

# World Journal of *Gastroenterology*

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## Retrospective Study

# Prolonged hyperthermic intraperitoneal chemotherapy duration with 90 minutes cisplatin might increase overall survival in gastric cancer patients with peritoneal metastases

Heinrich Steinhoff, Miklos Acs, Sebastian Blaj, Magdolna Dank, Magdolna Herold, Zoltan Herold, Jonas Herzberg, Patricia Sanchez-Velazquez, Tim Strate, Attila Marcell Szasz, Pompiliu Piso

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## Abstract

### BACKGROUND

Advanced gastric cancer with synchronous peritoneal metastases (GC-PM) is associated with a poor prognosis. Although cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) is a promising approach, only a limited number of Western studies exist.

### AIM

To investigate the clinicopathological outcomes of patients who underwent CRS-HIPEC for GC-PM.

### METHODS

A retrospective analysis of patients with GC-PM was conducted. All patients were seen at the Department of General and Visceral Surgery, Hospital Barmherzige Brüder, Regensburg, Germany between January 2011 and July 2021 and underwent CRS-HIPEC. Preoperative laboratory results, the use of neoadjuvant

trastuzumab, and the details of CRS-HIPEC, including peritoneal carcinomatosis index, completeness of cytoreduction, and surgical procedures were recorded. Disease-specific (DSS), and overall survival (OS) of patients were calculated.

## RESULTS

A total of 73 patients were included in the study. Patients treated with neoadjuvant trastuzumab ( $n = 5$ ) showed longer DSS ( $P = 0.0482$ ). Higher white blood cell counts (DSS:  $P = 0.0433$ ) and carcinoembryonic antigen levels (OS and DSS:  $P < 0.01$ ), and lower hemoglobin (OS and DSS:  $P < 0.05$ ) and serum total protein (OS:  $P = 0.0368$ ) levels were associated with shorter survival. Longer HIPEC duration was associated with more advantageous median survival times [60-min ( $n = 59$ ): 12.86 mo; 90-min ( $n = 14$ ): 27.30 mo], but without statistical difference. To obtain additional data from this observation, further separation of the study population was performed. First, propensity score-matched patient pairs ( $n = 14$  in each group) were created. Statistically different DSS was found between patient pairs (hazard ratio = 0.2843; 95% confidence interval: 0.1119-0.7222;  $P = 0.0082$ ). Second, those patients who were treated with trastuzumab and/or had human epidermal growth factor receptor 2 positivity (median survival: 12.68 mo *vs* 24.02 mo), or had to undergo the procedure before 2016 (median survival: 12.68 mo *vs* 27.30 mo;  $P = 0.0493$ ) were removed from the original study population.

## CONCLUSION

Based on our experience, CRS-HIPEC is a safe and secure method to improve the survival of advanced GC-PM patients. Prolonged HIPEC duration may serve as a good therapy for these patients.

**Key Words:** Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Peritoneal metastasis; Stomach neoplasms; Gastric cancer

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**Core Tip:** Advanced gastric cancer (GC) cases with peritoneal metastases are known for their poor survival rates. It has been previously reported that these patients benefit from cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) but available data on this treatment are scarce. In this study, we retrospectively analyzed the clinicopathological and laboratory data of 73 patients with advanced GC and synchronous peritoneal metastases. It was found that prolonged HIPEC duration after macroscopic complete CRS in the scope of multimodal treatment along with advanced perioperative chemotherapy and biologicals may serve as the best currently available therapy for these patients.

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## INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer, with a worldwide incidence of 1,089,103 new cases and 768,793 deaths based on the 2020 GLOBOCAN results[1,2]. The majority of the new cases are diagnosed in Asia, where occurrence is 6-fold higher than in Europe; a similar distribution is observed in GC mortality[1]. In Germany, 15322 new cases and 9196 deaths were reported in 2020[1]. GC is known for its morphological diversity[3], and the most commonly used classifications are those outlined by Nakamura *et al*[4], Lauren[5], and the World Health Organization (WHO)[6]. The treatment of gastric cancer is multidisciplinary and depends on the clinical staging of the tumor. While early-stage GC (stage T1a) can be endoscopically resected[7], stage T1 with positive lymph node(s) and T2-T4a tumors regardless of lymph node status are treated by surgical resection and peri- or postoperative chemotherapy[8]. Advanced resectable GCs are typically treated with neoadjuvant chemotherapy followed by gastrectomy and adjuvant chemotherapy[9]; if not amenable to resection, then the treatment of choice is chemotherapy[8].

A recent analysis of 18,000 United States patients showed that advanced GC with PM has a median survival of 8.6 mo if treated with chemotherapy only[10], while studies from the United States[11], China[12] and Germany[13] have shown that advanced GCs with peritoneal carcinomatosis benefit significantly from cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC)[11–15] when complete macroscopic resection of the tumor tissue can be achieved[16]. Nevertheless, the available data regarding the use of CRS and HIPEC in advanced GC with PM is scarce, and this multimodal therapy has infrequently been recommended in any national or international guidelines. To date, the Japanese[17] and the United States[18] guidelines do not include CRS and HIPEC as therapeutic options. In France, the guidelines for treatment of advanced GC with PM[19] are yet to be defined in future randomized phase III studies. The same is true in Germany, where an expert consensus-based recommendation calls for the implementation of CRS and HIPEC in clinical studies[8]. The European Society for Medical Oncology guidelines for the treatment of gastric cancer describe CRS and HIPEC as safe procedures, but with unclear oncological outcomes[20]. Accordingly, the aim of this retrospective study was to investigate the clinical outcome after administration of this multimodal therapy in a tertiary center to treat patients with primary advanced GC with PM.

