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Retrospective Study

Prolonged HIPEC duration with 90 minutes cisplatin might increase overall survival in gastric cancer patients with peritoneal metastases

CRS + HIPEC in gastric cancer

Abstract

BACKGROUND

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

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 attended 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 somewhat 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-minutes (N = 59): 12.86 mo; 90-minutes (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 (HR = 0.2843; 95%CI: 0.1119 – 0.7222; P = 0.0082). Second, those patients who 1.) were treated with trastuzumab and/or had HER2 positivity (median survival: 12.68 *vs*. 24.02 mo), or 2.) had to undergo the procedure before 2016 (median survival: 12.68 *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

Steinhoff H, Acs M, Blaj S, Dank M, Herold M, Herold Z, Herzberg J, Sanchez-Velazquez P, Strate T, Szasz AM, Piso P. Prolonged HIPEC duration with 90 minutes cisplatin might increase overall survival in gastric cancer patients with peritoneal metastases. *World J Gastroenterol* 2023; In press

Core Tip: Advanced gastric cancer (GC) cases with peritoneal metastases are known for their poor survival rate. It has been previously reported that these patients highly benefit from cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) but the available data on this treatment is 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 cytoreductive surgery in the scope of multimodal treatment along with advanced perioperative chemotherapy and biologicals may serve as the best currently available therapy for these patients.

INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer with a worldwide incidence of 1,089,103 new cases and 768,793 deaths worldwide, respectively, based on the 2020 GLOBOCAN results[1,2]. The majority of the newly diagnosed cases are located in Asia, which occurrence is 6-fold higher than the one in Europe; and similar distribution can be observed in the mortality data[1]. In Germany, 15,322 new cases and 9,196 deaths have been reported for 2020[1]. GC is known for its morphological diversity[3] and the most commonly used classifications are from Nakamura *et al*.[4], Laurén[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 resected by the endoscope[7], the clinically staged T1 but lymph node-positive, and T2-T4a staged tumors of any lymph node statuses are treated by surgical resection and a peri- or postoperative chemotherapy[8]. Advanced GCs, which are resectable receive neoadjuvant chemotherapy followed by gastrectomy and adjuvant chemotherapy[9], but if not, then the treatment of choice is chemotherapy[8].

A recent analysis of 18,000 U.S. patients has shown that advanced GC with PM have a median survival of 8.6 mo if treated with chemotherapy only[10], while studies from the U.S.[11], China[12] and Germany[13] have shown that advanced GCs with peritoneal

carcinomatosis significantly benefit 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 with CRS and HIPEC in advanced GC with PM is scarce and the option of this multimodal therapy has hardly been included as a recommendation in any national or international guidelines. To date, the Japanese[17] and the U.S.[18] guidelines do not include CRS and HIPEC as therapeutic options, while in the French guidelines[19] their position in the treatment of advanced GC with PM is weak and to be defined in further randomized phase III studies. Same in the German national GC guideline, where an expert consensus-based recommendation calls for the implementation of CRS and HIPEC in clinical studies[8]. Whereas in the European Society for Medical Oncology (ESMO) guidelines for the treatment of gastric cancer CRS and HIPEC are described as safe procedures but with questionable oncological outcomes[20]. Accordingly, the aim of this retrospective study was to investigate the clinical outcome after this multimodal therapy in a tertiary center in patients with primary advanced GC and PM with the assumption that increased survival can be achieved in selected patients.

MATERIALS AND METHODS

Patients and study design

The HIPEC database of a single center was analyzed in a retrospective manner. A total of 73 patients who attended the Department of General and Visceral Surgery, Hospital Barmherzige Brüder, Regensburg, Germany between January 2011 and July 2021, and were diagnosed with primary GC and synchronous PM were included (**Figure 1**). All the patients gave written and verbal informed consent for data recording for the national HIPEC registry, administered by the German Society for General and Visceral Surgery (DGAV), and to 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 (inter)national multidisciplinary recommendations[8,20].

