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ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Gastric Cancer with Peritoneal Carcinomatosis: Multicenter Study of Spanish Group of Peritoneal Oncologic Surgery (GECOP)

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ABSTRACT

Background. Gastric cancer (GC) with peritoneal carcinomatosis (PC) is traditionally considered a terminal stage of the disease. The use of a multimodal treatment, including cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), can benefit these patients. Our goal was to evaluate the morbidity and survival outcomes of these patients.

Methods. This is a retrospective, multicenter study from a prospective national database of patients diagnosed with PC secondary to GC treated with CRS and HIPEC from June 2006 to October 2017.

Results. Eighty-eight patients from seven specialized Spanish institutions were treated with CRS and HIPEC, with median age of 53 years; 51% were women. Median Peritoneal Cancer Index (PCI) was 6, and complete cytoreduction was achieved in 80 patients (90.9%). HIPEC was administered in 85 cases with 4 different regimens (Cisplatin + Doxorubicin, Mitomycin-C + Cisplatin, Mitomycin-C and Oxaliplatin). Twenty-seven cases (31%) had severe morbidity (grade III–IV) and 3 patients died in the postoperative period (3.4%). Median follow-up was 32 months. Median overall survival (OS) was 21.2 months, with 1-year OS of 79.9% and 3-year OS of 30.9%. Median disease-free survival (DFS) was 11.6 months, with 1-year DFS of 46.1% and 3-year DFS of 21.7%. After multivariate analysis, the extent of peritoneal disease (PCI $\geq$ 7) was identified as the only independent factor that influenced OS (hazard ratio [HR] 2.37, 95% confidence interval [CI] 1.26–4.46, $p = 0.007$).

Conclusions. The multimodal treatment, including CRS and HIPEC, for GC with PC can improve the survival results in selected patients (PCI < 7) and in referral centers.

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Gastric cancer (GC) is the second cause of death from cancer in the developed world, causing 10% of cancer-related deaths, despite of being the fifth most common cancer.[1] Approximately one-third of patients have peritoneal spread at diagnosis, and half of patients will have a peritoneal relapse after a potential curative resection as the

only site of recurrence.[2–4] Therefore, peritoneal carcinomatosis (PC) is the most frequent localization of metastatic spread in GC.

Until a few years ago, PC was considered as terminal stage of the disease. The presence of macroscopic PC, and even microscopic PC (positive peritoneal cytology), are classified as stage IV (metastatic disease) with poor prognosis and traditional median overall survival (OS) around 6 months, although it has improved to around 12 months with contemporary systemic chemotherapy (SCT).[5] Currently, standard treatment for these cases is SCT, and surgery is reserved only for palliation of symptoms.[6] From the 2000s, the combination of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has been gaining popularity for different neoplastic diseases that involve peritoneal surface. Macroscopic disease is treated by CRS, which includes peritonectomy procedures, and HIPEC is used to treat microscopic residual disease.[7–9] Currently, CRS + HIPEC is the standard treatment for pseudomyxoma peritonei, peritoneal mesothelioma, and in selected cases of PC from colorectal cancer.[10–12] Its use in PC of ovarian and gastric origin is still under investigation, but preliminary results are promising.[13–15]

In this study, we analyze the results of the treatment with CRS + HIPEC for patients with GC and PC, through the collaboration of seven Spanish centers that belong to the Spanish Group of Peritoneal Oncologic Surgery (GECOP: "*Grupo Español de Cirugía Oncológica Peritoneal*").

PATIENTS AND METHODS

This is a retrospective, multicenter study from a prospective national database of patients diagnosed of PC secondary to GC and treated with CRS and HIPEC from June 2006 to October 2017. Both patients with macroscopic peritoneal disease (tumor implants on peritoneal surface) and those with isolated positive cytology (microscopic disease) have been included. Patients selected for this treatment should have apparently resectable peritoneal disease and no distant metastases. Most patients have synchronous PC, but exceptionally metachronous PC is treated this way. The study was approved by the institutional review board and the ethics committee of the organizing center. Finally, seven Spanish centers participate in the study (Table 1).

The extension diagnosis is performed in all cases with a thoracic-abdominopelvic computed tomography (CT) with double contrast; positron emission tomography (PET) was selectively performed in doubtful cases. Laparoscopy is performed routinely, except in case of extensive prior abdominal surgery, to assess the peritoneal extension of the disease using the Peritoneal Cancer Index (PCI), and to obtain a peritoneal cytology.[16] When the diagnosis is completed, patients are systematically treated with neoadjuvant chemotherapy (NACT) whenever possible.

