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Advanced Gastric Cancer: Single-Center Experience

Massimo Framarini [1], Fabrizio D'Acapito [1], Daniela Di Pietrantonio [1,*], Francesca Tauceri [1], Giovanni Vittimberga [1], Leonardo Solaini [1,2], Giulia Elena Cantelli [1], Giulia Marchetti [1], Paolo Morgagni [1] and Giorgio Ercolani [1,2]

[1] General and Oncologic Surgery, Morgagni-Pierantoni Hospital, AUSL Romagna, 47121 Forlì, Italy
[2] Department of Medical and Surgical Science (DIMEC), University of Bologna, 40123 Bologna, Italy
* Correspondence: danidipietrantonio@gmail.com

Abstract: Gastric cancer (GC) is the fifth most diagnosed cancer, but it is the third leading cause of cancer death worldwide. Despite the likelihood of gastric cancer metastasizing to the peritoneum, optimal management strategies for this population remain undefined. We carried out a retrospective analysis to present our findings on patients with advanced gastric cancer (AGC) with peritoneal metastases (CP) who underwent neoadjuvant chemotherapy followed by gastrectomy + hyperthermic intraperitoneal chemotherapy (HIPEC). To better understand the data, we compared these patients with AGC patients without CP who were treated with neoadjuvant chemotherapy and surgery, as well as with another group of patients who underwent upfront surgery. Patients who undergo surgery and HIPEC achieve a higher survival rate than patients in the literature who undergo only palliative chemotherapy with a median overall survival of 28 months with a low incidence of major complications.

Keywords: advanced gastric cancer; HIPEC; hyperthermic intraperitoneal chemotherapy

Citation: Framarini, M.; D'Acapito, F.; Di Pietrantonio, D.; Tauceri, F.; Vittimberga, G.; Solaini, L.; Cantelli, G.E.; Marchetti, G.; Morgagni, P.; Ercolani, G. Advanced Gastric Cancer: Single-Center Experience. *Surgeries* **2024**, *5*, 465–475. https://doi.org/10.3390/surgeries5020038

Academic Editor: Makoto Endo

Received: 15 May 2024
Revised: 3 June 2024
Accepted: 11 June 2024
Published: 15 June 2024

1. Introduction

Gastric cancer (GC) is the fifth most diagnosed cancer, but it is the third leading cause of cancer death worldwide [1]. Its poor prognosis is because it is often diagnosed at an advanced stage, with peritoneal metastases present in 15–30% of patients. The five-year survival rate is only 25% [2–6].

The treatment of GC is multidisciplinary and stage-dependent. Although early neoplasms can be removed endoscopically [7], locally advanced neoplasms require curative treatment with surgery, with or without systemic chemotherapy, to achieve a 5-year survival rate of 55% [5,8].

Despite numerous therapeutic advances, the standard treatment for metastatic gastric cancer remains palliative chemotherapy, resulting in a median overall survival (OS) of 6 months [4,9]. Nevertheless, in other studies, these patients may respond remarkably well to palliative chemotherapy, converting their disease into a radically operable stage and demonstrating promising results in a selected group. The literature has also reinforced the notion that conversion surgery, even in the presence of peritoneal carcinosis, is associated with longer survival than chemotherapy alone, with reported survival times ranging from 37 to 56 months [10,11]. As a result, there is increasing interest in further improving the survival of patients with stage IV gastric cancer, particularly those with peritoneal carcinomatosis (PC). Recent evidence suggests that surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC) may be a promising multidisciplinary approach for a selected subset of GC patients with limited PC when a complete resection can be achieved [2,12].

The objective of this study is to show our findings on patients with advanced gastric cancer (AGC) with peritoneal metastases (CP) who underwent neoadjuvant chemotherapy followed by gastrectomy + HIPEC. To better understand the data, we compared these patients with AGC patients (clinically T3–4 or N1–2–3) without CP who were treated with

neoadjuvant chemotherapy and surgery, as well as with another group of patients who underwent upfront surgery.

