspond with a 5-year survival rate of

18.7%, contrasting with negative cytology exhibiting 51.5% survival rate. However, these studies did not adequately report the status of peritoneal cytology in patient selection. Distinguishing between these two groups will better define patients at high risk of developing peritoneal spread of the disease and allow for identification of prognostic factors with greater sensitivity and specificity.

Second, consistent with the evidence that HIPEC has no antitumor effect on cancer cells that have penetrated deeply into the subperitoneal layers(28, 47) or when extensive lymph node metastasis is present(27), our meta-analysis did not demonstrate any differences amongst the studied groups in local or lymph nodal recurrence. Similarly, no benefit was attributable to preventing liver metastases or the systemic spread of the disease. Ikeguchi reported a 5-years survival analysis based on the number of retrieved metastatic lymph nodes.(15) In the cases of no nodal involvement, he observed overlapping results between groups (65% in the HIPEC vs. 68% in the control group), while the involvement of more than 10 lymph nodes paradoxically led to a reversal of the survival rate in favor of the control group (10% vs. 29%). Instead, a greater effect of HIPEC was seen in patients with 1 to 9 metastatic lymph nodes (66% vs. 44%). Thus, Ikeguchi suggested that HIPEC may improve the prognosis for patients who do not have heavy load lymph node metastases.(15) These findings reveal two essential selection criteria for the use of HIPEC in prevention of peritoneal disease and strongly suggest that patients who have cytology positive disease and limited lymph node involvement may benefit the most.

Third, HIPEC is part of multidisciplinary management. Thus, the final effect on survival involves a combination of surgery and systemic chemotherapy. Some considerations emerged though a deeper analysis of Cui's RCT.(19) The study reported data from subgroups of patients who underwent or did not undergo a neoadjuvant therapy and its correlation with HIPEC administration. Comparing groups yielded a result strongly in favor of the use of neoadjuvant chemotherapy that appears independent from the use of HIPEC, as no statistical significance appeared in the comparison of the neoadjuvant+gastrectomy versus the neoadjuvant+gastrectomy+HIPEC group ($P=0.19$).

Fourth, proper estimation of the morbidity associated with HIPEC remains problematic in its real world applicability. The selected studies come from tertiary referral centers with low reported rates of procedure-related complications in both the standard gastrectomy and HIPEC group, even if the latter associated with an increase of overall complications.

This shows, as also reported in the literature for other complex surgeries, that procedures at such high risk of complications should be proposed in a high-volume tertiary center setting. Consideration should be given to advocating for centralization of the care of gastric cancer patients with advanced gastric cancer to offer the optimum evaluation, treatment plan, and outcomes, especially in patients at risk of peritoneal disease progression and recurrence.

For treatment of peritoneal carcinomatosis

For patients with gross peritoneal carcinomatosis, the efficacy of HIPEC depends on the possibility of achieving complete cytoreduction due to the limited drug action on a residual tumor larger than 2.5 mm (CC0-1).(48) Yang's study analyzed the latter category in depth.

The authors showed that the possibility of achieving CC0–1 was associated with longer survival irrespective of HIPEC administration, obtaining overlapping results between the CRS+HIPEC group (OS=12.0 months, 95%CI= 8.1–16.0 months) and CRS alone group (OS=11.0 months, 95%CI= 8.8–13.2 months).(22) Therefore, the completeness of cytoreductive surgery is a critical prognostic factor for survival.

CRS+HIPEC for gastric cancer is considered by most an aggressive palliative procedure. This meta-analysis allocates a median survival benefit of 4.04 months in favor of the CRS +HIPEC group, which, however, is associated with significantly systemic toxicity, particularly respiratory and renal failure. A challenging perioperative management reveals a substantial systemic stress on the patients as demonstrated by the mortality and morbidity rates in CRS+HIPEC procedures, reported to be 3% to 10% and 10% to 55%, respectively(49–53) with an expected 19% grade IV complication rate in tertiary referral centers.(54)

Patient selection may play a key role in demonstrating potential benefit in HIPEC use. If patients are able to overcome the postoperative complication rates associated with CRS +HIPEC, survival advantages can be had. Good preoperative functional status, no evidence of extraperitoneal metastases, imaging which suggests a CC0-1 resection might be achieved, represents the starting point. Surgeons must carefully balance the post-operative risks of extensive surgery and the potential benefit in survival and quality of life.

Limitations and future direction

There are limitations to the current meta-analysis which help direct future investigations of HIPEC in gastric cancer. First, most of the the RTC and NRCT to date are studies, which have been performed by Asian Institutions, limiting the interpretation of their results for Western populations. This reflects the difficulty of planning this type of studies in Western centers. However, among the ongoing trials, significant contribution to this field is expected from the completion of two relevant European randomized and multicenter phase III studies.

