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Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy and intraoperative radiation therapy in the management of gastric cancer: a 10-year single center experience

Marwan M. Alaswad[1*], Tarek Z. Arabi[1], Asma S. Alshahrani[2,3], Belal N. Sabbah[1], Heba W. Jaamour[1], Abdullah A. AlOtry[1], Tariq W. Saleh[1], Ziad H. Alhosainy[1], Fadwa H. Elkordy[1], Aya I. Elnegali[1], Mohamed H. Tlayjeh[1], Firas E. Kseibi[1], Ayman Z. Azzam[4,5] and Tarek M. Amin[4]

Abstract

Background The rationale behind the use of HIPEC involves targeted elimination of microscopic peritoneal metastasis, a common route for GCa dissemination, thereby improving the overall survival and reducing recurrences. Moreover, the reasoning behind the use of IORT is enhanced loco-regional control and, therefore, reducing recurrence rates.

Methods From February 2013 to June 2023, all GCa patients who underwent HIPEC plus IORT during surgery were included in this study. Median overall survival (OS) and disease-free (DFS) survival were used to evaluate the efficacy of this treatment strategy amongst GCa patients, along with the rate of occurrence and severity of post-operative complications associated with this treatment strategy.

Results The median OS and DFS were 63 and 87 months, respectively. More than one-third of the patients in our cohort did not develop any post-operative complications. In patients who developed post-operative complications, the median number of post-operative complications was 1 (IQR 1–2). Most encountered complications were Clavien-Dindo (CD) grade II complications (33.33%) and no in-hospital mortality was observed.

Conclusions This complex, multimodal treatment strategy results in a significantly prolonged OS and DFS when compared to other treatment strategies for gastric cancer patients, with no added morbidity or mortality.

Keywords Gastric cancer, Hyperthermic intraperitoneal chemotherapy, Intraoperative radiation therapy, Peritoneal carcinomatosis, Overall survival, Disease free survival

*Correspondence:
Marwan M. Alaswad
Marwanalaswad21@outlook.com
[1]College of Medicine, Alfaisal University, Al Zahrawai Street, Riyadh, Saudi Arabia
[2]Department of Population Health, King Abdullah International Medical Research Center, Riyadh, Saudi Arabia
[3]King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
[4]Department of Surgical Oncology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
[5]Department of General Surgery, Faculty of Medicine, Alexandria University, Alexandria, Egypt

Background

Gastric cancer (GCa), known for its aggressive nature, stands as the third most lethal cancer globally [1]. Its grim prognosis is often linked to the common occurrence of peritoneal metastasis (PM), posing significant treatment challenges. Despite advancements, the standard treatment guidelines for GCa with PM predominantly leans towards palliative care, underscoring the need for innovative therapeutic approaches in managing this malignancy [1]. Hyperthermic intraperitoneal chemotherapy (HIPEC) and intraoperative radiation therapy (IORT) have garnered attention for their potential to address the limitations of conventional treatments [2]. Studies on GCa have explored the use of HIPEC and IORT, often revealing encouraging outcomes in treatment efficacy [3]. However, outcomes from using HIPEC and IORT in GCa have shown variability. For instance, a meta-analysis indicated that while IORT did not significantly impact overall survival rates, it did enhance loco-regional control in patients at specific stages of the disease [4]. The rationale behind HIPEC involves the targeted elimination of microscopic peritoneal metastases, a common route of GCa dissemination, thereby improving survival outcomes and reducing recurrence rates [1, 5]. The application of HIPEC in GCa spans various clinical scenarios, from adjunctive therapy post-curative resection in high-risk, non-metastatic cases to palliative care in metastatic settings, aiming to control symptoms like ascites [2].

Parallelly, IORT presents an innovative approach to maximize local control while sparing surrounding healthy tissues, especially pertinent in the intricate anatomical confines where gastric tumors reside [6]. This modality's integration into GCa treatment protocols underscores the shift towards more personalized, site-specific cancer care. Despite promising results from randomized control trials and meta-analyses underscoring HIPEC's efficacy, its adoption in clinical practice is nuanced, influenced by factors such as disease stage, patient health status, and the risk-benefit ratio of potential postoperative complications [7]. Similarly, the strategic application of IORT requires careful patient selection and optimization of treatment parameters to enhance therapeutic efficacy while minimizing adverse effects [6].

In our study, we analyzed the outcomes of 81 GCa patients with peritoneal carcinomatosis (PC) or are at high risk of developing PC treated with cytoreductive surgery (CRS) in combination with HIPEC and IORT, focusing on their overall survival rates among other key metrics. This in-depth investigation sheds light on the potential benefits and challenges associated with the usage of HIPEC and IORT in GCa, contributing valuable insights to the ongoing discourse on optimizing GCa management.

Methods and materials

Design and inclusion criteria

This study was approved by the Institutional Review Board (IRB) at our institution (RAC# 2241047). The present study is a single center, retrospective study that was conducted at a tertiary care center in Riyadh, Saudi Arabia. Data was obtained retrospectively through the patient`s electronic medical records. From February 2013 to June 2023, all patients with a diagnosis of GCa were included in the study. All operations were performed with a curative intent and by the same surgeon. The primary endpoints of this study were overall survival (OS), disease-free survival (DFS) and overall morbidity and mortality associated with this treatment strategy.

The inclusion criteria for this study specified any adult aged 18 years and older diagnosed with GCa with peritoneal carcinomatosis or at high risk of developing peritoneal carcinomatosis and were treated with cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy (HIPEC) and intraoperative radiation therapy (IORT). Patients diagnosed with squamous cell carcinoma extending to the gastroesophageal junction, esophageal cancer, patients who were treated with a treatment strategy than the above-mentioned strategy, and patients not treated with a curative intent were excluded from this study.