Details of CRS + HIPEC

Every single case was discussed by a multidisciplinary board of experts (oncologists, surgeons and anesthesiologists) before any treatment descision. Preoperatively, the extent of peritoneal dissemination was assessed using abdominal and chest CT scans, and the peritoneal carcinomatosis index (PCI)[21] was based on diagnostic laparoscopy, which were performed from T3 stage and/or CT morphological evidence of peritoneal carcinomatosis[22]. Prior surgery, all patients prehabilitated as per the "Enhanced recovery after surgery" (ERAS)-protocol. During CRS, the completeness of cytoreduction (CC) was scored as proposed by Sugarbaker[21]: no residual disease, residual nodules measuring less than 2.5 mm, between 2.5 mm and 2.5 cm and greater than 2.5 cm were defined as CC-0, CC-1, CC-2 and CC-3, respectively.

A closed HIPEC with a goal temperature of 42 °C with bidirectional HIPEC with cisplatin (75 mg/m^2) and doxorubicin (15 mg/m^2) was administered immediately after CRS for 60 or 90 min of 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-to-4000 mL isotonic saline solution with a mean flow rate of 1400–1800 mL/minute. 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 8th 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), and 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 docetaxel-

based first-line chemotherapy (FLOT protocol: 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; or DCF protocol: docetaxel, cisplatin, and 5-fluorouracil) at least. Chemotherapy was administered in accordance with the German guidelines on GC and 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 recorded in addition to the former.

Complete blood count, liver enzymes, lipase, creatinine, and tumor markers were determined at the Department of Laboratory Medicine, Microbiology and Hospital Hygiene, Hospital Barmherzige Brüder, Regensburg, Germany. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations were used to calculate the estimated glomerular filtration rate[26]. The Clavien–Dindo Classification[27] was used to assess postoperative adverse events. Although some recent publications suggest including all patient deaths within 90 days as post-procedure death[28,29], HIPEC related post-procedure deaths were defined as follows: 1.) It had to occur during our observation period at the intensive-care unit or at the surgical inpatient unit prior the discharge of the patients, or 2.) between discharge and adjuvant chemotherapy. If a patient 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 is 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*-values, 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, 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. 64, 13, and 1 cancer-related death events, tumor recurrence and death due to postoperative complications occurred, respectively. The complete list of pre-, peri- and postoperative clinicopathological characteristics of study participants can be read in **Supplementary Table 1**. In general, the average operating times (excluding the time for HIPEC) improved significantly over the years ($P = 0.0097$; **Figure 2**)

First, it was investigated whether any of the CRS + HIPEC-related or clinicopathological features have 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; $P = 0.0482$). Furthermore, tendentiously longer RFS was found in those patients who did not have to undergo peritonectomy of the pelvis (HR: 0.3382; 95%CI: 0.1099 – 1.0410; $P = 0.0588$). OS was significantly better in those patients without peritonectomy of the pelvis (HR: 0.5459; 95%CI: 0.3152 – 0.9454; $P = 0.0307$).

It was found, that longer HIPEC duration (60 *vs.* 90 min) was associated with more advantageous median survival times: 12.86 mo (95%CI: 11.01 – 17.31 mo) for the 60-minute and 27.30 mo (95%CI: 16.20 – NA mo) for the 90-minute cohorts (**Supplementary Table 1**). However, despite the clinically different median survival times, the survival of the two groups did not differ based on the results of the statistical models, neither for 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; $P = 0.1790$), nor for 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 ($P = 0.2799$). It has to be mentioned though, that the RFS survival curves of the three 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 could be observed in patients with higher RDW levels (HR: 1.2190; 95%CI: 1.0030 – 1.4810; $P = 0.0466$). Moreover, similarly to that observed in the cases of 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 further investigated in a multivariate setting as well (**Table 1**). DSS of patients were marginally affected by the duration of HIPEC [60 (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 obtained 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-minute-long HIPEC patient groups

Further comparison of patients by creating two groups according to the duration of HIPEC was also performed. 59 and 14 study participants were enrolled in the 60-minute and 90-minute groups, respectively. Except for the above-described median survival differences (12.86 mo *vs*. 27.30 mo, **Figure 3**), no difference could be justified in any of the clinicopathological characteristics between the two groups, if *P*-value adjustment was applied (**Supplementary Table 1**).