The GASTRICHIP trial (55) (NCT01882933) is currently enrolling patients with resectable T3 or T4 gastric adenocarcinoma with or without lymph node metastases (determined by endoscopic ultrasound and CT scan) plus or minus positive peritoneal cytology (at the time of preoperative laparoscopy), for which a curative gastrectomy is scheduled. This large trial with an estimated enrollment of 322 patients started in May 2013 with a planned evaluation of its primary and secondary outcomes in May 2023. Its primary outcome is the overall survival at 5-years follow-up and the secondary outcomes investigate the recurrence free survival (at 3 and 5 years), morbidity and mortality during the 2 post-treatment months and Quality of Life with EORTC questionnaire OLQ-C30 and QLQ-STO 22.

The GASTRIPEC trial (NCT02158988) is recruiting patients with gastric cancer and synchronous peritoneal carcinomatosis. The CRS+HIPEC is compared with CRS alone. This study started in March 2014 with an expected enrollment of 180 subjects and aims to evaluate the overall survival through a 2.5 years maximum follow-up per patient. Complication rate, time to disease progression, and quality of life are among the secondary outcomes. By September 2020, GASTRIPEC trial is anticipated to be completed.

Second limitation is that the studies thus far have not specifically addressed the role and timing of adjuvant chemotherapy and its impact within a multimodality treatment pathway. HIPEC did not demonstrate efficacy in preventing local or lymph nodal recurrence and no benefit can be attributable to preventing liver metastasis or the systemic spread of the disease. These findings are consistent with the evidence that HIPEC cannot kill cancer cells that have penetrated deeply into the subperitoneal layers. The decreased overall survival of patients who have involvement of more than 10 lymph node in the HIPEC group versus the control group suggest that delay in adjuvant systemic chemotherapy may have an adverse effect on the patient outcome and timely systemic chemotherapy remains the best treatment option for these patients. A relevant issue is to verify if HIPEC associated complications may retard adjuvant chemotherapy. This represents a major point for future investigations. In summary, our study highlights the need to find a balance between locally and peritoneally directed treatment of the disease with systemic therapies.

Third, Comprehensive molecular profiling studies, such as that conducted by the Asian Cancer Research Group (ACRG), may provide insight into selecting patients with the optimal disease biology for HIPEC.(44) The ACRG observed that gastric cancers defined as a microsatellite stable/epithelial-to-mesenchymal transition (MSS/EMT) molecular classification exhibited peritoneal seeding as the preferential pattern of disease recurrence with a very low proportion of liver metastases. Future clinical studies evaluating the impact of HIPEC will greatly be enhanced with correlative molecular analyses of tumor to explore if this MSS/EMT subset derives the greatest benefit from HIPEC. At the same time, evaluation that focuses on specific treatment protocols for patients with positive cytology after peritoneal lavage may provide a category of patients for whom HIPEC may have the greatest potential benefit, since they are classified as stage IV with serious risk of peritoneal progression.(56)

Conclusions

Thirty-years since the initial application HIPEC for the treatment of gastric cancer for peritoneal metastases, surgical techniques and chemotherapeutic regimens which include HIPEC have not been adopted into common practice and peritoneal disease remains. In this context, the next steps in developing a therapeutic program should consider investing peritoneal surface disease burden, reduction of morbidity, timing of interventions, and tailored chemotherapy in a study protocol.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Flowchart of the records selection process.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cui 2014	?	+	?	+	+	+	+
Fujimoto 1999	?	?	?	+	+	+	+
Fujimura 1994	?	?	?	+	+	+	+
Hamazoe 1994	+	?	?	+	+	+	+
Huang 2002	?	?	?	+	+	+	+
Ikeguchi 1995	?	?	?	+	+	+	+
Kaibara 1989	?	?	?	+	+	?	?
Koga 1988	?	?	?	+	?	?	?
Rudloff 2014	+	+	?	+	+	+	+
Yang 2011	+	+	?	+	+	+	+
Yonemura 2001	?	?	?	+	+	+	+

Figure 2.
Quality Assessment of Randomized Controlled Studies based on the Cochrane Risk of Bias Tool.

Figure 3.

AGC without carcinomatosis - overall survival at different endpoints. 1 year (A), 3 years (B), and 5 years (C) follow-up.

Table 1

Modified MINORS score of all eligible Nonrandomized Comparative Studies. Only studies with 12 or more points were included in the final analysis.