## MATERIALS AND METHODS

### *Patients and study design*

The HIPEC database of a single tertiary care center was analyzed in a retrospective manner. A total of 73 patients seen at the Department of General and Visceral Surgery, Hospital Barmherzige Brüder, Regensburg, Germany between January 2011 and July 2021 with primary GC and synchronous PM were included (Figure 1). All patients gave written and verbal informed consent to be included in the national HIPEC registry, administered by the German Society for General and Visceral Surgery (DGAV), and for the use of their anonymized data for research purposes and quality assurance prior to any study-specific procedures. All 73 patients underwent CRS + HIPEC and were treated according to national or international multidisciplinary recommendations[8,20].

### *Details of CRS + HIPEC*

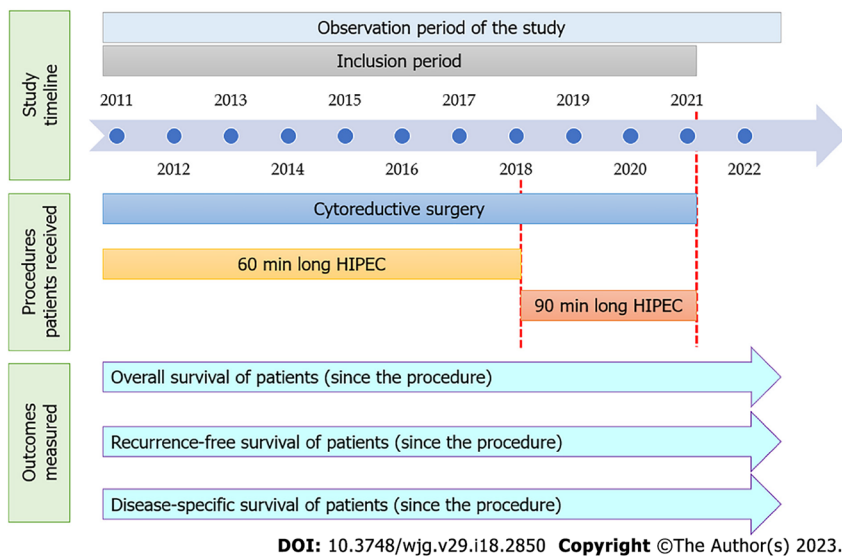
Each of the 73 cases was discussed by a multidisciplinary board of experts (oncologists, surgeons and anesthesiologists) before any treatment decision was made. Preoperatively, the extent of peritoneal dissemination was assessed using abdominal and chest computed tomography (CT) scans. The peritoneal carcinomatosis index (PCI)[21] was calculated based on diagnostic laparoscopy performed on tumors of T3 stage or higher or CT evidence of peritoneal carcinomatosis[22]. Prior to surgery, all patients were preconditioned as per the enhanced recovery after surgery (ERAS) protocol. During CRS, the completeness of cytoreduction (CC) was scored as proposed by Jacquet and Sugarbaker[21]: No residual disease, residual nodules measuring less than 2.5 mm, between 2.5 mm and 2.5 cm, or greater than 2.5 cm were defined as CC-0, CC-1, CC-2, and CC-3, respectively.

Closed HIPEC with a goal temperature of 42 °C with bidirectional HIPEC with cisplatin (75 mg/m<sup>2</sup>) and doxorubicin (15 mg/m<sup>2</sup>) was administered immediately after CRS for 60 min or 90 min duration (Figure 1). The duration of HIPEC was changed from 60 min to 90 min in 2018 based on the findings of van Driel's study[23]. The cytotoxic agents were added to a 3000 mL–4000 mL isotonic saline solution with a mean flow rate of 1400 mL/min–1800 mL/min. During the treatment, temperature probes for monitoring the 42 °C goal temperature were placed in the right subphrenic and pelvic areas.

### *Clinicopathological and laboratory data measurements*

Clinicopathological and laboratory data were obtained from the DGAV HIPEC registry and the electronic medical system of Hospital Barmherzige Brüder, Regensburg, Germany. The staging of the tumors was unified using the 8<sup>th</sup> American Joint Committee on Cancer (AJCC) TNM system[24]. Histopathology types of the tumors were categorized as diffuse type adenocarcinoma (ACD), intestinal type adenocarcinoma (ACI), or signet-ring cell adenocarcinoma (SRC)[3]. Neoadjuvant chemotherapeutic treatment of patients was recorded as the latest lineage the patient received prior to CRS + HIPEC. Except for a single patient, all study participants were treated with at least docetaxel-based first-line chemotherapy (FLOT protocol: 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; or DCF protocol: docetaxel, cisplatin, and 5-fluorouracil). Chemotherapy was administered in accordance with the German guidelines on GC; when recommendation changed from EFC/ECX (Epirubicin, Cisplatin, Fluorouracil/Epirubicin, Cisplatin, Capecitabine) to FLOT after Al-Batran's FLOT-4 study in 2019[25], chemotherapy was accordingly changed. The additional use of trastuzumab (trade name: Herceptin) was also recorded.

Complete blood count, liver enzyme, lipase, creatinine, and tumor marker blood tests were performed at the Department of Laboratory Medicine, Microbiology, and Hospital Hygiene, Hospital Barmherzige Brüder, Regensburg, Germany. The Chronic Kidney Disease Epidemiology Collaboration equations were used to calculate estimated glomerular filtration rate[26]. The Clavien–Dindo Classification[27] was used to assess postoperative adverse events. Although some recent publications have



**Figure 1** Timeline of the study. HIPEC: Hyperthermic intraperitoneal chemotherapy.

suggested including all patient deaths within 90 d as post-procedure deaths[28,29], HIPEC-related post-procedure deaths were defined as follows: (1) Those occurring during the observation period at the intensive care unit or at the surgical inpatient unit prior to discharge; or (2) Between discharge and adjuvant chemotherapy. If a patient had started adjuvant chemotherapy, their death was defined as GC-related. Recurrence-free (RFS), disease-specific (DSS), and overall survival (OS) were calculated from the date of surgery (CRS + HIPEC) to the date of tumor recurrence, cancer-related death, or death from any cause, respectively. The follow-up of patients was terminated on 30 September 2022 and the patients alive at this time point were right censored (Figure 1).