2. Materials and Methods

This is a retrospective analysis of a prospective database that includes patients with advanced GC who underwent gastrectomy (total or subtotal) with or without HIPEC, with or without adjuvant chemotherapy at the General and Oncological Surgery of the Morgagni-Pierantoni Hospital in Forlì (Italy) between June 2005 and May 2022.

Area Vasta Romagna Ethics Committee approved the protocol with Protocol Code 5707/2020-I.5/264 on 3 July 2020, with the 1964 Declaration of Helsinki and its later amendments, and with Good Clinical Practice (GCP) guidelines. All patients provided written informed consent.

All patients were regularly discussed at multidisciplinary meetings, during which a variety of approaches were explored, including upfront surgery and conversion, in accordance with the prevailing guidelines at the time.

The patients were divided into three groups according to the treatment they received: (a) patients who underwent upfront surgery; (b) patients who underwent chemotherapy and then gastrectomy alone; (c) patients who underwent chemotherapy and then gastrectomy plus HIPEC.

The preoperative diagnostic workup for all these patients included esophagogastroduodenoscopy, measuring tumor markers (CEA and CA 19-9), and a chest–abdomen contrast-enhanced CT scan. The results were evaluated by an expert radiologist to identify serosa invasion and direct or indirect markers of peritoneal or node involvement. Staging laparoscopy with peritoneal cytology or endoscopic ultrasound was integrated into diagnostic and staging programs but was not performed in all patients in accordance with the guidelines in use at the time of diagnosis.

The clinical stage of GC (cTMN) was considered advanced if preoperative staging showed T 3–4, N 1–2–3, the presence of peritoneal carcinomatous nodules, or positive peritoneal cytology. Patients with ECOG PS > 2, elderly, symptomatic, and all those who refused neoadjuvant systemic chemotherapy were included in Group A and received upfront surgery. Patients with ECOG performance status $\leq$2 with negative cytology and no evidence of peritoneal carcinomatosis were enrolled in Group B. Patients with positive cytology or the presence of limited peritoneal carcinomatosis were enrolled in Group C. The tumor stage was presented in accordance with the 8th edition of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) pathologic staging system [13].

All patients underwent total omentectomy. Removal of the anterior pancreatic capsule (omental bursa) has been performed only in cases of tumor infiltration of the posterior gastric wall serosa.

Cytoreductive surgery (CRS) with HIPEC was reserved for patients with limited peritoneal involvement in whom a complete response (CR) could be achieved and those with a previous positive peritoneal cytology. We used the semi-closed colonic approach [14]. The chemotherapeutic agents administered were mitomycin (2 mg/peritoneal dialysis fluid liter) and cisplatin (25 mg/peritoneal dialysis fluid liter). The amount of fluid circulated was approximately 4 L of peritoneal dialysis solution (2.2 L/sq m of body surface area), in which the chemotherapy drug was diluted and circulated at a rate of 1200 cc/min. Hyperthermic intraperitoneal chemotherapy perfusion was initiated when the intraperitoneal temperature reached 42 °C and maintained at 42–43 °C for 60 min.

The Peritoneal Cancer Index (PCI) was used to measure peritoneal status [15].

Morbidity was classified using the Clavien-Dindo classification [16].

A follow-up visit was made to assess the patient's nutritional status one month after the operation. The patient was then followed up annually for the first five years. During this time, abdominal and chest computed tomography were performed and tumor markers (CEA and CA 19-9) were measured every three months for the first year and then every six

months for the following four years. Upper endoscopy was performed once a year for the first two years, then every two years until year five.

3. Results

A total of 86 patients with advanced gastric cancer were included in the study. Of these patients, 29 were in Group A (upfront gastrectomy), 28 were in Group B (gastrectomy after systemic chemotherapy) and 29 were in Group C (CRS + HIPEC after systemic chemotherapy).