By investigating the results without *P*-value adjustment, the following clinically notable observations could be justified. The length of the CRS was somewhat shorter in the 90-minute group (299 ± 76 min *vs*. 264 ± 82 min, crude *P* = 0.0718). Peritonectomy of the omental bursa had to be performed only in the 60-minute group (30.5% *vs*. 0%; crude *P* = 0.0157), while lesser omentectomy was more common in the 90-minute group (33.9% *vs*. 71.4%; crude *P* = 0.0153). Fresh frozen plasma (FFP) was needed only once (7.1%) in the 90-minute groups, while in the 60-minute group FFP was administered for 32 (54.2%) patients (crude *P* = 0.0009). On average, the length of hospital stay was shorter in the 90-minute group (crude *P* = 0.0134); a more detailed examination of the data revealed that hospitalization longer than 20 days was more common in the 60-minute 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**) levels were observed more often in the 60-minute group (**Supplementary Table 1**).

To further investigate what could possibly be behind the clinically significant difference in median survival, the following adjustments to the groups were performed, in order to identify any possible confounding effects. First, propensity score-matched patient pairs (*N* = 14) were created, where patients were matched by age, sex, PCI score, CC

score, time spent in the intensive care unit after CRS + HIPEC, the duration of CRS, and the presence of lymph node metastasis (stage n = 0 *vs.* stage N ≥ 1). No differences – neither in adjusted nor in crude P-values – were found in any of the preoperative, perioperative, and postoperative parameters between the two, propensity score-matched groups. However, the previously just seemingly different survival between the two 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 mo) and 27.30 mo (95%CI: 16.20 – NA mo) median survivals for the 60-minute and 90-minute groups, respectively.

Furthermore, it was also investigated whether the results change, if those patients were removed from the original cohort who 1.) received trastuzumab and/or had immunohistochemically positive pathological results against human epidermal growth factor receptor 2 (HER2; N = 7), or 2.) had to undergo the procedure before 2016 (N = 44). For the first one, we could obtain the same results as the ones for the full cohort. 12.68 and 24.02 mo median survivals for the 60-minute and 90-minute groups, respectively, and no statistical difference was detected in the survival models (DSS: P = 0.1540; OS: P = 0.2040; **Supplementary Figure 2A**). Whereas the same significant difference was justified for the second modified population as the one detailed for the propensity-matched pairs. 12.52 and 27.30 mo median survival and a statistically significant difference were found favoring the 90-minute groups (HR: 0.4225; 95%CI: 0.1789 – 0.9975; P = 0.0493; **Supplementary Figure 2B**).

DISCUSSION

In the literature, there are only a few studies in the western world 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 non-existence of prospective clinical studies – except for two studies with small sample sizes[12,32] – on CRS and HIPEC makes all additional information and data essential. Moreover, randomized trial results are strongly necessary 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 besides FLOT-chemotherapy should be measured and is currently recruiting patients, are eagerly anticipated[33].