Data collection

The following parameters were retrieved and included in the analysis: age, date of birth, gender, body mass index (BMI), comorbidities, date of diagnosis, pre-operative chemotherapy, date of surgery, type of surgery performed, peritoneal carcinomatosis index (pPCI), cytoreduction of completeness (CC) score, intraoperative complications, chemotherapeutic agent and dose used in HIPEC, adjusted HIPEC chemotherapy dose, number of IORT applications, dose of IORT received (measured in Gray (Gy) units), post-operative complications and their treatment, length of post-operative hospital stay, post-operative chemotherapy, histologic tumor type, tumor location in the stomach, signet ring sign, pathologic TNM staging, resection margin status, perineural invasion, lymphovascular invasion, Her-2 neu expression, recurrence, recurrence date, date of last follow-up, status of the patient at last follow-up, and date of death.

Pre-operative work-up and surgery

Pre-operative work-up was uniform for all patients and included a full history and physical examination, complete blood count, liver function tests and coagulation profile, renal function tests and electrolytes, bone profile, tumor markers, CT and PET scans of the chest, abdomen, and pelvis for tumor localization and staging.

At the start of the operation, a midline incision extending from the xiphoid process to the pubic symphysis was performed to allow for maximal exploration. Pathologic peritoneal carcinomatosis (pPCI) was used to evaluate the extent of peritoneal carcinomatosis (PC) [8]. Following the completion of the cytoreduction phase, assessment of residual tumors was determined intraoperatively using the completeness of cytoreduction (CC) scores, graded from CC-0 to CC3. CC-0 means no residual disease was left behind following cytoreduction, CC-1 indicates residual tumor volume of less than 2.5 mm, CC-2 indicates residual volume between 2.5 mm and 2.5 cm, and CC-3 indicates residual tumor volume of more than 2.5 cm in diameter [9].

IORT

Following the completion of the surgical resection phase, IORT was performed using the Mobetron electron beam machine. Three different energies are available including 6 MeV, 9 MeV, and 12 MeV, and selection is made based on the target thickness. Cones vary from 3 to 10 cm, and three different angled applicators are available: 0, 15, and 30 degrees. Applicator diameter was chosen based on the size of the treatment area, while taking into consideration the size of the pre-operative tumor volume. Two different boluses are available, 0.5 cm and 1 cm, and are used to increase the surface dose. The IORT dose given is measured in Gray (Gy) units and four different doses were used based on the tumor burden after surgical resection, depth of target volume, degree of previous irradiation, and the location of dose limiting normal structures: 10, 12, 12.5, and 15 Gy. In patients with no obvious residual disease after surgical resection, a dose ranging between 10 and 12 Gy was given; however, in patients with minimal residual disease following surgical resection, a dose of 12 to 15 Gy was given. Patients who had gross, macroscopic residual disease following surgical resection were given a dose ranging between 15 and 20 Gy. Lead shields were used to shield organs not affected by the cancer in efforts of minimizing radiation exposure.

HIPEC

Following the completion of IORT, HIPEC was performed. Prior to HIPEC, we copiously lavaged the abdominopelvic cavity with large amounts of normal saline. HIPEC was performed using the open abdomen technique. Three inflow and two outflow drains were placed accordingly, and all of the drains were connected to an extracorporeal closed sterile circuit perfusion machine. The total amount of circulating perfusate was 1.5 L/m2 circulating for 60 to 90 min depending on the agent used in HIPEC. All patients received the approved chemotherapeutic agents for GCa at our institution. Continuous monitoring of the intraperitoneal temperature was performed using thermal probes to ensure that the temperature range remains at a range of 41-42.2 degrees Celsius. During the HIPEC phase, continuous, intraoperative monitoring of the hemodynamic and cardiopulmonary parameters was performed. After completion of the HIPEC phase we again copiously lavaged the abdominopelvic cavity with normal saline, followed by removal of the HIPEC drains, and insertion of Jackson-Pratt as indicated by the Enhanced Recovery After Surgery Society (ERAS) recommendations [10].

The most common chemotherapeutic regimen used in HIPEC was cisplatin 100 mg/m2 + mitomycin C 30 mg/m2 circulating for 60 min. Dose reduction by 50% for cisplatin and 30% for mitomycin C in patients aged 65 years and older, renal impairment defined as GFR < 45 mL/min, and in patients who received chemotherapy within 1 month before the HIPEC. The second regimen used was bidirectional HIPEC using IV ifosfamide 1300 mg/m2 in addition to cisplatin 50 mg/m2 and doxorubicin 15 mg/m2 intraperitoneal circulating for 90 min. Dose reduction for cisplatin by 50% was done in patients aged 65 years and older and in patients with GFR < 60 mL/min, while dose reduction by 50% for doxorubicin was done in patients with bilirubin levels > 22 umol/L or AST/ALT levels > 60 units/L. The third regimen used was melphalan 60 mg/m2 circulating for 60 min and was only used in one patient due to cisplatin allergy.

Follow-up

Following completion of the procedure, all patients were moved to the intensive care unit for the first 3 days and then transferred to the ward for recovery. After the recovery plan is complete, patients were discharged home with instructions for follow-up. Post-operatively, all patients were followed up in the clinic with laboratory and radiologic work-up to detect recurrences as early as possible. Our follow-up protocol consists of a follow-up appointment every 3 months for the first two years following treatment, followed by a follow-up appointment every 6 months for the third and fourth year, and a single follow-up appointment annually from fifth year and onwards. Complete biochemical workup, including tumor markers, and a CT scan were performed for all patients during follow-up appointments. PET and MRI scans were only performed when indicated.