A summary of the clinical and pathological characteristics of patients is presented in Tables 1 and 2.

Table 1. Clinical characteristics of patients.

Variables	Group A (N = 29)	Group B (N = 28)	Group C (N = 29)
Age	72.65 (range 46–90)	63.5 (range 39–75)	63 (range 28–75)
ASA-Score			
1	1		1
2	17	22	14
3	11	6	14
Charlson Comorbidity Index	4 (range 1–8)	3.3 (range 0–6)	4.5 (range 1–9)
0–3	12	15	6
4–6	15	13	16
7–9	2	0	5
Gastrectomy			
Subtotal	10	18	8
Total	19	10	21
Lymphadenectomy			
D1	6	0	0
D2	19	10	13
D2+	2	14	15
D3	2	4	1
UICC			
0	24	28	27
1	5	0	2
2	0	0	0
Admission to the intensive care unit (ICU)			
Yes	3	7	29
Not	26	21	0
Hospital Stay (day)	14 (range 6–45)	13 (range 6–73)	16 (range 9–33)
Severe Complication	6	2	4
Bleeding	1	0	0
Anastomotic leak	3	1	2
Duodenal leak	1	0	1
Bowel occlusion	0	1	0
Biliary stenosis	1	0	0
Abdominal collection	0	0	1
90-Day Mortality	3	0	1
Adjuvant chemotherapy	29	23	16

Group A (upfront gastrectomy); Group B (gastrectomy after systemic chemotherapy); Group C (surgical debulking + HIPEC after systemic chemotherapy).

Table 2. Pathological characteristics of patients.

Variables	Group A (N = 29)	Group B (N = 28)	Group C (N = 29)
p T stage			
T1a	0	0	0
T1b	0	3	3
T2	2	5	4
T3	11	13	10
T4a	14	7	8
T4b	2	0	1
p N stage			
N0	1	8	9
N1	3	5	3
N2	4	5	5
N3	21	10	12
M stage			
M0	12	23	16
M1	17	5	13
Distal Lymphonodes	0	3	0
Liver metastases	0	1	0
Peritoneal Carcinoses	12	1	12
Positive peritoneal cytology	5	0	1
Peritoneal Cancer Index	0.5 (range 0–3)	0	3 (range 0–8)
Peritoneal Cancer Index > 6	0	0	2
Lauren histotype			
Intestinal	16	17	16
Diffuse	9	5	5
Mixed	4	6	8
Signet ring cells	11	6	13
Grading			
G1	2	0	1
G2	8	9	8
G3	19	19	20
Site			
Cardias	7	4	5
Fundus	2	1	2
Corpus	13	14	14
Antrum	6	9	6
All	1	0	2
Lymph nodes harvested	33 (range 13–65)	38 (range 19–56)	47 (17–126)
Metastatic lymph nodes	16 (0–42)	8 (0–23)	8 (0–26)

Group A (upfront gastrectomy); Group B (gastrectomy after systemic chemotherapy); Group (surgical debulking + HIPEC after systemic chemotherapy).

A summary of neoadjuvant and adjuvant chemotherapy regimens is presented in Tables 3 and 4.

The mean age of Group A was 72.65 years (range 46–90), that of Group B was 63.5 years (range 39–76), and 63 years (range 28–77) for Group C.

A total of 58 patients underwent total gastrectomy, while 42 patients underwent subtotal one. The details of the surgical procedures and perioperative outcomes are reported in Table 1. The median PCI score was 0.5 (range: 0–3) in Group A patients, 0.04 (range 0–1) for Group B patients and 3 (range 0–8) for those of Group C. Complete resection was achieved in 24 Group A patients (83%), 27 Group C patients (93%) and all Group B patients

(100%). The median length of hospital stay was 14 days (range 6–45) in Group A patients, 13 days in Group B patients (range 6–73) and 16 days in Group C ones (range 9–33).

