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Indication of Hyperthermic Intraperitoneal Chemotherapy in Gastric Cancer (Gastripec, Gastrichip)

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Abstract
Background: Gastric cancer (GC) is associated with a poor prognosis mostly due to peritoneal metastasis, which will develop in time during the patient's disease history. To prevent and treat peritoneal metastasis, different kinds of treatment regimens have been described. ***Summary:*** In this review, we addressed two main topics – prophylaxis and treatment of peritoneal metastasis in GC. Prevention should be directed towards diminishing cancer cell spillage and reducing adherence of cancer cells to the abdominal cavity. Postoperative washing of the abdomen with or without chemotherapy and additional heat are herein discussed. ***Key Messages:*** Treatment of existing peritoneal metastasis is effective in patients with limited disease and tumour spread. Cytoreductive surgery including resection of peritoneal metastasis followed directly with hyperthermic intraperitoneal chemotherapy can increase overall survival and progression-free survival in selected patients. Drugs, duration and time schedules of intraperitoneal chemotherapy are reviewed and presented. Intraperitoneal chemotherapy seems to improve the prognosis of patients with GC and peritoneal metastasis after complete resection of both primary and metastatic tumours.

Introduction

With a global incidence of 11.1 cases per 100,000, gastric cancer (GC) ranges among the most common neoplastic diseases and with more than 700,000 deaths per year also represents one of the deathliest neoplasms worldwide [1]. According to national register studies, the peritoneum is the second most common site of GC metastasis, especially in younger patients [2, 3]. Peritoneal metastasis of GC (pmGC) is associated with low survival rates of only months [2, 4] with palliative intravenous chemotherapy as the only recommended treatment option in national and international guidelines [5–8].

Therefore, the first aim was to hinder development of peritoneal metastases to maximize overall survival (OS).

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The MAGIC trial established perioperative chemotherapy with epirubicin, cisplatin, and 5-fluorouracil showing an OS benefit compared to surgery without chemotherapy [9]. Based on the fluorouracil, oxaliplatin (OX), and docetaxel (FLOT)-4 trial, perioperative chemotherapy including 4 preoperative and 4 postoperative cycles of 5-FLOT could further improve OS significantly HR 0.77 (95% CI 0.63–0.94) compared to ECF/ECX (epirubicin, cisplatin, fluoruracil, or capecitabine) reaching a 3-year OS rate of 57% [10]. Since then, perioperative FLOT is the new standard. Nevertheless, 43% of patients treated with curative intent have died after 3 years. Because OS and disease-free survival (DFS) are still disappointing even with optimal systemic treatment, there is a high medical need for further treatment options.

Regarding locally advanced GC, even after curative treatment in accordance with the guidelines, median OS and DFS is disappointing [11]. Therefore, additional adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) might help improve DFS.

In the presence of peritoneal metastasis, palliative treatment strategies and locoregional treatment options for peritoneal metastases such as gastrectomy and metastasectomy, also known as cytoreductive surgery (CRS) in combination with HIPEC, have proven survival benefit in several tumour entities such as ovarian cancer [12, 13], pseudomyxoma peritonei [14, 15], and peritoneal mesothelioma [16]. In this comprehensive review, we would like to address new aspects in treatment strategies for prophylactic and for curative attempt in locally advanced GC in patients with or without peritoneal metastasis.

Pathogenesis of Peritoneal Recurrence after Curative Treatment of Advanced GC and Rationale for the Use of Prophylactic HIPEC