Statistical analysis

Descriptive statistics were computed using median and interquartile ranges (IQR) for continuous variables. Frequencies and percentages for categorical variables. The Kaplan-Meier method and log-rank test were used to estimate and compare OS and DFS between pPCI and CC groups. The Cox proportional hazards regression model was used to estimate HRs and 95% CIs in

Table 1 Patient characteristics and peri-operative details

Parameter	Number of patients	Percentage (%)
Age at diagnosis in years, median (IQR)	57 (44–67)	
Gender		
Female	27	(33.33)
Male	54	(66.67)
BMI		
< 18.5	6	(7.41)
18.5–29.9	62	(76.54)
≥ 30	13	(16.05)
Comorbidities		
No	45	(55.56)
Yes	36	(44.44)
Number of Comorbidities		
No comorbidities	45	(55.56)
1–2	23	(28.40)
> 2	13	(16.05)
Renal impairment		
No	78	(96.30)
Yes	3	(3.70)
Neoadjuvant (Pre-operative chemotherapy)		
No	5	(6.17)
Yes	76	(93.83)
Adjuvant (Post-operative chemotherapy)		
No	41	(50.62)
Yes	40	(49.38)
Length of hospital stay in days, median (IQR)	21 (16–35)	

Note: IQR: Interquartile range; BMI: Body mass index

univariable model to identify independent prognostic factors for OS and DFS among the variables included in the analyses (age at diagnosis, gender, BMI, Comorbidities, pre-post operative chemotherapy, pPCI, CC, post-operative complications, length of hospital stay, tumor type, tumor location, surgery type, signet sign, staging, resection margin, lymphovascular invasion, perineural invasion, Her 2 neu expression and Clavien-Dindo ≥ III). For the Clavien-Dindo grade, if a patient had multiple complications, the highest Clavien-Dindo grade was reported. Overall survival (OS) was calculated from the date of surgery to the date of death or last follow up and Disease-free survival (DFS) was calculated from the date of surgery to the date of documented recurrence, death, or last follow up. Local recurrence was considered in patients who achieved CC 0 and 1, while CC 2 and 3 patients already had remnant disease following surgery, and therefore were considered as disease progression. Hence, the DFS calculation was limited to patients with CC0 and CC1. Variables with $P < 0.1$ on univariable analysis were used in a parsimonious multivariable model using stepwise backward elimination with an entry criterion of $P < 0.1$. All tests were 2-sided, and a P-value of ≤ 0.05 was considered statistically significant. All analyses were performed using StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.

Results

Patient characteristics

A total of 81 patients met the inclusion criteria and were included in this study. The median age at diagnosis was 57 years (IQR 44–67); 66.6% ($n = 54$) were males and 33.3% ($n = 27$) were females. Only 7.41% ($n = 6$) were underweight. Less than half of the study population presented with comorbidities ($n = 36$), amongst which 3 patients had renal impairment. Median length of hospital stay was 21 days (IQR 16–35). Majority of the cohort 93.83% ($n = 76$) received pre-operative chemotherapy, while only 40 patients received post-operative chemotherapy. Patient characteristics and perioperative details can be found summarized in Table 1.

Pathology and staging

Pathologic TNM staging was done in accordance with the 8th edition of the American Joint Committee on Cancer (AJCC) staging manual [11]. The most common tumor histology was diffuse adenocarcinoma (43.21%), followed by intestinal adenocarcinoma (39.51%). Antrum was the most common tumor location (30.86%), followed by gastroesophageal junction (24.69%) and pylorus (17.28%). Signet-ring sign was present in 48.15% of the cohort.

The most common pathologic T stage was T3 (38.27%), followed by T4a (25.93), and T2 (20.99%). N0 was the most common pathologic N stage (43.21%), followed by N1 (19.75%), and N3b (14.81%). Metastasis (M1) was seen in 38.27% of the cohort. Tumors were most commonly stage 4 (38.30%), followed by stage 1b (14.81%), and stage 2a (13.58%). Four patients (4.94%) had complete tumor regression post chemotherapy (T0N0M0) and hence were not staged.

Resection margin was negative in 69 patients (85.19%). Lymphovascular and perineural invasion were present in 32 (39.51%) and 38 (46.91%) patients, respectively. Her-2 neu status was positive in only 19.75% of this cohort. Pathologic characteristics can be found summarized in Table 2.

Treatment and post-operative complications

The majority of the cohort (87.65%) underwent radical total gastrectomy with D2 lymphadenectomy, while the rest (12.35%) underwent subtotal esophagectomy and radical total gastrectomy with D2 lymphadenectomy and colon interposition due to the extensive nature of their disease. Median pPCI was 4 (IQR 2–7), with 59 patients having pPCI of ≤ 6, while 22 patients had pPCI of > 6. A pPCI of 0 was observed in 4 patients, and this is due to