### Statistical analysis

Statistical analyses were performed within the R for Windows version 4.2.1 environment (R Foundation for Statistical Computing, 2022, Vienna, Austria). Wilcoxon rank sum test and Fisher's exact test were used for group comparisons. Linear models were used to investigate whether there was an improvement in the duration of the procedure (learning curve). Matching of patient pairs was done *via* propensity score matching (R-package "Matching" version 4.10-8). DSS, OS, and RFS were determined using the cause-specific competing risk Cox survival model (R packages "survival" version 3.4-0 and "survminer" version 0.4.9). Parameter selection for multivariate survival models was not based on univariate *P* value, but on literature data and the medical/clinical importance of the given parameter. *P* < 0.05 was considered statistically significant, and *P* values were corrected with the Holm method[30] for the multiple-comparisons problem. Continuous, survival, and count data were expressed as the mean ± standard deviation (SD), the hazard ratio (HR) with a 95% confidence interval (95%CI), and the number of observations (percentage), respectively.

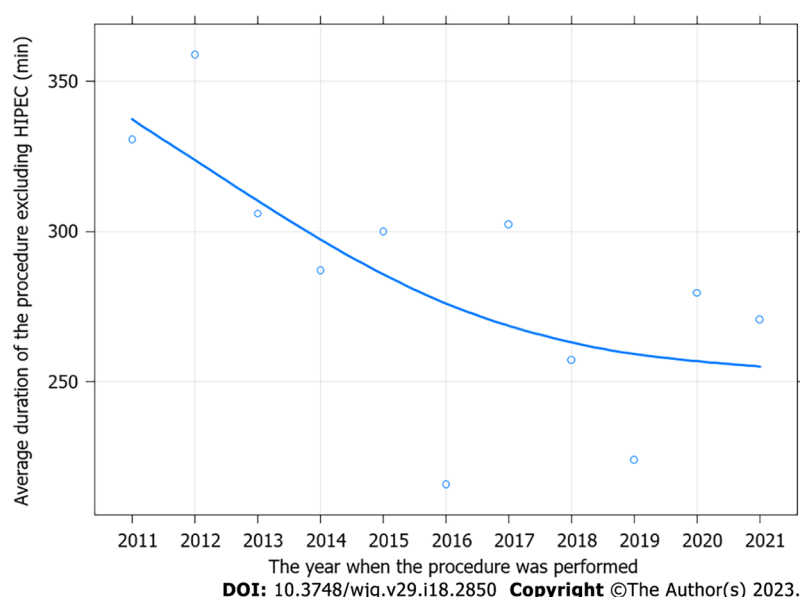
## RESULTS

A total of 73 GC patients with PM were included in the study. Sixty-four cancer-related death events, 13 tumor recurrence events, and 1 death due to postoperative complications occurred. The complete list of pre-, peri- and postoperative clinicopathological characteristics of study participants are listed in [Supplementary Table 1](#). In general, the average operating times (excluding the time for HIPEC) improved significantly over observation period (*P* = 0.0097; [Figure 2](#)).

First, it was investigated whether any of the CRS + HIPEC-related or clinicopathological features had a significant effect on patient survival. The need to remove any further organs, such as the removal of the bladder or the appendix during CRS (*n* = 9), was associated with a negative effect on DSS (HR: 2.0538; 95%CI: 1.2715-3.3179; *P* = 0.0033). Those patients who received additional trastuzumab treatment during neoadjuvant chemotherapy (*n* = 5) before the CRS + HIPEC procedure had better DSS (HR: 0.4446; 95%CI: 0.1989-0.9937; *P* = 0.0482). A trend towards longer RFS was found in patients who did not require pelvic peritonectomy (HR: 0.3382; 95%CI: 0.1099-1.0410; *P* = 0.0588). OS was significantly better in patients without pelvic peritonectomy (HR: 0.5459; 95%CI: 0.3152-0.9454; *P* = 0.0307).

Longer HIPEC duration (60 min *vs* 90 min) was associated with more advantageous median survival times: 12.86 mo (95%CI: 11.01-17.31) for the 60 min and 27.30 mo (95%CI: 16.20-NA) for the 90 min cohorts ([Supplementary Table 1](#)). However, despite the clinically different median survival times, the





**Figure 2** Improvement of the operating times of cytoreductive surgery (excluding hyperthermic intraperitoneal chemotherapy) in our surgical center during the study period. HIPEC: Hyperthermic intraperitoneal chemotherapy.

survival of the groups did not differ based on the results of the statistical models with respect to DSS (HR: 0.6239; 95%CI: 0.3413-1.1410;  $P = 0.1250$ ; **Figure 3**), OS (HR: 0.6134; 95%CI: 0.3007-1.2510;  $P = 0.1790$ ), or RFS ( $P = 0.9650$ ). Furthermore, the type of histology (ACD *vs* ACI *vs* SRC) did not affect DSS ( $P = 0.4096$ ; **Supplementary Figure 1**), OS ( $P = 0.2422$ ), or RFS ( $P = 0.2799$ ). However, the RFS survival curves of the different histology types seemed to be visually different (**Figure 4**).