Understanding the physiopathology of peritoneal metastasis after curative surgery of advanced GC appears mandatory in order to appreciate the use of prophylactic HIPEC. Several factors associated to peritoneal recurrence have been identified: invasion of the serosa (T3, T4 tumours) [17], detection of free cancer cells in the peritoneal wash cytology samples [18], invasion of the lymph nodes, and signet ring cells adenocarcinoma [19]. Indeed, peritoneal recurrence usually results from the presence of free intraperitoneal cancer cells originating from the spontaneous exfoliation of cancer cells from large primary tumours. They may also directly result from the surgical trauma during the intervention as both the excision of the primary tumour and the lymph node dissection provoke the release of microscopic tumour emboli, which can adhere the completely peritoneal cavity and mostly the traumatized surface as part of the wound healing mechanism. Furthermore, this creates a hypoxic environment that protects the cancer cells from both the immune system and the effects of systemic chemotherapy (sCTx) [20]. This key process constitutes the theory of what Paul Sugarbaker has called "tumour cell entrapment" [21]. Hence, the addition of HIPEC after resection intends to clear those persisting free cancer cells. Firstly, the large volumes of fluid used during HIPEC at the end of surgery dilute the potential intraperitoneal free cancer cells burden. Secondly, the intraperitoneal administration of chemotherapy results in a higher chemotherapy concentration inside the peritoneum while limiting the systemic concentrations and thereby the risk of toxicity. Finally, the hyperthermia, by increasing the drug penetration and uptake into the tumour cells, and by activating the lysosomal activity, the denaturation of proteins and impairing DNA repair in tumour cells, synergistically enhances the effects of chemotherapy thanks to both indirect and direct cytotoxic actions [22].

Survival Data

Since the late 1980s, dozens of small randomized control trials (RCTs) and as many retrospective case-control studies addressing the use of HIPEC as adjuvant therapy after radical gastrectomy for locally advanced GC have been published. Controversial results mainly due to unicentric design, major heterogeneity in inclusion criteria, lack of statistical power and therefore major risk of bias were reported [23]. However, several recent well-conducted meta-analyses compiled this mosaic of studies in order to shed some light on the prophylactic role of HIPEC consistently acknowledging that HIPEC could effectively reduce peritoneal recurrences and improve survival. Hence, the meta-analysis by Sun et al. [24], based on 10 RCTs, included 1,062 patients with serosal invasion and reported a significant lower peritoneal recurrence rate with HIPEC (RR: 0.45, 95% CI 0.28–0.72, $p = 0.001$) resulting in a significant improvement in OS (RR: 0.73, 95% CI 0.64–0.83, $p < 0.001$). Similarly, in a large meta-analysis of 11 RCTs and 21 NRCT, Desiderio et al. [25] included 1,810 patients with advanced GC without peritoneal metastasis of which 731 underwent gastrectomy and HIPEC and 1,079 gastrectomy alone. The overall disease recurrence rate was in favour of HIPEC with lesser peritoneal recurrences (RR: 0.63, 95% CI 0.45–0.88, $p < 0.001$) and no difference concerning lymph node, liver, or distant recurrences. Only a trend in survival rates between the two groups after a 1-year follow-up was observed in the HIPEC group (RR: 0.55, 95% CI 0.23–1.30), whereas a significant improvement in 3-year (RR: 0.71, 95% CI 0.53–0.96, $p = 0.03$) and 5-year (RR: 0.82, 95% CI 0.70–0.96, $p = 0.01$) OS was found favouring the HIPEC procedure [25]. Both meta-analyses included advanced

GC without macroscopic peritoneal metastasis whatever the status of the peritoneal cytology. Being that peritoneal cytology positivity is classified as a proven peritoneal metastatic spread, performing HIPEC in such patients might be considered already a therapeutic HIPEC. Consequently, Brenkman et al. [26] performed a systematic review of prophylactic HIPEC after excluding patients with positive peritoneal cytology (2 RCTs – 8 case-control studies – 964 patients). Peritoneal recurrence rates occurred in 6.8–26.7% with a median peritoneal recurrence-free survival of 34.5 months in the HIPEC group compared to 14.1–45% and 24.7 months without HIPEC. Median OS and 5-year OS ranged from 32 to 34.6 months and 39–86.8% in the HIPEC group compared to 22–28.2 and 17.3–61% months in the control group [26].

Nevertheless, in addition to their design and despite the results of those meta-analyses, other serious oncological and technical limitations to actual published data remain and need to be pointed out. Indeed, most of reported studies included patients, who were almost exclusively of Asian origin. It has been formally demonstrated that Asian and Caucasian GCs differ in terms of epidemiology, diagnosis, treatment, and prognosis being significantly favourable to Asian patients. Thus, the results cannot be fully applied to Western populations. Moreover, strategies concerning the use of perioperative chemotherapy are different between Asian and Western countries. Preoperative chemotherapy has long been considered as a standard of care with potential better patient selection and greater pathological down staging of primary tumour, lymph node metastasis, and eradication of occult potential micro metastases. Since the wide use of taxan-based triplet chemotherapy regimens, such as the FLOT-4 protocol, were implemented into the guidelines, better results have been observed [27, 28]. The efficacy of such strategy might also attenuate the potential effect of HIPEC. Hence, in the meta-analysis by Desiderio et al. [25], no statistical significance was observed in the comparison between the neoadjvant chemotherapy + gastrectomy group versus the neoadjuvant chemotherapy + gastrectomy + HIPEC group ($p = 0.19$). Furthermore, and probably more importantly, a considerable heterogeneity between the HIPEC technic itself (variables such as time, temperature, choice and dose of intraperitoneal chemotherapy regimen, etc.) exists making extremely difficult the generalization and application of the procedure.