Table 2 Pathologic characteristics observed in our cohort

Parameter	Number of patients	Percentage (%)
Tumor type		
Intestinal	32	(39.51)
Adenocarcinoma NOS	4	(4.94)
Diffuse	35	(43.21)
Mixed	10	(12.35)
Tumor location		
Fundus	3	(3.70)
GEJ	20	(24.69)
Antrum	25	(30.86)
Body	6	(7.41)
Cardia	6	(7.41)
Overlapping location	7	(8.64)
Pylorus	14	(17.28)
Signet sign		
Absent	42	(51.85)
Present	39	(48.15)
Pathologic T stage		
T0	4	(4.94)
T1a	2	(2.47)
T1b	2	(2.47)
T2	17	(20.99)
T3	31	(38.27)
T4a	21	(25.93)
T4b	4	(4.94)
Pathologic N stage		
N0	35	(43.21)
N1	16	(19.75)
N2	11	(13.58)
N3a	7	(8.64)
N3b	12	(14.81)
Pathologic M stage		
M0	50	(61.73)
M1	31	(38.27)
Staging		
1a	4	(4.94)
1b	12	(14.81)
2a	11	(13.58)
2b	4	(4.94)
3a	7	(8.63)
3b	2	(2.46)
3c	6	(7.40)
4	31	(38.30)
Complete tumor regression post-chemotherapy	4	(4.94)
Resection Margin		
Negative	69	(85.19)
Positive	12	(14.81)
Lymphovascular invasion		
Absent	49	(60.49)
Present	32	(39.51)
Perineural invasion		
Absent	43	(53.09)
Present	38	(46.91)
Her 2 neu expression		

Table 2 (continued)

Parameter	Number of patients	Percentage (%)
Negative	65	(80.25)
positive	16	(19.75)

Note: NOS: Not otherwise specified; GEJ: Gastroesophageal junction

one of the following three reasons: acellular mucin, adhesions, or tumor regression due to complete response to chemotherapy. A CC score of 0 was observed in 86.42% of the cohort, CC score of 1 was observed in 8.64%, CC score of 2 is 3.70%, and CC score of 3 in 1.23% of this cohort. No intraoperative complications or mortality was observed in this cohort.

The most frequent chemotherapeutic regimen used in HIPEC in this cohort was cisplatin 100 mg/m2 + mitomycin C 30 mg/m2 in 50 patients (61.73%), followed by cisplatin 100 mg/m2 (50% dose reduction) + mitomycin C 30 mg/m2 (30% dosed reduction) in 26 patients (32.1%). One patient (1.23%) received Melphalan 60 mg/m2 due to platinum drug allergy. Among 28 patients who had their HIPEC dose reduced, the most common reason for dose reduction was old age ($n = 22$). A total of 83 applications of IORT was performed, with the majority of the cohort having received a single application of IORT (97.53%), while only 2 patients (2.47%) received a second IORT application due to extensive disease. Most common dose of IORT given was 12 Gy units (43.38%), followed by 10 and 12.5 Gy units (20.48% each), and 15 Gy units (15.66%).

Post-operative complications occurred in more than half of the cohort (64.20%) with more than one complication occurring in 25 patients (48.07%). The median number of post-operative complications was 1 (IQR 1–2). Most encountered complications were CD grade II complications (33.33%), followed by CD grade IIIa (9.88%). The remainder of the cohort (35.80%) did not develop post-operative complications and had a smooth recovery course postoperatively. No in-hospital mortality (CD grade V) was observed in the study population. Grading of post-operative complications was performed based on the Clavien-Dindo classification of post-operative complications [12]. Treatment details and post-operative complications can be found summarized in Table 3.

Overall survival and disease-free survival

At the end of the study, 33 were dead (40.74%), and 11 patients were lost to follow-up (13.58%). The median OS was 63 months (IQR 35.3 months to not reported) and the median DFS was 87 months (IQR 30.4 months to not reported) (Figs. 1A and 2A). Median follow-up time was 17 months (IQR 7.16– 43.03). The median OS for patients with CC 0–1 was 73 months vs. 3.96 months for those with CC 2–3 ($p < 0.001$) (Fig. 1B). For DFS, the median survival was 87.3 for CC0 vs. 9 months for CC1 ($P < 0.01$) (Fig. 2B). Since more than half of the patients are still alive, the median OS of patients with pPCI ≤ 6 could not be reached on Kaplan–Meier analysis. Instead, the 25th percentile was calculated at 29.6 months vs. 4.8 months for patients with pPCI > 6 ($p < 0.001$) (Fig. 1C). The median DFS for patients with pPCI ≤ 6 was not reached either since more than half of the patients did not have disease recurrence. Therefore, the 25th percentile was calculated instead and was 30.4 months after the surgery compared to 5.7 months for patients with pPCI > 6 ($p < 0.001$) (Fig. 2C).

In the univariable Cox regression analysis, worse OS was associated with pPCI > 6, occurrence of post-operative complications, longer hospital stay, subtotal esophagectomy and total gastrectomy with D2 lymphadenectomy, stage 4 tumor, pathologic N2-N3a/b stage, pathologic M1 stage, positive resection margin, lymphovascular invasion, perineural invasion, and Clavien-Dindo grade ≥ III. Furthermore, the risk of death was lower in patients with tumor located in the antrum. On multivariable analysis, pPCI > 6, CC 2–3, perineural invasion, and Clavien-Dindo ≥ III were associated with worse OS. While patients having a tumor located in the antrum still in lower risk of death (Table 4).

In the univariable for DFS, there was a trend toward a higher risk of death in patients with pPCI > 6, CC 1, stage 4 tumor, pathologic N2-N3a/b stage, pathologic M1 stage, and lymphovascular invasion. On multivariable analysis, only pPCI > 6 was associated with 4-fold increase in the risk of having worse DFS (Table 5).