Table 3. Neoadjuvant chemotherapy regimens.

Variables	Group B (N = 28)	Group C (N = 29)
DCF		2
ECX	2	1
FLOT	6	6
FOLFOX	4	9
PELF	1	8
TOX	14	1
Other	1	2
Number of cycles (Range)	**3.5 (1–6)**	**5 (1–12)**

Table 4. Description of adjuvant chemotherapy regimens.

Variables	Group A (N = 29)	Group B (N = 23)	Group C (N = 16)
De Gramont	7	9	4
ECX	1		1
EOX	1		
FLOT	3	1	3
Folfiri	1	3	1
Folfox	8	7	1
PELF	1		1
Ramucirumab + Paclitaxel	2	2	
TOX	3		3
Other	2	1	2
Number of cycles (Range)	**6 (1–12)**	**7 (1–12)**	**4 (1–8)**

Major surgical complications were observed in 6 Group A patients (20.7%), 2 Group B patients (7%) and 4 Group C patients (13.8%). Ninety-day mortality happened in four patients; three deaths were related to surgical complications and one death to another cause. Of the three patients who died from surgical complications, two were in Group A (7%) and one in Group C (3.5%). In Group A, two patients presented with multi-organ failure leading to death due to sepsis following anastomotic dehiscence, one patient required reoperation for hemoperitoneum, another patient underwent reoperation for duodenal stump dehiscence, one patient presented with anastomotic leak which was treated endoscopically, and another presented with biliary stenosis which was treated with endoscopic stenting. The major surgical complications observed in Group B patients were as follows: one patient had an intestinal obstruction requiring re-operation and one patient had an endoscopically treated anastomotic leak. Major surgical complications in Group C (14%) were as follows: one patient had multi-organ failure due to sepsis with death related to anastomotic dehiscence, one patient had an endoscopically treated anastomotic leak, one patient had a duodenal stump dehiscence requiring re-operation and one patient had an abdominal collection requiring percutaneous drainage. A multivariate analysis was conducted to ascertain whether any risk factors were associated with complications of a severity greater than two, as defined by the Clavien–Dindo classification. The analysis revealed that none

of the parameters examined (age, number of anastomoses, type of anastomoses, Charlson's morbidity score, neoadjuvant chemotherapy) exhibited a statistically significant association with the outcome. The mean overall survival (OS) was 63 months (95% CI 36–90) for the 29 Group A patients, 112 months (95% CI 82–141) for the 28 Group B patients, and 69 months (95% CI 34–104) for the 29 Group C patients. Median overall survival was 30 months (95% CI 19–112) for patients in Group A, 28 months (95% CI 16–60) for patients in Group C, while it was not reached for patients in Group B. The one-, three-, and five-year survival rates for the three groups are as follows. Group A: 1-year survival rate, 81.1%; 2-year survival rate, 64.4%; 3-year survival rate, 36.8%. Group B: 1-year survival rate, 84.1%; 2-year survival rate, 75.7%; 3-year survival rate, 71.0%. Group C: 1-year survival rate, 88.0%; 2-year survival rate, 57.2%; 3-year survival rate, 42.9%. These results are shown in Figure 1.