Morbidity and Mortality Results after Prophylactic HIPEC

Data on morbidity are available only in few RCTs and case series, and results are controversial. Morbidity ranges from 25 to 45% after standard gastrectomy and 15–60% with HIPEC. In the meta-analysis by Desiderio et al. [25], HIPEC was associated with a higher risk of postoperative complication (RR: 2.17, $p < 0.001$) namely, higher renal dysfunction (RR: 2.23, $p = 0.01$). Kunisaki et al. [29] also suggested an increased risk of respiratory failure with HIPEC (73 vs. 19%) whereas other studies did not. Similarly, in the meta-analysis by Sun et al. [24] and the review by Brenkman et al. [26], no statistical significance existed concerning overall morbidity, including bone marrow suppression, anastomotic leak, bowel fistula, ileus, or liver dysfunction rates. No significant difference concerning mortality was reported in any study [24, 26]. Furthermore, advances during the last decades in patient selection, prevention, and perioperative management of all adverse events linked either to surgery or to HIPEC technics make a proper estimation of the real morbidity problematic with probably even no added morbidity as suggested by recent large RCTs and series with curative HIPEC.

HIPEC and Choice of Intraperitoneal Regimen

Multiple drugs have been used in HIPEC for GC, and despite it represents probably one of the most important issues, there is currently no consensus regarding the optimal drug regimen, dosing strategy or the duration of exposure. Mitomycin C and cisplatin are the most commonly used agents as they display some characteristics of an ideal drug including proven systemic activity, synergistic activity with hyperthermia, and concentration-related toxicity. Mitomycin C is an alkylating tumour antibiotic and was historically the first drug used as monotherapy for HIPEC. It is usually given in a dose of 15 mg/m^2 for 90 min or a total dose of 40 mg for 90 min as per the by an American consensus [30]. Platinum-based alkylating agents such as cisplatin and OX are commonly employed for gastric peritoneal metastasis. Cisplatin given typically in combination with mitomycin C. Doses range from 50 to 200 mg/m^2 with perfusion time between 60 and 90 min [31, 32]. HIPEC with cisplatin (at a 100 mg/m^2 dose) and sodium thiosulfate during 90 min was validated in a RCT for ovarian cancer, and should therefore represents the standard protocol for cisplatin [13]. In the CYTOCHIP study, that demonstrated a major benefit of adding HIPEC after CRS for gastric peritoneal metastasis, almost 70% of patients benefited from mitomycin C and/or cisplatin [33].

Based on a French phase I study in colorectal cancer, OX is usually dosed at 460 mg/m^2 for 30 min [34]. However, since the recent negative results of both PRODIGE 7 and ProphyloCHIP trials evaluating new HIPEC strategies because due to the study results the use and the efficacy of intraperitoneally administered OX for 30 min has

been widely questioned. Nonetheless, an OX protocol, arbitrarily reduced at 250 mg/m^2 to avoid an excessive rate of postoperative complications, is under investigation and administered in the prophylactic GASTRICHIP trial in high-risk GC [35].