In all centers, CRS + HIPEC is performed by a multidisciplinary team specialized in peritoneal cancer surgery and in management of intraoperative chemotherapy. The first goal of CRS is to remove all visible disease by resecting the primary tumor if not performed previously (gastrectomy and lymphadenectomy) and/or removing all peritoneal implants, which may include peritonectomies and visceral resections on demand. The radicality of CRS is assessed by the Completeness of Cytoreduction Score (CCS) according to the volume of residual tumor (CCS-0, no macroscopic residue; CCS-1, macroscopic residue $<$ 2.5 mm; CCS-2, 2.5 mm–2.5 cm; CCS-3, $>$ 2.5 cm).[17] After CRS, HIPEC is administered; exposure technique (open, close, or close with CO_2 recirculation) and type of drug used are variable among the participating centers (Table 2).

Postoperative morbidity is scored following the Dindo-Clavien classification, recording most severe complication for each patient.[18] After hospital discharge and complete recovery from surgical intervention, it is intended that patients complete perioperative SCT with the same regimen used preoperatively.

Recurrences and deaths due to disease or any other cause are documented during follow-up. Disease-free survival (DFS) is defined as the time from date of surgery until date of relapse. OS is defined as the time from first treatment received until date of death for any cause.

The statistical analysis was performed by using IBM SPSS software, version 22.0. P value ≤ 0.05 was considered significant. Analysis of variables is done using Chi square test, t test, Mann–Whitney U test and contingency tables. Kaplan–Meier and log-rank test are used to calculate and compare survival curves. Cox multiple regression is used to investigate the influence of various risk factors on survival.

RESULTS

Eighty-eight patients with GC and PC from seven Spanish institutions were treated with CRS and HIPEC. PC was metachronous in only five cases. Preoperative laparoscopy was performed in 58 patients, with a median laparoscopic PCI of 6 (range 0–20). A sample was taken for peritoneal fluid cytology in 52 cases and was positive in 26 patients. Four patients had only positive cytology without macroscopic peritoneal involvement. Eighty-four patients received NACT, with a median of 4 cycles (range

TABLE 1 Centers participating in the study and number of patients per center

Center	City	No. of patients
Hospital Universitario de Fuenlabrada	Fuenlabrada (Madrid)	44
Hospital Príncipe de Asturias	Alcalá de Henares (Madrid)	22
Clínica Universitaria de Navarra (CUN)	Pamplona	10
Hospital Virgen de la Arrixaca	Murcia	5
Hospital Reina Sofía	Córdoba	5
Instituto Valenciano de Oncología (IVO)	Valencia	1
Hospital Universitario Donostia	San Sebastián	1

2–23). After surgery 61 patients completed adjuvant chemotherapy. Table 2 shows preoperative, surgical, and postoperative characteristics of the 88 patients.

Simultaneous gastrectomy was performed in 78 cases (14 subtotal, 64 total, being palliative in one of them). Gastrectomy was previously performed in 5 cases (metachronous PC) and in 5 cases gastrectomy was not performed, because PC was deemed unresectable.

Radicality of CRS was maximum (CCS-0) in 80 cases (90.9%), with visible residual tumor after unsuccessful attempt at complete resection in two patients (one CCS-1 with minimal residual disease, and the other one CCS-2 with a significant volume of peritoneal disease remained in pelvis; both received HIPEC) and unresectable disease, CCS-3, in six cases (all of them synchronous). In one of these six cases, palliative total gastrectomy was performed to prevent impending complications, and no gastrectomy was performed in the other five patients. Three of these six patients with unresectable disease received HIPEC to treat ascites, and the other three patients did not receive HIPEC.

Severe morbidity (grade III–IV of Dindo-Clavien classification) was observed in 27 patients (31%), and the 90-day postoperative mortality was 3.4% (3 deaths). One of them developed a massive hemoperitoneum that forced a reintervention, with secondary multiorgan failure that eventually lead to his death. In the second case, cause of death was a septic shock in the context of severe pancytopenia, without evidence of anastomotic complications (toxicity of HIPEC). The cause of death in the last deceased patient was a respiratory failure secondary to acute respiratory distress syndrome.

Median follow-up was 32 months (reverse Kaplan–Meier), and no patient was lost. Median OS was 21.2 months, and OS at 1, 3, and 5 years were 79.9%, 30.9%, and 27.5%, respectively. Median DFS was 11.6 months, and DFS at 1, 3, and 5 years were 46.1%, 21.7%, and 14%, respectively (Fig. 1).