Discussion

In this study, we reviewed the clinical outcomes of patients with GCa who received HIPEC with IORT during cytoreductive surgery (CRS) at our center. The median OS was 63 months, and median DFS was 87 months. More than half of patients suffered from post-operative complications. We present a novel approach for the treatment of GCa, which may prolong OS and DFS.

GCa patients with peritoneal carcinomatosis have an exceedingly poor survival time, ranging from 3 to 9 months [13]. HIPEC has emerged as a strategy to directly tackle peritoneal carcinomatosis in these patients. In a meta-analysis of randomized, controlled trials by Deng et al., HIPEC significantly prolonged OS after 5 years of follow-up in GCa patients with/without peritoneal carcinomatosis [7]. In the recent phase 3 GASTRIPEC-1 trial, GCa patients with histologically confirmed peritoneal

Table 3 Treatment characteristics and post-operative complications observed in our cohort

Parameter	Number of patients	Percentage
Surgery type		
Radical total gastrectomy with D2 lymphadenectomy	71	(87.65)
Subtotal esophagectomy and total gastrectomy with D2 lymphadenectomy and colon interposition	10	(12.35)
Chemotherapeutic regimen used in HIPEC		
Cisplatin 100 mg/m2 (50% dose reduction) + Mitomycin C 30% mg/m2 (30% dosed reduction)	26	(32.10)
Cisplatin 100 mg/m2 + Mitomycin C 30% mg/m2	50	(61.73)
Cisplatin 50 mg/m2 + Doxorubicin 15 mg/m2	2	(2.47)
Cisplatin 50 mg/m2 + Doxorubicin 15 mg/m2 reduced dose by 50%	2	(2.47)
Melphalan 60 mg/m2 (Allergic to cisplatin)	1	(1.23)
Adjusted Dose		
No	53	(65.43)
Yes	28	(34.57)
Reasons for adjustment		
Renal impairment	3	(10.71)
Myelosuppression	3	(10.71)
Old age	22	(78.57)
Number of applications		
1	79	(97.53)
2	2	(2.47)
Dose of IORT received (if received 1 application)		
10 Gy	16	(19.75)
12 Gy	36	(44.44)
12.5 Gy	17	(20.99)
15 Gy	12	(14.81)
Dose of IORT received (second application)		
10 Gy	1	(50)
15 Gy	1	(50)
pPCI, median (IQR)	4(2–7)	
pPCI		
≤ 6	59	(72.84)
> 6	22	(27.16)
CC score		
0	70	(86.42)
1	10	(8.64)
2	3	(3.70)
3	1	(1.23)
Postoperative complications		
No	29	(35.80)
Yes	52	(64.20)
Total number of Complications	105	
Number of complications, median (IQR)	1(1–2)	
Clavien-Dindo grades		
No complications	29	(35.80)
Grade I	6	(7.41)
Grade II	27	(33.33)
Grade IIIa	8	(9.88)
Grade IIIb	6	(7.41)
Grade IVa	5	(6.17)
Clavien-Dindo grade ≥ III		
No	62	(76.54)
Yes	19	(23.46)

Note: Gy: Gray, unit used to measure dose of IORT delivered; IQR: Interquartile range; pPCI: Pathologic peritoneal carcinomatosis index; CC: Cytoreduction of completeness score