Historically, very few HIPEC protocols included taxan-based regimen. However, the use of palliative repeated intraperitoneal taxan infusions, in normothermic condition, has been largely studied, namely in Japan, with remarkable antitumour effects against gastric peritoneal metastasis making those protocols ones of the most promising and exciting avenues of research [36]. Indeed, according to some pharmacokinetic studies, mitomycin and cisplatin, which are both small hydrophilic molecules, may not stay in the abdominal cavity for a long time. When comparing peritoneal to systemic levels of chemotherapy, drugs with large molecular diameter (10–12 nm) and their hydrophobic character, paclitaxel or docetaxel show a gradual lymphatic absorption and a prolonged retention within the peritoneal cavity resulting in higher area under the curve ratios [31, 37]. Moreover, murine studies have shown that intraperitoneal paclitaxel directly infiltrates up to several hundred micrometers beneath the surface of peritoneal nodules and induces massive destruction of tumour cells as well as microvessels in the tumour periphery [38]. Nonetheless, results concerning the potential reinforcement of taxans' cytotoxicity through the concomitant administration of heat are more conflicting. The PERISCOPE I study showed that in case of peritoneal metastasis, gastrectomy combined with CRS and HIPEC was safe and feasible using 460 mg/m^2 OX and 50 mg/m^2 normothermic docetaxel [39]. The ongoing PERISCOPE II study is now evaluating the efficacy of such association [40]. Finally, the combination of chemotherapy also needs to be further investigated in order to overcome potential chemoresistance and to enhance the cytotoxic effect as suggested by recent results published by Bagdwell et al. [41] with cytoreduction, gastrectomy, and HIPEC with 30 mg mitomycin C and 200 mg cisplatin for patients with peritoneal metastases.

Ongoing Randomized Trials on Prophylactic HIPEC

While the efficacy of systemic perioperative chemotherapy has been largely admitted and considering the poor level of evidence concerning the use of prophylactic HIPEC in advanced GC, prospective randomized trials are urgently needed. The French prospective randomized GASTRICHIP trial led by Glehen et al. [35] commenced in 2014 to investigate the effects of low dose OX-based prophylactic HIPEC on patients with GC and one or more of the following factors: involvement the serosa, involvement of the lymph nodes and positive cytology. The Chinese DRAGON II trial led by Beeharry et al. [42] will investigate the association of neoadjuvant laparoscopic HIPEC with sCTx followed by curative surgery with intraoperative HIPEC in advanced GC patients with serosal involvement with or without occult peritoneal dissemination. Results from those studies and their associated translational research results are expected in the upcoming years. For sure, while bearing in mind their design and specific HIPEC protocol used, they will be the next essential steps to validate (or not) and standardize this strategy.

Other Alternative Intraperitoneal Treatments and Strategies to Prevent Peritoneal Recurrence

Despite initial promising results, the last RCTs failed to demonstrate a benefit of extensive intraperitoneal lavage associated or not to HIPEC immediately after gastrectomy in advanced GC to prevent peritoneal metastasis [43–45]. Similarly, early postoperative intraperitoneal chemotherapy (EPIC) was also proposed as an adjuvant treatment after gastrectomy for advanced GC. Data are relatively scarce. In a phase III trial, Yu et al. [46] evaluated EPIC for additional treatment. The study enrolled almost 30% of patients with stage IV disease and showed a benefit of EPIC after surgery independent of the presence (5-year OS: EPIC vs. surgery alone, 57% and 23%, $p = 0.002$) or absence of peritoneal disease (stage IIIA: EPIC vs. surgery, 52.5% vs. 39.6%, stage IIIB: EPIC vs. surgery, 53.5% vs. 11.0%, $p = 0.003$) [46]. Nonetheless, the overall morbidity rate was in favour of EPIC. In the INPACT trial, Takahashi et al. [47] evaluated this strategy in 83 patients and failed to demonstrate the superiority of weekly intraperitoneal paclitaxel administration in comparison with intravenous administration immediately after gastrectomy.

Treatment Options for Locally Advanced GC with Peritoneal Metastasis

The current National Comprehensive Cancer Network (NCCN) guidelines for GC recommend gastrectomy with lymph node dissection for patients with resectable locoregional GC [6]. However, synchronous peritoneal metastasis is observed in 10–20% of patients who are scheduled for surgery [48]. Although pmGC is known to be associated with limited survival, tumour burden is of major prognostic importance [49]. Only in selected patients with a peritoneal cancer index (PCI) <6–10 will benefit from CRS and HIPEC, if peritonectomy and gastrectomy achieve complete cytoreduction (CCR 0) [33, 50].

Multidisciplinary approaches for the treatment of GC with advanced peritoneal metastasis are currently chemo-

therapy based with regimens containing a platinum/fluorouracil backbone in the 1st line due to the encouraging results of the AIO-FLOT 3 trial. Cytologic findings of free cancer cells in peritoneal washings in the absence of macroscopic peritoneal involvement are thereby considered as an early metastatic stage [51, 52], associated with significantly worse survival than non-metastatic GC [53, 54].