Author	Year	Consecutive Patients	Prospective Data Collection	Reported Endpoints	Unbiased Outcome Evaluation	Appropriate Controls	Contemporary Groups	Groups Equivalent	Sample Size	Score
AGC without Carcinomatosis										
Yonemura	1995	2	2	2	2	2	2	1	2	15
Kang	2013	2	1	2	2	2	2	2	1	14
Koga	1988	1	1	2	2	2	2	1	2	13
Hirose	1999	2	2	2	2	2	2	1	1	14
Yarema	2014	2	1	2	2	2	2	1	1	13
Kunisaki	2002	2	2	2	2	2	2	1	2	15
Zhu	2006	2	2	2	2	2	2	2	2	16
Akiyama	1998	2	1	2	2	2	2	2	1	14
Fujimoto	1989	2	1	2	2	2	2	1	0	12
Liu	2015	2	2	0	0	1	2	1	2	10
Akiyama	2002	0	0	1	1	1	1	1	2	7
Kobayashi	1998	0	0	2	0	1	1	0	2	6
Gastric Cancer Peritoneal Carcinomatosis										
Kang	2013	2	1	2	2	2	2	2	1	14
Fujimoto	1997	2	2	2	2	2	2	1	2	15
Hallman	2012	2	2	2	2	2	2	2	0	14
Kim	2014	2	1	2	2	2	2	1	0	12
Kunisaki	2006	2	2	2	2	2	2	2	1	15
Li	2010	2	2	2	2	2	2	1	0	13
Hirose	1999	2	2	2	2	2	2	2	1	15
Yarema	2014	2	1	2	2	2	2	1	1	13
Zhibing	2013	2	1	2	2	2	2	2	2	15
Zhu	2006	2	2	2	2	2	2	2	0	14
Akiyama	1998	2	1	2	2	2	2	2	1	14
Fujimoto	1989	2	1	2	2	2	2	1	1	13
Hall	2004	1	1	1	1	2	1	1	2	10
Akiyama	2002	0	0	1	1	1	1	1	2	7
Kirsch	1989	0	0	1	0	0	0	1	1	3
Kono	1991	0	0	1	0	0	0	1	2	4
Fujimoto	1996	2	1	0	0	1	0	0	2	6

Table 2

Summary of the Studies Included in the Meta-Analysis. Matching: 1, Age; 2, Gender; 3, Histology; 4, Stage; 5, Lymphadenectomy; 6, Type of gastrectomy.

Author	Year	Total sample	HIPEC	Control	Selection Criteria	Matched Factors	Not Matched
RCTs							
Yonemura	2001	95	48	47	cT3-T4	1,2,3,4,5,6	-
Fujimoto	1999	141	71	70	cT4	1,2,3,4,6	-
Ikeguchi	1995	174	78	96	cT3	1,2,3,4,6	-
Hamazoe	1994	82	42	40	cT4	1,2,3,4,6	-
Fujimura	1994	40	22	18	cT4	1,2,3,4,5,6	-
Koga	1988	60	32	28	cT4	1,2,4	-
Kaibara	1989	82	42	40	cT4	1,2,3,4,6	-
Cui HB	2014	192	96	96	cT4	1,2,3,4	-
Huang	2015	42	21	21	cT3-T4	1,2,3,4,5	-
Rudloff	2014	17	9	8	GCPC	1,2,3,4	-
Yang	2011	68	34	34	GCPC	1,2,3,4	-
NonRCTs							
Yonemura	1995	160	79	81	cT4	1,2,3,4	-
Kang	2013	112	29	83	cT4	1,2,3,4,5,6	-
Koga	1988	137	59	78	cT4	1,2,4	-
Hirose	1999	55	15	40	cT4	2,3,4,5,6	1
Yarema	2014	38	19	19	cT4	1,2,3,4,5	-
Kunisaki	2002	124	45	79	cT4	1,2,3,4,5,6	-
Zhu	2006	118	42	54	cT3-T4	1,2,3,4,5,6	-
Akiyama	1998	64	29	35	T4	1,2,4	-
Fujimoto	1989	32	10	22	T4	2,3,4,6	1
Kang	2013	47	16	31	GCPC	1,2,3,4,6	-
Fujimoto	1997	66	48	18	GCPC	1,2,4,6	3
Hultman	2012	20	10	10	GCPC	1,2,4	-
Kim	2014	26	9	17	GCPC	1,2,3	4

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Author	Year	Total sample	HIPEC	Control	Selection Criteria	Matched Factors	Not Matched
Kunisaki	2006	73	21	52	GCPC	1,2,3,4	–
Li	2010	54	10	44	GCPC	1,3	2,4
Hirose	1999	37	17	20	GCPC	1,2,3,4,6	–
Yarema	2014	40	20	20	GCPC	1,2,3,4	–
Zhibing	2013	101	52	49	GCPC	1,2,3,4	–
Zhu	2006	22	10	12	GCPC	1,2,3,4,6	–
Akiyama	1998	22	13	9	GCPC	1,2,4	–
Fujimoto	1989	27	20	7	GCPC	2,3,4,6	1