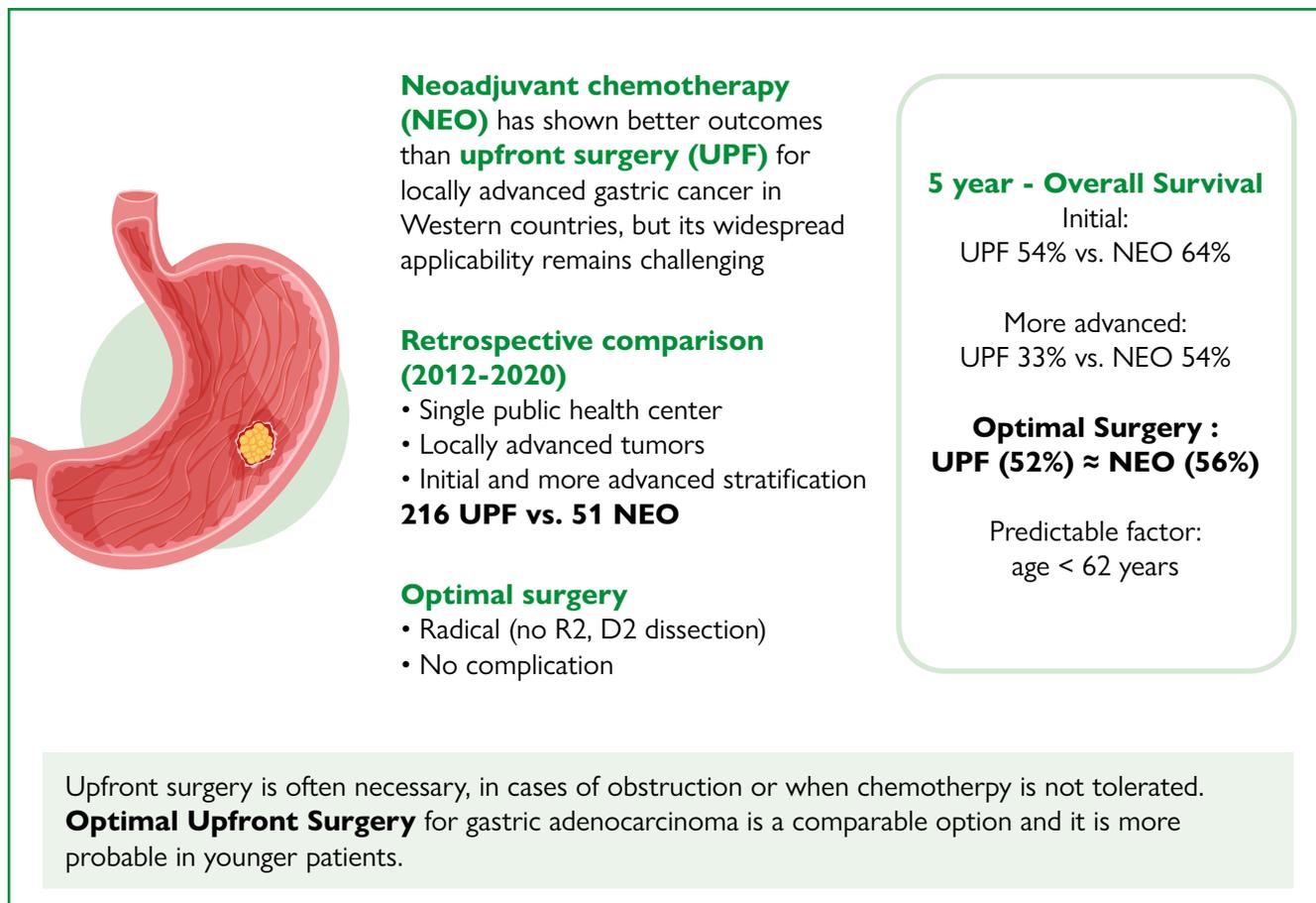




Optimal upfront surgery for gastric adenocarcinoma. Real life situation in Brazil. Results comparable to neoadjuvant treatment

VISUAL ABSTRACT



AUTHORS

Augusto Canton GONÇALVES ,
Rodrigo Silveira RACY , Anna Clara Hebling MITIDIERI ,
Beny Goulart Dias de CASTRO ,
Caio de Carvalho ZANON ,
Wilson Rodrigues FREITAS JUNIOR ,
Osvaldo Antonio Prado CASTRO , Paulo KASSAB

CORRESPONDENCE

Augusto Canton Gonçalves.
Email: cantonaugusto@gmail.com

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ARTICLE HIGHLIGHTS

- Preoperative systemic treatment is indicated for locally advanced gastric cancer in Western countries.
- However, especially in obstructive tumors, it is not tolerated.
- Optimal upfront surgery — radical and without complications — has demonstrated similar results to perioperative treatment.