Staging

The standard imaging technique for pmGC is the computer tomography scan [55, 56], although other imaging modalities such as magnetic resonance imaging or positron emission tomography offer potential as an alternative or second choice [56–58]. Nonetheless, current imaging technologies still tend to underestimate peritoneal cancer burden and are associated with insufficient sensitivity and Response Evaluation Criteria in Solid Tumour criteria are not fulfilled [59, 60].

Therefore, staging laparoscopy represents an integral element of staging after initial diagnosis and should be performed in every patient with locally advanced GC before any treatment starts [61]. If not, progress or response to treatment cannot be accurately defined. Staging laparoscopy has the potential to detect peritoneal metastasis in up to 40% of patients during the initial staging [62]. Moreover, staging laparoscopy changes clinical decisions in up to 36% of patients and reduces unnecessary explorative laparotomies [63]. As intraperitoneal free cancer cells represent a metastatic disease stage with severely worse survival [51], a peritoneal cytology should be performed to detect microscopic metastasis. Positive cytology can be found in up to 13.2% of patients during initial staging laparoscopy [64].

Histopathological features associated with findings of peritoneal metastasis or positive cytology include diffuse type histology according to Lauren classification [61, 64, 65], Borrmann type 3 or 4 classification, T3 or T4 tumour stage, and tumour size greater than 4 cm [63, 66]. Furthermore, if the cytology turns negative after neoadjuvant chemotherapy, patients are expected to have a better survival outcome [18].

Therapeutic Cytoreduction and HIPEC in GC with Peritoneal Metastasis

Palliative resection of metastatic GC without complete resection of the metastasis did not show any beneficial results on survival compared to systemic palliative chemotherapy alone [67, 68]. The combination of complete tumour resection of the primary GC including metastatic disease demonstrates significant increased survival, if sCTx was included. However, the metastatic site in the trial was mainly liver and lung metastasis. Only 4 patients had peritoneal metastasis.

Peritoneal metastasis compared to liver or lung metastasis is associated with significant worst prognosis [2]. However, in selected patients – if the tumour burden is low with a PCI less than 10 – gastrectomy and CRS with parietal peritonectomy and HIPEC might improve survival.

HIPEC combines the concept of direct delivery of the chemotherapeutic agent to the peritoneum, enabling the application of higher local doses with low systemic toxicity, with the enhancement of its cytotoxic effects using hyperthermia [69–71]. HIPEC even offers the possibility of cure for a highly selected cohort of patients in case of complete surgical resection of all peritoneal metastases and simultaneous oncologic gastrectomy with tumour-free resection margins and D2-lymphadenectomy [39, 72, 73] HIPEC as treatment for pmGC is not yet a standard treatment due to missing prospective trials.

In a retrospective analysis from prospective databases, identified 277 patients with pmGC who were treated with complete CRS with curative intent (no residual nodules or <2.5 mm) at 19 French centres from 1989 to 2014. Of these patients, 180 underwent CRS and HIPEC and 97 only CRS. CRS in combination with HIPEC demonstrated an improved OS with a median OS of 18.8 months (including patients with PCI 0). Authors conclude that CRS and HIPEC is a valuable therapy for strictly selected patients with limited pmGC [33].

In a recent published Phase II trial, patients with gastric adenocarcinoma and positive peritoneal cytology or metastasis who had completed sCTx and laparoscopic HIPEC underwent cytoreduction, gastrectomy, and HIPEC with 30 mg mitomycin C and 200 mg cisplatin. In this trial, HIPEC was delivered twice: preoperatively and after gastrectomy. Twenty patients were enrolled. Six patients had positive cytology only and 14 had metastasis. All patients underwent sCTx with a median of eight cycles of chemotherapy (range 5–11 cycles) and at least one laparoscopic HIPEC. The median PCI at cytoreduction/gastrectomy/HIPEC was 2 (range 0–13). After surgery, the 90-day morbidity and mortality rates were 70% and 0%, respectively. Median length of hospital stay was 13 days (range 7–23 days); median follow-up was 33.5 months. The median OS from the date of cytoreduction, gastrectomy, and HIPEC was 16.1 months [74].