The univariate analysis identified CCS (higher than CCS-1) and PCI (higher than 6) as the only prognostic factors with influence on OS. Age, gender, type of gastrectomy, association of other visceral resections, origin center, synchronicity, type of HIPEC, severe morbidity, prolonged hospital stay (> 14 days) or adjuvant therapy did not influence OS in the univariate analysis.

Only seven patients had a CCS higher than CCS-1, and their median OS was 11.3 months. For the 81 patients with CCS-0 or CCS-1, median OS was 21.7 months (HR 3.10, 95% CI 1.32–7.32, $p = 0.006$).

Forty-six patients had a PCI of 6 or lower with a median OS of 26.1 months, and their OS at 1, 3, and 5 years were 88.7%, 46.8% and 46.8%, respectively. Median OS for the 42 patients with PCI higher than 6 (among which are included the 7 patients with CCS > 1) was 18.9 months with OS at 1, 3, and 5 years of 70.4%, 15.1%, and 0.0%, respectively (HR 2.23, 95% CI 1.28–3.88, $p = 0.003$; Fig. 2). In per protocol analysis, excluding the six unresectable patients (all with PCI > 6), median OS for the 36 patients with PCI > 6 was 20 months, with OS at 1, 3, and 5 years of 76.9%, 24.6%, and 0.0%, respectively, with significant difference compared with OS for the 46 patients with PCI 6 or lower ($p = 0.009$). Median OS for the six patients with unresectable disease (median PCI 21.5) was 11.3 months with OS at 1, 3, and 5 years of 33.3%, 16.7%, and 0.0%, respectively. Finally, median OS for the four patients with microscopic disease (isolated positive cytology) was not reached, but if we exclude these patients from the analysis, the previous results do not change.

After multivariate analysis, the only prognostic factor that had an independent negative influence on OS was PCI higher than 6, with HR of 2.37 (95% CI 1.26–4.46, $p = 0.007$).

DISCUSSION

In the past years, advances in systemic chemotherapy have improved the prognosis of patients with metastatic GC, reaching 8–14 months in selected series, although in most current population-based studies the survival reported continues to be poor, around 3–4 months.[5,6,19–23] PC has even worse prognosis than other metastatic locations, although there also has been improvement in OS of up to 10–12 months in the most selected cases.[6,14,24–27]

TABLE 2 Preoperative, surgical and postoperative characteristics

Age, median (range), yr	53 (23–74)
Gender	
Male	43 (49%)
Female	45 (51%)
Performance status	
ECOG 0	51 (57.9%)
ECOG 1	23 (26.1%)
ECOG 2	6 (6.8%)
No data	8 (9.1%)
Chemotherapy regimen[a]	
EOX	21 (23.9%)
DCF	17 (19.3%)
ECX	9 (10.2%)
ECF	8 (9.1%)
FLOT	6 (6.8%)
Others	27 (30.7%)
PCI median (range)	6 (0–30)
PCI 0 (isolated Cyt +)	4
PCI 1–6	42
PCI 6–12	21
PCI > 12	21
Surgical gastric procedure	
Previous gastrectomy	5 (5.7%)
Partial gastrectomy	14 (15.9%)
Total gastrectomy	64 (72.7%)
Not done[b]	5 (5.7%)
Lymphadenectomy[c]	
D1	4 (5%)
D2	70 (90%)
D3	4 (5%)
Visceral resections	
Right colectomy	14 (15.9%)
Left colectomy	3 (3.4%)
Rectal resection	4 (4.5%)
Small bowel resection	14 (15.9%)
Hysterectomy with adnexectomy	23 (26.1%)
Peritonectomies	
Left diaphragm	17 (19.3%)
Right diaphragm	20 (22.7%)
Pelvic peritoneum	19 (21.6%)
Completeness Cytoreduction Score (CCS)	
CCS-0	80 (90.9%)
CCS-1	1 (1.1%)
CCS-2	1 (1.1%)
CCS-3	6 (6.8%)
HIPEC drug	
Cisplatin + doxorubicin	44 (50%)
Mitomycin C + cisplatin	20 (22.7%)
Mitomycin C	10 (11.4%)
Oxaliplatin	11 (12.5%)
Not administrated	3 (3.4%)
HIPEC technique	
Open	63 (71.6%)
Closed with CO_2 recirculation	22 (25%)
Not administrated	3 (3.4%)
Postoperative complications (Clavien-Dindo)	
No complication	34 (38.6%)
Minor (I–II)	24 (27.3%)
Major (III-IV)	27 (30.7%)
Grade V	3 (3.4%)
Surgical reintervention	11 (12.5%)
Hospital stay (days), median (range)	14 (4–93)