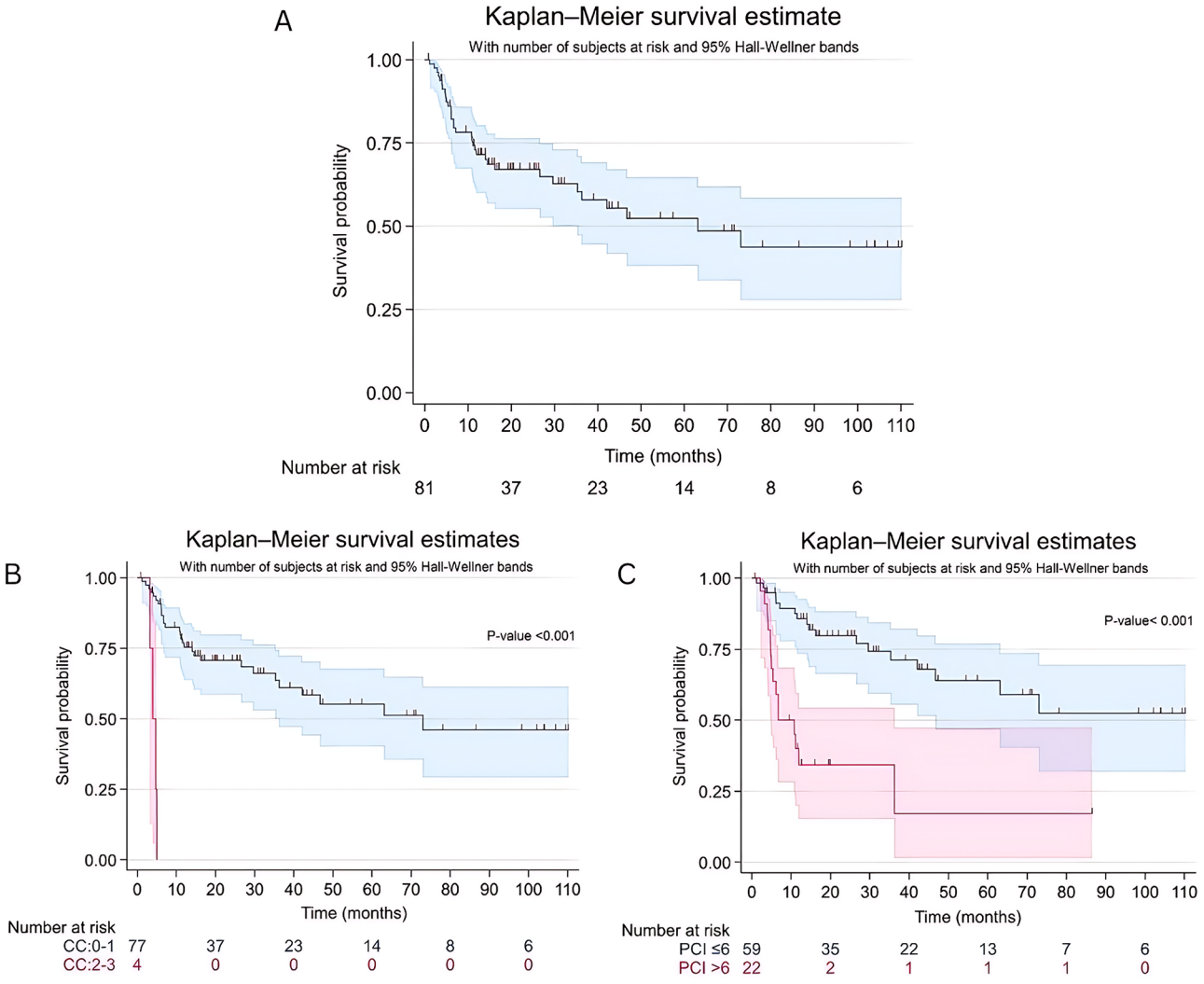

Fig. 1 Kaplan Meier estimates of overall survival. Figure 1**A:** Kaplan-Meier estimate of overall survival of all patients included in this cohort; Fig. 1**B:** Kaplan-Meier estimate of overall survival of all patients included in this cohort stratified by cytoreduction of completeness (CC) scores; Fig. 1**C:** Kaplan-Meier estimate of overall survival of all patients included in this cohort stratified by pathologic peritoneal carcinomatosis index (PCI)

metastasis were randomized to CRS alone or CRS with HIPEC [14]. Although the trial found no difference in trial, PFS and metastasis-free survival increased significantly (from 3.5 to 7.1 months and 9.2 to 10.2 months, respectively). Prophylactic HIPEC increases 1-, 3-, and 5-year survival and reduces overall and peritoneal recurrence rates [15]. However, there have yet to be any clinical trials determining its efficacy as a prophylactic measure. Nevertheless, the randomized, phase 3 GOETH trial aims to compare prophylactic surgery plus HIPEC with standard surgery for patients at high-risk for peritoneal carcinomatosis and is currently enrolling patients [16].

The majority of our patients received a combination of mitomycin C and cisplatin. This combination has been tested successfully in several trials [14]. However, some patients in our sample received melphalan due to allergic reactions and cisplatin with doxorubicin due to mitomycin C allergy. Variations in HIPEC protocol have not been extensively studied. Reutovich et al. found that docetaxel with cisplatin increases progression-free and dissemination-free survival [17]. Studies are needed to compare between HIPEC combinations, as some treatment choices have been found to be less toxic in colorectal cancer patients [18].

Data reporting on the utility of IORT in GCa are limited. Besides direct cytotoxic effects, IORT alters the tumor microenvironment and blunts angiogenesis, thereby hindering further tumor growth [19]. The incorporation of IORT into surgery prolongs OS in stage 3 GCa patients and significantly improves locoregional control [20]. Furthermore, studies have found no increase in surgical complications when using IORT for GCa [21]. It is worth noting, however, that most reports utilize only one dose of IORT [21], while two patients received a