Only three prospective trials (Table 1) have investigated the potential additional effect of HIPEC in the treatment of pmGC. The first trial was conducted in China and was a randomized phase III study. They included synchronous (n = 51) and metachronous (n = 17) pmGC with a limited number of patients (n = 68). The CCR was identical in both groups (58.8%). There was no significant dif-

Table 1. Study protocols for Phase III studies evaluating CRS and HIPEC with unpublished results in patients with pmGC

NCT number	Patients	Arm intervention	Arm control	HIPEC drug	HIPEC solution/ duration	Temperature	Primary outcome measures	Secondary outcome measures
NCT03023436	220	CRS + HIPEC + sCTx	Single arm	DTX 120 mg	5 L saline; 70 min	43±0.5°C	MS 2-year (24 months)	1. 2-year OS
								2. 2-year PFS
								3. M&M (30 d; 24 months)
NCT02158988 gastripec trial	105	CRS + HIPEC + sCTx	CRS + sCTx	MMC 15 mg/m^2 CDDP 75 mg/m^2	5 L saline; 60 min	41–42°C	OS (2.5 years)	1. PFS
								2. M&M (30 d; 24 months)
								3. MFS
								4. QoL (every 6 months)
NCT03348150	182	CRS + HIPEC + sCTx	Palliative sCTx	OX 460 mg/m^2 DTX 50 mg/m^2	ns; 30 + 90 min	41–42°C + 37°C	OS (5 years)	1. PFS
								2. toxicity
								3. Cost and health benefits

MMC, mitomycin C; CDDP, cisplatin; MS, median survival; OS, overall survival; PFS, progression-free survival; QoL, quality of life; DTX, docetaxel; OX, oxaliplatin; sCTx, systemic chemotherapy; M&M, morbidity and mortality.

ference in mortality and morbidity. Median survival was significantly increased in the group who received HIPEC with 11 months compared to 6.5 months in the surgery alone group ($p = 0.046$). sCTx was not integrated in the trial, and it is not clear whether sCTx was delivered pre-, post-operatively or both. However, multivariate analysis found CRS and HIPEC, synchronous peritoneal metastasis, CCR 0–1, sCTx with 6 cycles, and no serious adverse events were independent predictors for better survival. The authors conclude that for synchronous pmGC, CRS, and HIPEC with mitomycin C 30 mg and cisplatin 120 mg may improve survival with acceptable morbidity [75].

The second trial was conducted to compare CRS and HIPEC to sCTx in metastatic GC not limited to peritoneal metastasis. They compared 7 patients treated by intravenous chemotherapy (FOFIRINOX) alone with 9 patients who were treated by intravenous FOLFIRINOX and additional CRS and HIPEC with OX. Median OS was 11.3 months in the test group (CRS and HIPEC plus sCTx) versus 4.3 months in the control group (chemotherapy alone). Due to the small sample size and heterogeneity of underlying disease, the interpretation of the results should be done with caution [76].

The only randomized clinical trial identified in the therapeutic indication in GC is the German GASTRIPEC trial with the aim to clarify the role of HIPEC in addition to sCTx, gastrectomy, and CRS in GC patients with limited peritoneal metastasis [77]. Patients with GC and histologically proven peritoneal metastasis were randomized into the CRS alone (with curative intent) (CRS-A) arm or into the CRS and HIPEC (CRS+H) with pre- and postoperative chemotherapy arm. The HIPEC treatment consisted of mitomycin C at a 15 mg/m^2 body surface area dose and cisplatin at a 75 mg/m^2 body surface area dose in 5 L of saline (for 60 min, at 42°C). Due to slow recruitment and progression of disease, the study had to be stopped. Only 105 from the originally 180 patients planned were enrolled. Fifty-two patients were randomized into the CRS+H arm and 53 patients into the CRS-A. The median OS for both groups was 14.9 months and was not statistically significant. However, after CCR 0 median OS in the CRS+H group was significantly better compared to the CRS-A group. Progression-free survival was significantly improved from 3.5 months (95% CI 3.0–7.0) in the CRS-A group to 7.1 months (95% CI 3.7–10.5; $p = 0.0472$) in the CRS+H group. Morbidity and mortality were not affected by HIPEC. These results are encouraging for further clinical trials [78].

Conflict of Interest Statement

O.G. consultant for GAMIDA. The remaining authors have no conflicts of interest to declare.

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