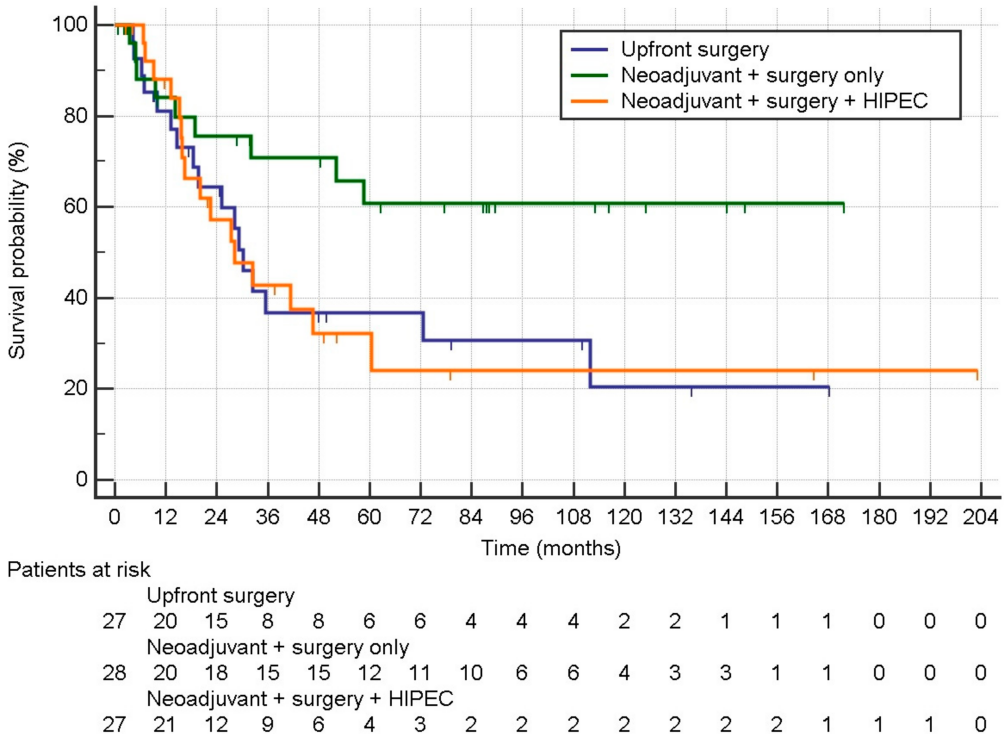

Figure 1. Description of overall survival in upfront surgery, neoadjuvant plus surgery, neoadjuvant + surgery + HIPEC patients.

The interquartile range (IQR) and median were used to present continuous data. The survival rates were calculated using the Kaplan-Meier curve. The time interval from surgery to death or the last follow-up was used to determine overall survival (OS). MedCalc Statistical Software v22.026 (MedCalc Software bvba, Ostend, Belgium) was used to conduct the analyses.

Table 3 shows a description of neoadjuvant chemotherapy regimens (DCF Docetaxel, Cisplatin, Fluorouracil; ECX Epirubicin, Cisplatin, Capecitabine; FLOT Fluorouracil, Oxaliplatin, Docetaxel; FOLFIRI Irinotecan, Fluorouracil, Leucovorin; FOLFOX Oxaliplatin, Fluorouracil, Leucovorin; PELF Epirubicin, Cisplatin, Fluorouracil, Leucovorin; TOX Docetaxel, Oxaliplatin, Capecitabine).

Table 4 shows a description of adjuvant chemotherapy regimens (De Gramont Leucovorin, Fluorouracil; ECX Epirubicin, Cisplatin, Capecitabine; EOX Epirubicin, Oxaliplatin, Capecitabine; FLOT Fluorouracil, Oxaliplatin, Docetaxel; FOLFIRI Irinotecan, Fluorouracil, Leucovorin; FOLFOX Oxaliplatin, Fluorouracil, Leucovorin; PELF Epirubicin, Cisplatin, Fluorouracil, Leucovorin; TOX Docetaxel, Oxaliplatin, Capecitabine).