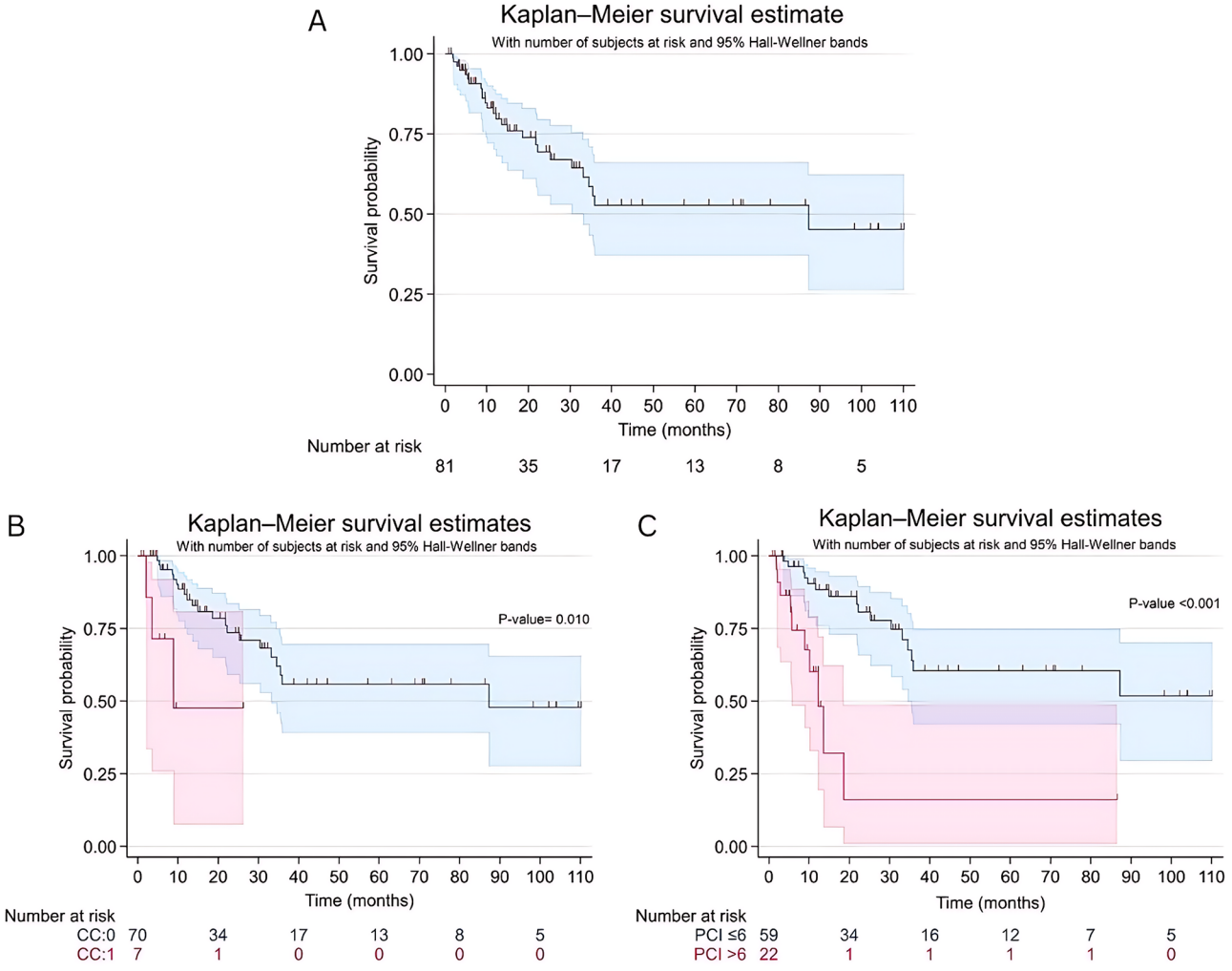

Fig. 2 Kaplan Meier estimates of disease-free survival. Figure 2**A:** Kaplan-Meier estimate of disease free-survival of all patients included in this cohort; Fig. 2**B:** Kaplan-Meier estimate of disease free-survival of all patients included in this cohort stratified by cytoreduction of completeness (CC) scores; Fig. 2**C:** Kaplan-Meier estimate of disease free-survival of all patients included in this cohort stratified by pathologic peritoneal carcinomatosis index (PCI)

Table 4 Cox proportional regression analysis for predictors of disease-free survival

Parameter	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Gender		0.957		
Female	Ref			
Male	0.98(0.47–2.01)			
Age at diagnosis		0.841		
≤ 57 years	Ref			
> 57 years	0.93(0.43–1.84)			
BMI				
< 18.5	Ref			
18.5–29.9	0.66(0.19–2.19)	0.499		
≥ 30	0.37(0.08–1.70)	0.204		
Comorbidities		0.394		
No	Ref			
Yes	1.35(0.67–2.70)			
Adjuvant (Post-operative chemotherapy)		0.783		
No	Ref			
Yes	0.90(0.45–1.79)			

Table 4 (continued)

Parameter	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
PCI		**< 0.001**		
≤ 6	Ref		Ref	
> 6	4.44(2.17–9.11)		3.4(1.44- 8.00)	**0.005**
CC		**0.01**		
0	Ref			
1	4.27(1.40–12.9)			
Postoperative complications				
No	Ref			
Yes	2.18(0.98–4.86)	**0.056**		
Length of hospital stay		0.207		
≤ 21 days	Ref			
> 21 days	1.55(0.78–3.11)			
Tumor type				
Intestinal	Ref			
Adenocarcinoma	2.97(0.81–10.77)	**0.097**		
Diffuse	1.88(0.85–4.12)	0.114		
mixed	0.97(0.27–3.54)	0.975		
Tumor location				
GEJ junction	Ref		Ref	
antrum	0.35(0.12–0.96)	**0.043**	0.28(0.14–0.88)	**0.03**
body	0.30(0.03–2.36)	0.255		
cardia	0.39(0.08–1.83)	0.234		
overlapping location	1.90(0.68–5.28)	0.213		
fundus	1.02(0.22–4.67)	0.979		
pylorus	0.63(0.21–1.87)	0.416		
Surgery type				
-Radical total gastrectomy with D2 lymphadenectomy	Ref		Ref	
- Subtotal esophagectomy and total gastrectomy with D2 lymphadenectomy and colon interposition	3.43(1.52–7.75)	**0.003**	2.94(1.05–8.28)	**0.04**
Signet sign				
Absent	Ref			
Present	1.25(0.63–2.50)	0.512		
Staging				
Stage 1a/b- 3a/b/c	Ref			
Stage 4	3.13(1.52 6.42)	**0.002**		
Resection Margin				
Negative	Ref			
Positive	2.15(0.92- 5.00)	**0.074**		
Lymphovascular invasion				
Absent	Ref			
Present	2.37(1.19–4.73)	**0.014**		
Perineural invasion				
Absent	Ref		Ref	
Present	2.55(1.26–5.16)	**0.009**	3.02(1.28–7.11)	**0.012**
Her 2 neu expression				
Negative	Ref			
Positive	0.94(0.40–2.18)	0.895		
Clavien-dindo ≥ III				
No	Ref		Ref	
Yes	2.98 (1.49–5.96)	**0.002**	2.66 (1.15–6.13)	**0.021**

Note: **P*-value significant at < 0.1; †*P*-value significant at < 0.05; HR = Hazard Ratio; CI = Confidence interval