In the current retrospective study, we were able to show prolonged survival through multimodal therapy in primary GC patients with PM. The 27.3 mo median survival, which was observed, is in line with similar studies, *e.g.*, in the phase II trial of Badgwell *et al*. the median OS was 24.2 from the date of diagnosis and 16.1 mo from the date of CRS and HIPEC[11]. Similarly, a recent Spanish multicenter study has 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 to 21.2 mo[35]. The same can be applied to median PCI-scores: The median PCI was 2, 6, 6 and 8 in the studies of Badgwell[11], Bonnot[31], Manzanedo[34], and Rau[35], respectively, and the median PCI of 3 in the current study can be best compared to the first. In addition to the above, in the study by Rau *et al*.[35], 18, 12, and 5 mo OS have been found for the three patient groups having a PCI score of 0 – 6, 7 – 15, and 16 – 39, respectively, showing that significantly better outcomes are associated with higher completeness of cytoreduction. In our study 93.2% of our 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 justify the statistically significant benefit of reduced PCI scores, our results were in line with the previously described observations: patients with higher PCI scores had tendentiously shorter survival. Furthermore, an interesting observation emerged during the analysis of our data that in the course of time and an increasing number of cases, the duration of surgery to reach complete cytoreduction has become significantly shorter. These findings match with the results of a study outlining the technical aspects and learning curve of CRS/HIPEC of Vining *et al.*, where the authors describe a steep learning curve and a relation of the completeness of cytoreduction and the surgeons' expertise[36]. This fact underlines the treatment of advanced GC with PM should be performed in specialized centers with appropriate

expertise. Latest studies have also found that sodium thiosulfate can prevent renal impairment following HIPEC[37,38]. Although in the current population sodium thiosulfate was not used, since January 2022 have started to use it routinely in our center.

There is still no consensus about the ideal duration of HIPEC. In the current analysis, the median survival time was 27.30 mo in the 90-minute group, which was significantly longer than that of the 60-minutes group (12.86 mo). At the time of data appearance/publication of the van Driel[23] study for ovarian cancer, and later the PRODIGE-7 trial[39] for HIPEC in colorectal cancer, to some extent of arbitrary, our institutional HIPEC-protocol was changed in favor of the 90-minutes-long HIPEC perfusion. Even making the two study cohorts completely homogeneous could not change this significant difference. The advantages of prolonged duration of HIPEC have been recently described for primary peritoneal carcinoma, primary advanced epithelial carcinoma, and ovarian or fallopian tube by our group[40,41]. The longer duration of HIPEC does not affect adversely the perioperative morbidity and mortality and a potential survival benefit could be reached by the prolonged application of HIPEC[40,41], however, a recent study have 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[42]. These and the current findings suggest that a prolonged time perfusion of the therapeutical fluid in the peritoneal cavity may be more advantageous after complete cytoreduction, however, as the study of Roth *et al.*[42] have shown, gathering additional information is essential.

Another reason behind the better survival of patients with longer HIPEC duration might be the enhanced cytotoxicity and anti-tumor effects of chemotherapeutic drugs in hyperthermia, and this longer exposure allows them to exert their beneficial effects with greater efficiency[43]. The effects of cytoreductive surgery with macroscopic complete tumor reduction followed by HIPEC in addition to an effective preoperative (neoadjuvant) chemotherapy plays an important role to extend the time of survival of patients with advanced GC with PM as recently shown in the CYTO-CHIP study[31]. In

the neoadjuvant setting, since 2016, the most used combination of chemotherapy for advanced GC with PM is the FLOT-protocol, however, due to an ethnic-related difference in the metabolization of cytochrome P450 family 2 subfamily A member 6[44], in Asian countries, the S-1 regime (tegafur, gimeracil, and oteracil) is the standard adjuvant treatment[45,46]. The latest advancements in preoperative chemotherapy with[47] or without[25] biological agents can significantly extend the survival of GC patients. In the last years, it has also been found with a wide acceptance that the 15-20% of GC cases that overexpresses HER2 should be treated with monoclonal antibodies like trastuzumab in a neoadjuvant setting due to their positive influence on patient survival and fewer side effects than traditional chemotherapies[48]. In the current study, the individual responses to pre- and/or postoperative chemotherapy were not known for most study individuals, which was one of the biasing factors affecting patient survival in our study.