4. Discussion

Palliative systemic chemotherapy remains the standard of care for metastatic gastric cancer, with a poor prognosis and a median survival of six months [2,9]. The findings of the Korean and Japanese REGATTA trial indicate that patients with stage IV gastric cancer may only benefit from chemotherapy, regardless of the metastatic site [17]. The advent of new systemic treatments has led to a significant improvement in the survival rate of patients with stage IV disease. In selected cases, survival periods of up to 8–14 months have been achieved [9,18–20]. However, in the presence of CP, the prognosis is considerably worse, with patients surviving less than 6 months and no survival after 5 years [2,9]. However, in other trials, these patients might respond extraordinarily well to palliative chemotherapy, transforming their disease into a radically operable stage and exhibiting encouraging outcomes in a particular cohort. In 2016, Yoshida et al. provided a clarification of the definition of conversion therapy as a surgical treatment with the aim of achieving complete surgical resection after chemotherapy of metastatic gastric tumors that were originally considered to be technically and/or oncologically unresectable [10]. The authors classified all metastatic patients into four classes, differentiating between macroscopic and non-macroscopic peritoneal involvement. They proposed conversion surgery for patients without peritoneal involvement. Nevertheless, the author's observations indicated that in a selected group of patients with peritoneal carcinosis, a favorable survival time outcome was achieved. The literature has also reinforced the notion that conversion surgery, even in the presence of peritoneal carcinosis, is associated with longer survival than chemotherapy alone, with reported survival times ranging from 37 to 56 months [10,11]. For patients with peritoneal metastatic disease, a radical surgical procedure combined with HIPEC appears to be a valuable option for improving survival. A multiplicity of observational studies, clinical trials, and meta-analyses have demonstrated that carefully selected patients can achieve improved outcomes [5,6,21–29]. The extension of peritoneal disease must be meticulously evaluated, as the volume of peritoneal disease is an independent prognostic factor. The probability of achieving complete cytoreduction is inversely proportional to PCI. In recent years, several studies have recommended a PCI limit to propose curative treatment. In 2010, Glehen et al. proposed a PCI limit of 12, based on their analysis of 159 patients with GC and PM, in which no patient with PCI > 12 survived [21]. They also observed an improvement in survival if cytoreduction is complete. Since the publication of this study, patients with a PCI > 12 are typically excluded from cytoreductive surgery and HIPEC in experienced centers. The latest trend is to be more stringent with the PCI limit, aiming for a PCI below 7 and achieving complete cytoreduction as a potential cure. In 2016, Chia et al. reported a median OS of 26.4 months for patients with a PCI < 7, compared to 10.9 months for patients with a PCI of 7 [30]. In a 2019 Spanish registry publication, an analysis was conducted on 88 patients. Among them, individuals with a PCI of less than 7 had a median overall survival (OS) of 26.1 months (5-year OS of 46.8%). In contrast, patients with a PCI of 7 had a median OS of 18.9 months (5-year OS of 0.0%) [31]. The German registry of 2020, which included 235 patients, also demonstrated a higher overall survival (OS) with a PCI < 7. The median OS was 18 months for patients with a PCI of 0–6, 12 months for patients with a PCI of 7–15, and 5 months for patients with a PCI of 16–39 [28]. Our study confirms these data, our CRS + HIPEC patients also reported a median overall survival of 28 months. We generally use a PCI cut-off of less than 7 when selecting patients for CRS + HIPEC. This study included two patients who were given HIPEC despite having a PCI greater than 6 because they were patients who had responded very well, and we preferred to give them a chance.

Other factors associated with improved outcomes in patients undergoing surgery + HIPEC include optimal preoperative performance status, response to neoadjuvant chemotherapy, and more than six cycles of chemotherapy [21,26]. The presence of ascites, signet ring cell histology, diffuse or mixed type, poor tumor differentiation, a high T-stage, and nodal involvement have been identified as factors associated with poor survival [22,24]. The prognosis of patients with positive peritoneal cytology (disease without macroscopic

peritoneal carcinosis) is comparable to that of patients with visible CP because these circumstances are considered a stage IV disease.

Multiple studies have revealed that in these cases, HIPEC therapy produces positive survival outcomes [31,32]. Rihuete et al. (2018) showed a 5-year OS of more than 60% in patients with positive cytology.