PCI Peritoneal Cancer Index; *Cyt* + positive cytology; *HIPEC* hyperthermic intraperitoneal chemotherapy

[a]Chemotherapy regimens: EOX = Epirubicin + Oxaliplatin + capecitabine; DCF = Docetaxel + Cisplatin + 5-Fluorouracil; ECX = Epirubicin + Cisplatin + Capecitabine; ECF = Epirubicin + Cisplatin + 5-Fluorouracil; FLOT = 5-Fluorouracil + Leucovorin + Oxaliplatin + Topotecan

[b]Due to unresectable peritoneal disease

[c]In those with simultaneous gastrectomy

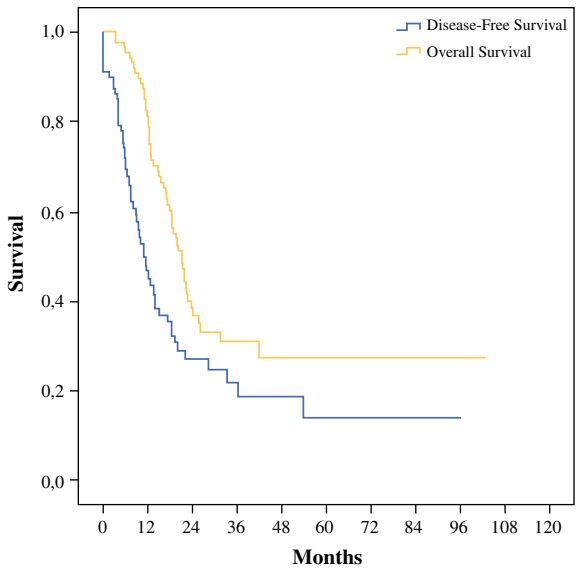

FIG. 1 Overall survival (OS) and disease-free survival (DFS) for the 88 patients

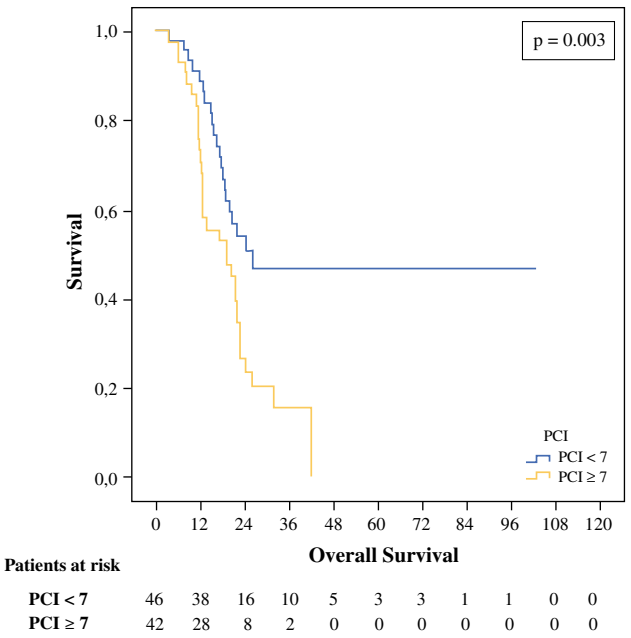

FIG. 2 Overall survival stratified by PCI < 7 and PCI ≥ 7

Treatment with CRS and HIPEC in patients with PC of GC origin has not been standardized despite promising published results.[6,14,15,28–36] Several randomized trials (mainly Asiatic) have demonstrated that HIPEC can prevent peritoneal relapse when it is administered to patients without PC but with a high-risk GC (European trial "GASTRICHIP" is ongoing). In case of macroscopic PC from GC origin, various retrospective series and case–control studies show a potential benefit with CRS and HIPEC. Only one published randomized, clinical trial in 2011 reported a significant improvement in survival when HIPEC was added to CRS (OS of 6.5 months for CRS alone vs. 11 months for CRS with HIPEC, with 3-year survival rates of 0% and 5.9% respectively).[15] The French Registry was published in 2010 by Glehen et al.[14]. Their analysis of 159 patients with PC from GC origin treated with CRS and HIPEC showed a median OS of 9.2 months (1-, 3-, and 5-year survival of 43%, 18%, and 13%, respectively), but median OS increased to 15 months if CRS was complete (CCS-0). They also recommended that patients with PCI higher than 12 should not been treated with CRS and HIPEC, because the benefit is extremely low or null.