The effect of pre-HIPEC laboratory results on patient survival was also investigated. Higher white blood cell counts (HR: 1.1319; 95%CI: 1.0037-1.2770;  $P = 0.0433$ ) and carcinoembryonic antigen (CEA) levels (HR: 1.1490; 95%CI: 1.0422-1.2667;  $P = 0.0053$ ) were associated with an increased risk for shorter DSS. In contrast, higher hemoglobin (HR: 0.7897; 95%CI: 0.6562-0.9505;  $P = 0.0125$ ) and serum total protein (HR: 0.6795; 95%CI: 0.4330-1.0660;  $P = 0.0928$ ) levels were associated with a significant and marginally decreased risk for shorter survival, respectively. The same results were found for OS (white blood cell count:  $P = 0.0945$ ; CEA:  $P = 0.0052$ ; hemoglobin:  $P = 0.0087$ ; serum total protein:  $P = 0.0368$ ), while shorter RFS times were observed in patients with higher RDW levels (HR: 1.2190; 95%CI: 1.0030-1.4810;  $P = 0.0466$ ). Moreover, similar to that observed with respect to OS and DSS, marginally advantageous RFS was justified for higher serum total protein levels ( $P = 0.0875$ ).

The effect of clinicopathological and laboratory data on survival was also further investigated in a multivariate setting (**Table 1**). DSS was marginally affected by the duration of HIPEC [60 min (ref.) *vs* 90 min: HR: 0.5252; 95%CI: 0.2565-1.0750;  $P = 0.0781$ ] and by PCI (HR: 1.0630; 95%CI: 0.9982-1.1310;  $P = 0.0569$ ), and significantly by preoperative serum CEA levels (HR: 1.2220; 95%CI: 1.0880-1.3720;  $P = 0.0007$ ). Similar trends were observed for OS, while worse RFS was more likely associated with lower preoperative white blood cell count (HR: 0.4616; 95%CI: 0.2270-0.9385;  $P = 0.0327$ ), lower T stage (HR: 13.1182; 95%CI: 1.0285-167.3080;  $P = 0.0475$ ), and higher N stage (HR: 5.6893; 95%CI: 0.7616-42.4972;  $P = 0.0902$ ).

### Comparison of the 60 and 90-min-long HIPEC patient groups

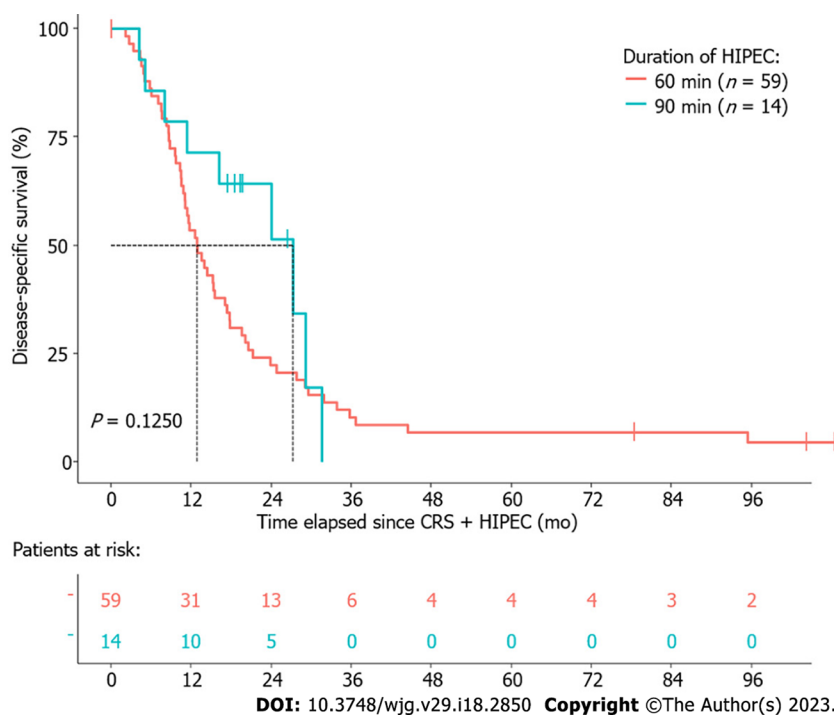
Further comparison was performed by creating 2 groups according to the duration of HIPEC. Fifty-nine and 14 study participants were enrolled in the 60 min and 90 min groups, respectively. Except for the above-described median survival differences (12.86 mo *vs* 27.30 mo; **Figure 3**), no difference was found in any clinicopathological characteristic between the two groups after  $P$  value adjustment (**Supplementary Table 1**).

By investigating the results without  $P$  value adjustment, several observations were made. The length of CRS trended toward being shorter in the 90 min group ( $299 \pm 76$  min *vs*  $264 \pm 82$  min; crude  $P = 0.0718$ ). Peritonectomy of the omental bursa was more frequently performed in the 60-min group (30.5% *vs* 0%; crude  $P = 0.0157$ ), while lesser omentectomy was more common in the 90-min group (33.9% *vs* 71.4%; crude  $P = 0.0153$ ). Fresh frozen plasma (FFP) transfusion was needed only once in the 90 min group, while in the 60-min group, FFP was administered in 32 patients (7.1% *vs* 54.2%; crude  $P = 0.0009$ ). On average, the length of hospital stay was shorter in the 90 min group (crude  $P = 0.0134$ ); a more detailed examination of the data revealed that hospitalization longer than 20 d was more common in the 60 min group (39.0% *vs* 7.1%; crude  $P = 0.0276$ ). Moreover, abnormal serum levels of gamma-glutamyl transferase (crude  $P = 0.0407$ , **Figure 5A**) and serum total protein (crude  $P = 0.0570$ , **Figure 5B**)