Peritoneal carcinosis represents the most prevalent tumor recurrence following radical gastrectomy with D2 lymphadenectomy in cases of locally advanced gastric carcinoma. Currently, the standard perioperative complementary therapy is systemic chemotherapy. Despite appropriate treatment, peritoneal relapse will still occur in approximately 40% of patients. The use of adjuvant HIPEC following curative gastrectomy in patients with locally advanced GC without CP may prevent peritoneal recurrence. A large number of studies have demonstrated the efficacy of HIPEC as a prophylactic treatment. In 2001, Yonemura et al. randomly assigned 139 patients to one of three treatment groups: surgery alone, surgery plus normothermic intraperitoneal chemotherapy (NIPEC), and surgery with HIPEC. The HIPEC group demonstrated the most favorable outcomes, with a 5-year overall survival (OS) rate of 61%, compared to 44% and 42% in the other two groups ($p = 0.021$) [33]. A few meta-analyses have demonstrated the efficacy of HIPEC as a prophylactic treatment [5,6,29]. Actually, we do not use hipec prophylactically, and the results of our study coincide with those in the literature which say that locally advanced patients who respond well to chemotherapy can only benefit from surgery. In our study, patients who underwent surgery for AGC without CP or positive peritoneal cytology (Group B) had excellent results and we found a 3-year survival rate of 73%. We need to wait for the results of large-scale prospective randomized studies on numerous patients to determine whether prophylactic HIPEC provides benefits over surgery alone. When comparing patients in Groups A and C, we observed similar survival rates. This might be because patients in Group C had received chemotherapy, suggesting that they were initially at a more advanced stage than those in Group A. Additionally, patients in Group C had more extensive PCI, indicating a more advanced disease. In our experience, the location of the peritoneal carcinosis (PC) also plays a significant role: perigastric carcinosis has a better prognosis than carcinosis located far from the main tumor site. However, we were surprised by the trend in Group A, which could be justified by the fact that surgery remains the primary treatment for this type of cancer when radical treatment is feasible.

The study has several limitations. Firstly, it is retrospective, which introduces a degree of bias. Second, over the 20-year study period, there were significant changes in the management of stage IV or advanced gastric cancer, leading to variability in treatment. Staging laparoscopy was not routinely performed before 2013, which may have influenced the type of treatment given. Finally, the group of patients undergoing preoperative surgery is very diverse and may have included a higher proportion of symptomatic cases and/or elected patients who were not suitable for preoperative treatment. These factors should be considered when interpreting survival curves. The results of our study indicate that the combination of CRS and HIPEC is a viable treatment option, with a low incidence of major complications and an overall favorable survival rate. In patients with advanced gastric neoplasia without evidence of CP and with negative cytology, chemotherapy followed by surgical resection we believe is an appropriate approach.

5. Conclusions

Despite the likelihood of gastric cancer metastasizing to the peritoneum, optimal management strategies for this population remain undefined.

Randomized controlled trials (RCTs), meta-analyses, and systematic reviews indicate that HIPEC may play a key role in improving the survival of patients with limited peritoneal carcinosis and our study confirms these data, while in patients with advanced gastric neoplasia without evidence of CP and with negative cytology, adjuvant chemotherapy followed by surgical resection we believe is an appropriate approach. We found that our patients who underwent CRS + HIPEC had a good survival rate. This suggests that our

approach to selecting and treating patients with limited CP may be effective. We want to emphasize the importance of carefully selecting patients and aiming for an oncologically radical approach.

Of course, large-scale randomized prospective studies are needed to assess which treatment options are best for these patients.

Author Contributions: Conceptualization, M.F. and G.E.; methodology, F.D. and D.D.P.; software, L.S.; validation, P.M. and G.V.; formal analysis, L.S.; data curation, F.T., G.E.C. and G.M.; writing—original draft preparation, M.F.; writing—review and editing, F.D. and D.D.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by Area Vasta Romagna Ethics Committee with the Protocol Code 5707/2020-I.5/264 on 3 July 2020.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets used/analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

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