Table 5 Cox proportional regression analysis for predictors of disease-free survival

Parameter	Univariable analysis		Multivariable analysis	
	HR (95% CI)	***P*-value***	**HR (95% CI)**	***P*-value†**
Gender				
Female	Ref			
Male	1.50(0.62–3.63)	0.36		
Age at diagnosis	0.98(0.96–1.01)	0.366		
BMI				
< 18.5	Ref			
18.5–29.9	0.87(0.20–3.75)	0.861		
≥30	0.42(0.06–2.56)	0.35		
Comorbidities				
No	Ref			
Yes	0.72(0.32–1.60)	0.43		
Adjuvant (Post-operative chemotherapy)				
No				
Yes	Ref			
	0.83(0.38–1.79)	0.64		
pPCI				
≤ 6	Ref	**< 0.001**	Ref	
> 6	5.20(2.18–12.42)		4.56 (1.81–11.45)	**0.001<**
CC				
CC0	Ref			
CC1	4.55(1.28–16.2)	**0.019**		
Postoperative complications				
No	Ref			
Yes	0.92(0.42–2.01)	0.837		
Length of hospital stay	1.00(0.99- 1.00)	0.702		
Tumor type				
Intestinal	Ref			
Adenocarcinoma	0.97(0.12–7.59)	0.979		
Diffuse	1.25(0.53–2.91)	0.603		
mixed	0.91(0.25–3.32)	0.896		
Tumor location				
GEJ junction	Ref			
antrum	0.48(0.16–1.42)	0.188		
body	0.96(0.20–4.66)	0.966		
cardia	0.48(0.09–2.45)	0.385		
overlapping location	0.93(0.19–4.49)	0.929		
fundus	2.99(0.76–11.69)	0.115		
pylorus	0.51(0.13–1.99)	0.337		
Surgery type				
-Radical total gastrectomy with D2 lymphadenectomy	Ref			
- Subtotal esophagectomy and total gastrectomy with D2 lymphadenectomy and colon interposition				
	0.81(0.27–5.09)	0.779		
Signet sign				
Absent	Ref	0.833		
Present	0.91(0.42- 2.00)			
Staging				
Stage 1a/b- 3a/b/c	Ref			
Stage 4	2.39(1.05–5.40)	**0.036**		

Table 5 (continued)

Parameter	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P*-value*	HR (95% CI)	*P*-value†
Pathologic T stage				
T0	Ref			
T1a/b- T2	0.30(0.04–1.82)	0.192		
T3- T4a/b	1.14(0.26–4.90)	0.857		
Pathologic N stage				
N0-N1	Ref			
N2-N3a/b	3.09(1.41–6.80)	**0.005**		
Pathologic M stage				
M0	Ref			
M1	2.02(0.91–4.45)	**0.082**		
Resection Margin				
Negative	Ref			
Positive	1.91(0.71–5.14)	0.195		
Lymphovascular invasion				
Absent	Ref			
Present	2.18(1.00- 4.77)	**0.049**		
Perineural invasion				
Absent	Ref			
Present	1.78(0.82–3.86)	0.142		
Her 2 neu expression				
Negative	Ref			
Positive	1.72(0.74–3.99)	0.203		
Clavien-dindo ≥ III				
No	Ref			
Yes	0.55(0.16–1.84)	0.337		

Note: *P-value significant at < 0.1; †P-value significant at < 0.05; HR = Hazard Ratio; CI = Confidence interval

second dose in our study. This is due to the fact that these patients had extensive tumor involvement and spread.

Reports of implementation of HIPEC with IORT during CRS are limited. Klaver et al. first reported on the combination in a series of five rectal cancer patients [22], where only one patient had passed away 11 months postoperatively. In a cohort of 30 patients, Van de Vlasakker et al. demonstrated a median OS of 31 months and DFS of 10 months in locally advanced or recurrent rectal cancer [23]. In both studies, the rate of postoperative complications was similar to that of other commonly accepted treatments of the neoplasm [22, 23]. The utilization of HIPEC plus IORT has also been reported in pheochromocytoma, pancreatic, colorectal, and gallbladder cancer patients with promising outcomes [24–28]. In our study, approximately one quarter of patients experienced complications of Clavien-Dindo grade 3 and above, which is in line with the other HIPEC plus IORT studies. Overall, HIPEC plus IORT appears well-tolerated in our patients and others with no significant treatment-related morbidity or mortality.

Our study faces several limitations. First, the retrospective nature of the study may create selection biases in our cohort. Additionally, the study was conducted in one center, which may limit the generalizability of the results of our study to different populations. Finally, our study lacks a comparator group and, hence, we are unable to directly compare the combination treatment with other widely used treatments in GCa. Double-armed studies are needed to fully understand the effectiveness of these treatment modalities.

Conclusions

This complex, multimodal treatment strategy results in a significantly prolonged OS and DFS when compared to other treatment strategies for gastric cancer patients, with no added morbidity or mortality.

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Author contributions
MMA: Conceptualization, acquisition of the data, manuscript drafting, gave final approval of the version to be published, and critical revision of the manuscript; TZA: Conceptualization, acquisition of the data, manuscript drafting, gave final approval of the version to be published, and critical revision of the manuscript; ASA: Statistical analysis and interpretation of the data, manuscript drafting, and gave final approval of the version to be published; BNS: Conceptualization, acquisition of the data, manuscript

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate
This study was approved by the Institutional Review Board (IRB) at our institution (RAC# 2241047). Written informed consent was signed by all the patients included in this study. All patient identifying information has been removed from this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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