**Table 1** *P* values of the multivariate survival model

Parameter	DSS	OS	RFS
HIPEC duration [60 min (ref.) <i>vs</i> 90 min]	0.0781	0.1541	0.5578
Age (yr)	0.1870	0.1331	0.3691
Sex [male <i>vs</i> female (ref.)]	0.3327	0.2943	0.8681
Stage T [1-2 (ref.) <i>vs</i> 3-4]	0.1205	0.1857	0.0475
Stage N [0 (ref.) <i>vs</i> 1-3]	0.5071	0.4511	0.0902
Histology			
ACD (ref.) <i>vs</i> ACI	0.3092	0.2335	0.2471
ACD (ref.) <i>vs</i> SRC	0.9456	0.8638	0.2227
Body-mass index (kg/m <sup>2</sup> )	0.6394	0.8365	0.3049
Peritoneal carcinomatosis index	0.0569	0.2530	0.2752
White blood cell count (10 <sup>9</sup> /L)	0.1843	0.2387	0.0327
Hemoglobin (g/dL)	0.2783	0.2924	0.7656
Carcinoembryonic antigen (ng/mL)	0.0007	0.0005	0.1089

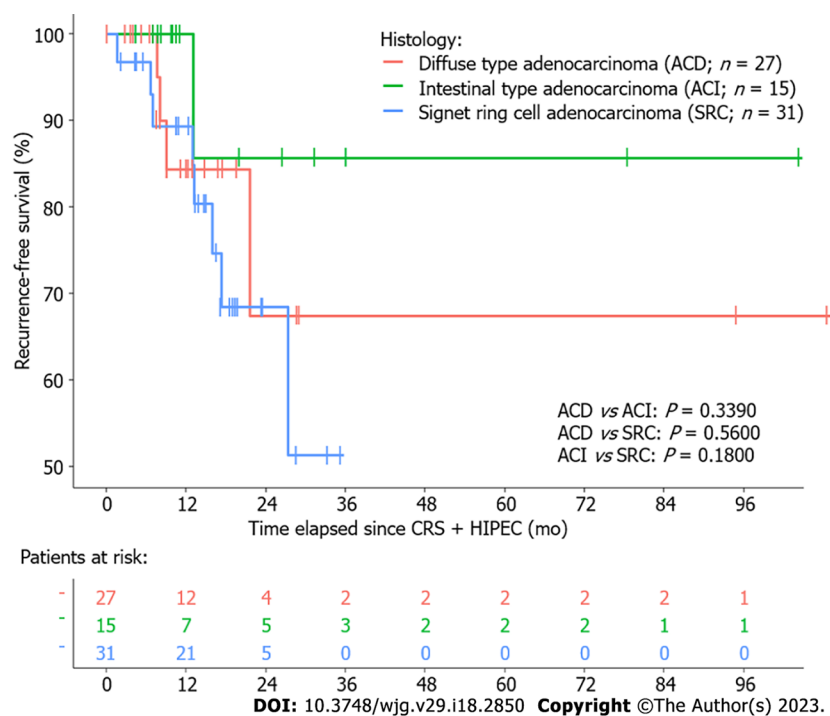
ACD: Diffuse type adenocarcinoma; ACI: Intestinal type adenocarcinoma; DSS: Disease-specific survival; ref.: Reference category; RFS: Recurrence-free survival; OS: Overall survival; SRC: Signet-ring cell adenocarcinoma.



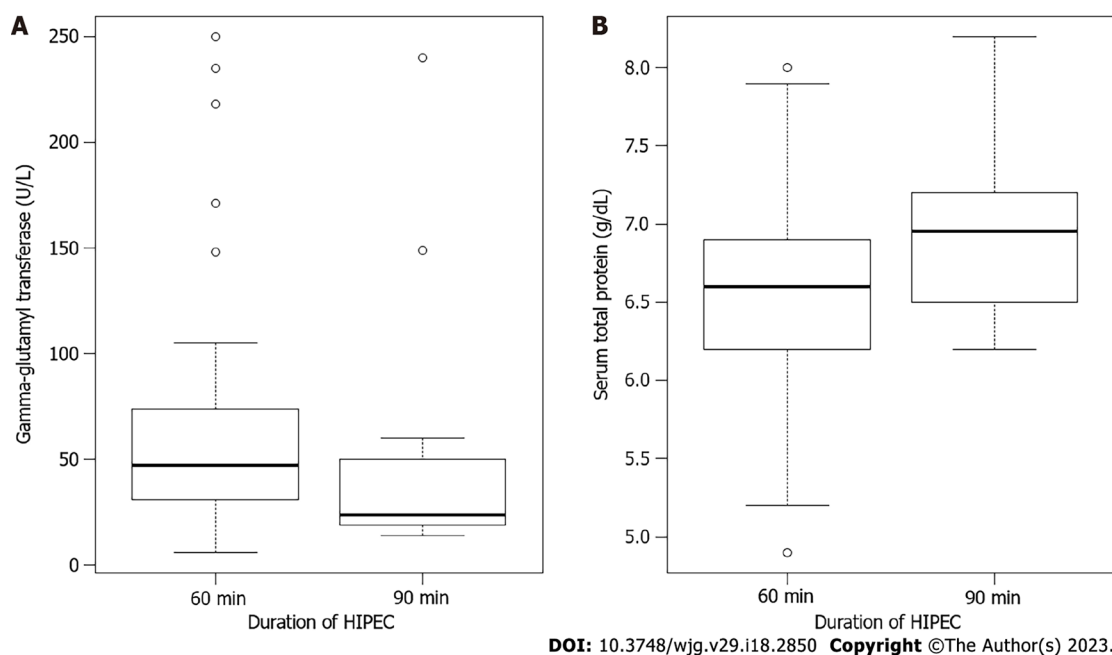
**Figure 3** Differences in disease-specific survival between patients with gastric cancer who underwent cytoreductive surgery and 60 min or 90 min hyperthermic intraperitoneal chemotherapy. The dotted line represents median survival. CRS: Cytoreductive surgery; HIPEC: Hyperthermic intraperitoneal chemotherapy.

levels were observed more often in the 60-min group (Supplementary Table 1).