The SRC differentiation is described as an aggressively growing tumor with a poorer prognosis than non-SRC carcinomas of the stomach[49]. In contrast, we found, that the type of histology did not take effect either on DSS, OS, or RFS. A similar finding has been 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[50]. Moreover, we could make the observation that if the procedure of peritonectomy of the pelvis during CRS is not necessary, the OS of the patient improved. We hypothesize that the extent of the tumor manifestation may have a bigger influence on patient survival than its histopathological differentiation. We assume that the improvement in patient survival may also be based rather on the advanced extent of the malignant disease than on the biology of the tumor, moreover, the learning curve in the experience of the surgical team might had also introduce some additional bias.

It was also investigated whether any of the preoperative laboratory results could have had the ability to predict patient survival. A strong connection was found between the survival of patients and white blood cell count, hemoglobin, CEA, and serum total

protein. These findings match with literature data of non-HIPEC-treated GC patients[51-56]. Furthermore, results of a recent German multi-center study[57] and WHO's urgent call[58] to implement blood management in surgical patients have shown that preoperative anemia is a serious threat to patient survival. Preoperative iron substitution in cases of preoperative anemia is also an important part of the recently published enhanced recovery after surgery (ERAS) protocol for CRS and HIPEC[59], and great emphasis should be placed on iron substitution and normalization of hemoglobin prior to surgery[59].

Limitations

The current study had a few limitations, including the small sample size, the retrospective nature of the study, data were available from a single center only, and the heterogeneity of the data. During the time of evaluation, the protocols concerning the preoperative chemotherapy treatment did significantly change and the surgeons' expertise grew. Furthermore, in this small cohort of patients with GC and PM there was only very limited data on post-HIPEC treatment. Our follow-up data could only differ between alive and dead patients and the recurrence of the tumor. Efforts were made to collect any post-HIPEC data of the patients, however, we could not collect these in a timely manner, as patients' routine oncological treatments were performed in another hospitals. Moreover, the lack of control for patients with chemotherapy-only treatments can be also mentioned as a limiting factor.

CONCLUSION

In summary, a single-center retrospective was conducted 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-minutes has a positive impact on disease-specific survival in comparison with CRS followed by 60-minutes of HIPEC. It has to be noted however, that the learning curve effect might introduce some bias regarding this former observation. Furthermore, the prehabilitation

of patients for surgery based on preoperative laboratory in tight adherence to current ERAS protocol might optimize the positive effect of CRS and HIPEC. To further assess the results obtained here, multi-institutional and cooperative group trials in a randomized setting 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 (inter)national guidelines only recommend it to be performed within clinical trials. It has to be noted that there is a proven and secure method to treat advanced GC with PM, and recent study results show encouraging results concerning the extension of patients' survival.

Research motivation

CRS and HIPEC are safe and secure therapeutical options for treating advanced GC with PM. To find an answer on the optimal length of HIPEC-procedure, it is important to define a comparable basis for further research. Improving the composition of HIPEC medications could further improve the outcomes of modern multimodal therapy. It is expected that the ongoing progress on the research of antibodies and checkpoint inhibitor therapies will strongly influence not only perioperative therapy but also the therapeutic agents used during HIPEC itself.

4

Research objectives

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

Research methods

A retrospective observational study was conducted 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 (OS), disease-specific (DSS), and recurrence-free survival 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 significant effect of longer HIPEC duration, higher white blood cell counts, lower hemoglobin and serum total protein, and higher carcinoembryonic antigen levels over the survival of patients was found.

Research conclusions

In addition to previous findings in the field, we concluded that 90-minute HIPEC treatment promises an improvement in the OS and DSS of patients compared to that of 60-minute HIPEC. Moreover, higher completeness of the cytoreduction can also contribute to longer patient survival and better disease management.

Research perspectives

The improvement of CRS and HIPEC in view of the duration and composition of HIPEC-therapeutic agents is a controversial research topic. The current study provided evidence from a single center, which could be implemented in future randomized multicenter studies.

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