Our Spanish Registry shows appealing results: median OS of 21.2 months, and survival rates at 1, 3, and 5 years of 79.9%, 30.9%, and 27.5%, respectively. At the time of analysis, eight patients were still alive 42 months after treatment, with three long-term, disease-free survivors (72, 77, and 102 months; Fig. 1). Our median DFS has been 11.6 months, and DFS at 1, 3, and 5 years were 46.1%, 21.7%, and 14%, respectively. The CCS 0 rate has been 90.9%, much higher than that of the French Registry (56%). These results are surely due to the selection of cases and the experience of the collaborating centers. The French Registry (with the recommendation not to select patients with PCI > 12) was published in 2010, and most cases in the Spanish Registry were treated after that date, so that French experience has improved the selection of patients as shown by our data (only 21 of our patients had PCI > 12) on complete cytoreduction and survival.

Therefore, the use of CRS and HIPEC for selected patients with GC and PC seems to improve survival rates, although this improvement is more limited than that observed in other indications for CRS and HIPEC (colorectal cancer, ovarian cancer, mesothelioma, or pseudomyxoma peritonei).[6,14,15,36] Moreover, this procedure is aggressive, and it carries an important morbidity. In our patients, severe morbidity has been observed in 30.7% of procedures with a 90-day mortality of 3.4%, similar to published results.[6,14,15,28–36] Therefore, correct selection of patients is essential to determine which cases will have the maximum benefit from this treatment, and also, this procedure must be performed in referral centers with demonstrated experience in the selection and treatment of peritoneal diseases.

In our study, univariate analysis identified CCS (higher than CCS-1) and PCI (> 6) as the only prognostic factors with influence on OS. As both factors are correlated, PCI assessment is fundamental to select patients for CRS with HIPEC. Patients with PCI of ≤ 6 have a median OS of 26.1 months, with 5-year OS of 46.8%; however, patients with PCI ≥ 7 have a median OS of 18.9 months with OS at 5-year of 0%. The only three long-term, disease-free survivors had a PCI < 7. We propose a PCI of 7 as the cutoff point for selecting patients for CRS and HIPEC in patients with GC and PC. This level of PCI has been proposed in other recent publications.[6,33–36] Chia et al. published in 2016 an analysis of 81 patients with GC and PC from 5 French institutions, treated with CRS and HIPEC, in which a complete CRS (CCS-0 or CCS-1) had been achieved. The median PCI was 6; median OS for patients with PCI of 0-6 was 26.4 months versus 10.9 months for patients with PCI of 7 or higher.[36] Most recently, Rihuete Caro et al. published the results of one Spanish institution (Hospital Universitario de Fuenlabrada); the analysis of 35 patients showed that the patients with PCI < 7 had a median OS of 19 months versus 12 months for patients with PCI ≥ 7 .[6]

Our study has some limitations. It is a retrospective and observational study, not experimental, so the conclusions may have the biases inherent to this type of studies. Although the selection of patients has improved greatly since the publication of the French registry (which referred up to 44% of CCS > 0), the incomplete cytoreduction rate of our study (9% of CCS > 0) is very striking. This could

suggest a bias of communication, on the part of some centers, of possible cases in which the procedure had to be aborted when finding unexpectedly in the laparotomy unresectable peritoneal disease, therefore overestimating the effect by "intention to treat" of the CRS and HIPEC. There is a great variability of HIPEC drugs used, and this can disturb the results, although we found no differences when we analyzed the influence of HIPEC drug in OS. This heterogeneity is due to the participation of multiple centers in the study. Nonetheless, this is one of the most important National Registries published so far.

As we said previously, there is only one clinical trial published.[15] Currently, there are several Asiatic trials recruiting patients, and there is one ongoing German phase III trial (GASTRIPEC) evaluating the role of HIPEC for PC of GC origin (NCT02158988). In a few years, we will have more information from these trials that are currently underway.

CONCLUSIONS

The multimodal treatment with SCT, CRS, and HIPEC for GC with PC can improve the survival results for selected patients in referral centers. Patients with low peritoneal disease volume (PCI < 7) are the best candidates to use this multimodal approach. Therefore, an adequate preoperative assessment is essential for the patient selection.

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