To further investigate the cause of the clinically significant difference in median survival, the following adjustments to the groups were performed with consideration of any possible confounding effects. First, propensity score-matched patient pairs (*n* = 14) were created in which patients were matched by age, sex, PCI score, CC score, time spent in the intensive care unit after CRS + HIPEC, duration of CRS, and the presence of lymph node metastasis (stage *N* = 0 *vs* stage *N* ≥ 1). No differences in adjusted or in crude *P* values were found in any of the preoperative, perioperative, and postoperative



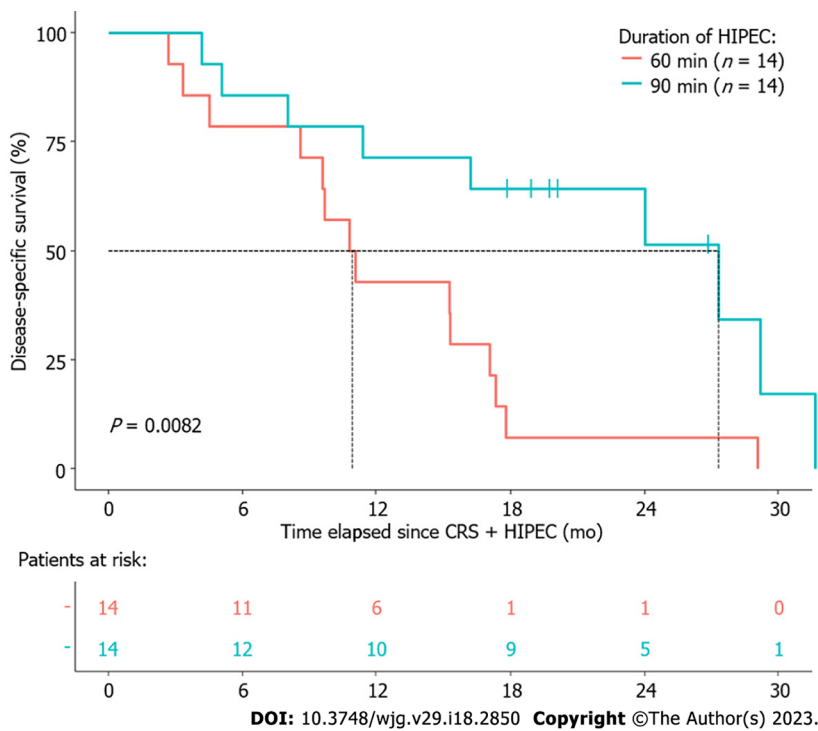
**Figure 4 Differences in recurrence-free survival between patients with gastric cancer of different histological types who underwent cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.** ACD: Diffuse type adenocarcinoma; ACI: Intestinal type adenocarcinoma; CRS: Cytoreductive surgery; HIPEC: Hyperthermic intraperitoneal chemotherapy; SRC: Signet-ring cell adenocarcinoma.



**Figure 5 Gamma-glutamyl transferase and total protein levels in 60 min and 90 min hyperthermic intraperitoneal chemotherapy groups.** Clinically abnormal serum levels of gamma-glutamyl transferase (crude  $P = 0.0407$ ) and total protein (crude  $P = 0.0570$ ) were observed more often in those gastric cancer patients who received hyperthermic intraperitoneal chemotherapy (HIPEC) for 60 min after the cytoreductive surgery. Thick lines and hollow circles represent the median and outliers, respectively. A: Gamma-glutamyl transferase; B: Total protein.

parameters between propensity score-matched groups. However, the seemingly different survival between the 2 groups became statistically significant [60 min (ref.) *vs* 90 min: HR = 0.2843; 95%CI: 0.1119-0.7222;  $P = 0.0082$ ; Figure 6] with 10.91 mo (95%CI: 9.56-17.77) and 27.30 mo (95%CI: 16.20-NA) median survivals for the 60 min and 90 min groups, respectively.

We also investigated whether results changed if patients who received trastuzumab and/or had immunohistochemically positive pathological results against human epidermal growth factor receptor 2



**Figure 6 Differences in disease-specific survival between propensity score in matched gastric cancer patient-pairs.** Patients were matched by age, sex, peritoneal carcinomatosis index score, Jacquet and Sugarbaker's completeness of cytoreduction score, time spent in the intensive care unit after cytoreductive surgery (CRS) + hyperthermic intraperitoneal chemotherapy (HIPEC), duration of CRS, and presence of lymph node metastasis (stage  $N = 0$  vs stage  $N \geq 1$ ). The dotted line represents median survival.

(HER2;  $n = 7$ ) or had the procedure before 2016 ( $n = 44$ ) were removed from the original cohort. For the former, we obtained the same results as those for the full cohort. Median survivals of 12.68 mo and 24.02 mo were observed for the 60-min and 90-min groups, respectively, and no statistical difference was detected in the survival models (DSS:  $P = 0.1540$ ; OS:  $P = 0.2040$ ; **Supplementary Figure 2A**). However, the same difference was seen for the modified patient population that seen with propensity-matched pairs. Median survivals of 12.52 mo and 27.30 mo were found for the 60 min and 90 min groups, respectively (HR: 0.4225; 95%CI: 0.1789-0.9975;  $P = 0.0493$ ; **Supplementary Figure 2B**).

## DISCUSSION

There are only a few Western studies concerning the treatment of advanced GC with CRS and HIPEC. Although the positive effects of cytoreduction and HIPEC on survival have been described[11-13,31], the practical nonexistence of prospective clinical studies (except for two studies with small sample sizes [12,32]) on CRS and HIPEC highlights the need for additional primary research. Moreover, more randomized trials are required to substantiate the effect of CRS and HIPEC. For example, the results of the German phase III PREVENT study, in which the effect of HIPEC applied for prevention in lieu of FLOT-chemotherapy, is currently recruiting patients, and results are eagerly anticipated[33].

In the current retrospective study, we demonstrated prolonged survival with multimodal therapy in the treatment of primary GC patients with PM. The 27.3 mo median survival that we observed is in line with similar studies. For example, in the phase II trial by Badgwell *et al*[11], the median OS was 24.2 mo from the date of diagnosis and 16.1 mo from the date of CRS and HIPEC. Similarly, a recent Spanish multicenter study found a median survival of 21.2 mo[34], while in the German retrospective HIPEC-register study the median survival times ranged from 7.9 mo to 21.2 mo[35]. The same is true of median PCI-scores; median PCI was 2, 6, 6, and 8 in the studies of Badgwell *et al*[11], Bonnot *et al*[31], Manzanedo *et al*[34], and Rau *et al*[35], respectively; a median PCI of 3 was calculated in the current study. In addition, Rau *et al*[35] reported OS of 18 mo, 12 mo, and 5 mo for the 3 patient groups, with corresponding PCI scores of 0-6, 7-15, and 16-39, respectively; this finding suggests that significantly better outcomes are associated with higher CC. In our study, 93.2% of patients underwent complete macroscopic tumor reduction. An important conclusion of the above presented studies is that patients with small tumor burden (PCI < 6, but maximally 9) benefit the most from this multimodal therapy. Although in the current study we could not confirm the benefit of reduced PCI scores, our results were in line with the previously described observations (*i.e.* patients with higher PCI scores trended toward shorter survival). Furthermore, an interesting observation emerged during the analysis of our data over



time and with an increasing number of cases: The duration of surgery to reach complete cytoreduction became significantly shorter. These findings match with the results of a study outlining the technical aspects and learning curve of CRS/HIPEC by Vining *et al*[36], where the authors describe a steep learning curve and a correlation between CC and surgeon expertise. This observation underscores the idea that treatment of advanced GC with PM should be performed in specialized centers by expert surgeons. Recent studies have also found that sodium thiosulfate can prevent impairment of renal function following HIPEC[37,38]. In the patient population analyzed in the current study, sodium thiosulfate was not used; however, since January 2022, we have started to use it routinely in our center.

There is still no consensus regarding the ideal duration of HIPEC. In the current analysis, the median survival time was 27.30 mo in the 90 min group, which was significantly longer than that of the 60 min group (12.86 mo). Near the publication date of the van Driel *et al*[23] study for ovarian cancer and the PRODIGE-7 trial[39] for HIPEC in colorectal cancer, our institutional HIPEC protocol was changed in favor of the 90 min HIPEC perfusion. Our group has recently described the advantages of prolonged HIPEC duration have been recently described for primary peritoneal carcinoma, primary advanced epithelial carcinoma, and ovarian or fallopian tube carcinoma[40,41]. Longer HIPEC duration does not adversely affect perioperative morbidity and mortality, and a potential survival benefit could be realized by the application of prolonged HIPEC[40]. However, a recent study found that a secondary inflammatory reaction might occur after 90 min HIPEC with mitomycin C/doxorubicin or cisplatin, but not with shorter duration and oxaliplatin[41]. These and the current findings suggest that a prolonged peritoneal perfusion time may be more advantageous after complete cytoreduction; however, as the study of Roth *et al*[41] has shown, gathering additional data is essential.

Another possible reason for better survival in patients with longer HIPEC duration is enhanced cytotoxicity and anti-tumor effects of chemotherapeutic drugs in hyperthermia; the longer exposure may allow for more effective drug action[42]. The effect of cytoreductive surgery with macroscopic complete tumor reduction followed by HIPEC with effective neoadjuvant chemotherapy extends survival time of patients with advanced GC with PM, as recently shown in the CYTO-CHIP study[31]. Since 2016, the most frequently used neoadjuvant chemotherapy for advanced GC with PM is the FLOT-protocol; however, due to differences in cytochrome P450 family 2 subfamily A member 6[43], the S-1 regime (tegafur, gimeracil, and oteracil) is the standard adjuvant treatment in Asia[44,45]. The latest advancements in preoperative chemotherapy with[46] or without[25] biological agents can significantly extend the survival of GC patients. Recently, it has also been demonstrated that the 15%-20% of GC cases that overexpresses HER2 should be treated with monoclonal antibodies like trastuzumab in a neoadjuvant setting due to the positive influence of these drugs on patient survival and fewer side effects than traditional chemotherapies[47]. In the current study, the individual responses to pre- and/or postoperative chemotherapy were not known for most patients, which was one of the biasing factors affecting patient survival in our study.

SRC differentiation is described as a tumor with aggressive growth and a poorer prognosis than non-SRC carcinomas of the stomach[48]. In contrast, we found that the type of histology did not affect DSS, OS, or RFS. A similar finding was reported in an Asian study of 136 advanced GC patients, in which the authors described no difference in median survival between the histopathologic entities after R0-resection[49]. Moreover, we observed that if pelvic peritonectomy during CRS is not necessary, the OS of the patient improved. We hypothesize that the extent of the tumor may have a greater influence on patient survival than the histopathological differentiation. Improvement in patient survival may also be influenced by the experience of the surgical team; this factor may have also introduced additional bias in the current study.

We also investigated whether any preoperative laboratory result was predictive of patient survival. Strong correlations were found between patient survival and white blood cell count, hemoglobin, CEA, and serum total protein. These findings match with previously reported data of non-HIPEC-treated GC patients[50-55]. Furthermore, results of a recent German multi-center study[56] and the WHO urgent call[57] to implement blood management in surgical patients have shown that preoperative anemia is a serious threat to patient survival. Preoperative iron supplementation in preoperative anemia is also an important part of the recently published ERAS protocol for CRS and HIPEC[58]. As such, emphasis should be placed on iron supplementation and normalization of hemoglobin prior to surgery[58].

### Limitations

The current study had a few limitations, including the small sample size, the retrospective nature of the study, the fact that data were available from a single center only, and the heterogeneity of the data. Also, during the study period, preoperative chemotherapy protocols changed and surgeon expertise grew. Furthermore, in this small cohort of patients with GC and PM, there were limited data regarding post-HIPEC treatment. Our follow-up data could only differentiate between alive and dead patients and tumor recurrence or no recurrence. Efforts were made to collect post-HIPEC patient data; however, we could not collect these in a timely manner, as routine oncological treatments were often performed in other hospitals. Moreover, the lack of chemotherapy-only control patients should also be mentioned as a limiting factor.

## CONCLUSION

In summary, we conducted a single-center retrospective observational study to investigate what factors influence the survival of advanced GC patients with PM who underwent CRS and HIPEC. We confirmed that CRS followed by HIPEC applied over 90 min has a positive impact on DSS in comparison with CRS followed by 60 min of HIPEC. Of note, the learning curve of surgeons may confound the interpretation of this observation. Furthermore, the preparation of patients for surgery based on preoperative laboratory testing according to the current ERAS protocol might optimize the positive effect of CRS and HIPEC. To further expand upon our findings, multi-institutional and cooperative randomized group trials should be organized to further support and confirm survival and safety outcomes.

## ARTICLE HIGHLIGHTS

### **Research background**

Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is one of the last options in the treatment of advanced gastric cancer (GC) with peritoneal metastasis (PM); however, most national and international guidelines only recommend it to be performed within clinical trials. Despite this, CRS with HIPEC is a safe and effective method to treat advanced GC with PM, and recent studies have shown encouraging results with respect to increased patient survival.

### **Research motivation**

CRS and HIPEC are safe and effective therapeutic options for the treatment of advanced GC with PM. To investigate the optimal length of HIPEC procedure, it is important to provide a basis for further research. Improving the composition of HIPEC medications could further improve the outcomes of this modern multimodal therapy. It is expected that ongoing research regarding antibody and checkpoint inhibitor therapies will strongly influence not only perioperative therapy but also the therapeutic agents used during HIPEC itself.

### **Research objectives**

The aim of the study was to explore the effect of CRS and HIPEC in the treatment of advanced GC with PM and find parameters that could further improve patient survival.

### **Research methods**

We conducted a retrospective observational study with the inclusion of 73 GC patients with synchronous PM. Details of CRS + HIPEC, preoperative laboratory results, and pre-, peri-, and postoperative surgical details of the patients were recorded. Overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) were calculated.

### **Research results**

In line with recently published data, we found that CRS + HIPEC had a measurable impact on the survival of advanced GC patients without significantly elevating the rate of postoperative complications. The effects of longer HIPEC duration, higher white blood cell count, lower hemoglobin and serum total protein, and higher carcinoembryonic antigen levels with respect to the survival of patients were found.

### **Research conclusions**

In general agreement with previously published findings, we concluded that 90 min HIPEC treatment correlates with improvement in the OS and DSS of patients compared to that of 60 min HIPEC. Moreover, more complete cytoreduction also contributes to longer patient survival and better disease management.

### **Research perspectives**

The improvement of CRS and HIPEC with respect to the duration and composition of HIPEC therapeutic agents is a controversial research topic. The current report provides evidence from a single center retrospective study that could be implemented in future randomized multicenter studies.

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## FOOTNOTES

**Author contributions:** Steinhoff H, Acs M, Szasz AM and Piso P built the study design; Steinhoff H, Acs M, Blaj S and Sanchez-Velazquez P were involved in the collection of patient data; Herold Z performed the statistical analysis of data; Steinhoff H, Acs M, Herold Z, Herold M, Herzberg J, Strate T and Szasz AM interpreted the data; Steinhoff H, Blaj S, Acs M, Sanchez-Velazquez P and Piso P were involved in patient selection; Steinhoff H, Acs M and Herold Z prepared the draft of the manuscript; All authors were involved in the manuscript editing and reviewing; Dank M and Piso P supervised the study; all authors have read and agreed to the published version of the manuscript.

**Institutional review board statement:** The study was conducted according to the guidelines of the Declaration of Helsinki. Ethical review and approval were waived for this study due to the retrospective nature of the study. All the patients had agreed to data recording for the national HIPEC registry and to the use of their anonymized data for quality assurance and research purposes by written and verbal informed consent prior to surgery. Therefore, no institutional or further approval of a review board was necessary.

**Informed consent statement:** Informed consent was obtained from all subjects before cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS + HIPEC). All patients agreed to their data being recorded for the national HIPEC registry, administered by the German Society for General and Visceral Surgery.

**Conflict-of-interest statement:** All the authors report having no relevant conflicts of interest for this article.

**Data sharing statement:** The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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