CENTRAL MESSAGE

The distal stomach remains an important site of gastric adenocarcinoma. Due to the high rate of late diagnoses, patients' nutritional status is commonly affected, sometimes with gastric outlet obstruction, which often requires intervention before systemic treatment. Patient morbidity, costs, side effects, and variable response rates also hinder the decision for neoadjuvant treatment. In this context, upfront surgery becomes an alternative.

PERSPECTIVES

The higher incidence of distal tumors and subtotal gastrectomies in the UPF group, within a context of more advanced stages, might suggest a higher proportion of obstructive tumors and patients with poorer baseline status. However, even in this context, the outcomes of optimal upfront surgery were similar to those of neoadjuvant treatment. Optimal upfront surgery followed by adjuvant therapy, particularly with D2 dissection, is effective and was not statistically inferior to neoadjuvant treatment.



Optimal upfront surgery for gastric adenocarcinoma. Real life situation in Brazil. Results comparable to neoadjuvant treatment

Cirurgia de princípio ótima para adenocarcinoma gástrico. Realidade brasileira com resultados comparáveis ao tratamento neoadjuvante

Augusto Canton GONÇALVES¹ , Rodrigo Silveira RACY¹ , Anna Clara Hebling MITIDIERI¹ , Beny Goulart Dias de CASTRO¹ , Caio de Carvalho ZANON¹ , Wilson Rodrigues FREITAS JUNIOR¹ , Osvaldo Antonio Prado CASTRO¹ , Paulo KASSAB¹

ABSTRACT

Background: Complete neoadjuvant treatment for gastric cancer is not always tolerated due to nutritional and clinical reasons, such as gastric outlet obstruction. In this context, upfront surgery becomes an alternative. **Aims:** The aim of the study was to compare upfront resection with neoadjuvant systemic therapy followed by surgery and identify factors influencing their outcomes. **Methods:** Retrospective study of 410 patients with locally advanced gastric adenocarcinoma followed between 2012 and 2020, comparing upfront surgery and perioperative treatment. Patients with early tumor (cT1N0), metastasis, and stump cancer were excluded. The comparison was stratified by stage without the influence of systemic treatment (primary stage). Resections with D2 dissection, no residual tumor (no R2), and no complications were considered optimal surgery. **Results:** Upfront resection was performed in 216 patients (85% of upfront surgeries). Gastrectomy after neoadjuvant treatment was performed in 47 cases (76% of indications), and another four were resected among 39 previous unsuccessful surgeries (10%). In total, there were 51 resections after chemotherapy. Independent factors associated with overall survival at 60 months were: preoperative chemotherapy (57.3% vs. 40.7%, $p=0.029$); complication rate; D2 lymphadenectomy; and primary stage. Initial cases showed a better outcome in the neoadjuvant group without statistical significance ($p=0.447$), but it was present in more advanced tumors ($p=0.027$). Optimal surgery was achieved in 68.6% of the neoadjuvant group and 51.9% of the upfront group ($p=0.030$) and resulted in similar overall survival (56.6% vs. 52.4%, $p=0.904$). **Conclusions:** Optimal upfront surgery followed by adjuvant therapy, particularly with D2 dissection, is effective and was not statistically inferior to neoadjuvant treatment.

Keywords: Stomach neoplasms. Gastrectomy. Neoadjuvant therapy. Gastric outlet obstruction.

RESUMO

Racional: O tratamento neoadjuvante completo para o câncer gástrico nem sempre é tolerado por razões nutricionais e clínicas, como obstrução antropilórica. Nesse contexto, a cirurgia de princípio torna-se uma alternativa. **Objetivos:** Comparar ressecção de princípio com terapia sistêmica neoadjuvante, e identificar fatores que influenciam os resultados. **Métodos:** Estudo retrospectivo entre 2012 e 2020, de 410 pacientes com tumores localmente avançados. Lesões precoces (cT1N0), metastáticas e câncer de coto gástrico foram excluídos. O estadiamento foi estratificado sem influência do tratamento sistêmico (estadiamento primário). Ressecções com dissecação D2, sem tumor residual (não R2) e sem complicações foram consideradas cirurgias ótimas. **Resultados:** A ressecção de princípio foi realizada em 216 pacientes (85% das cirurgias de princípio). A gastrectomia após o tratamento neoadjuvante ocorreu em 47 casos (76% das indicações), e outras 4 gastrectomias foram realizadas entre 39 pacientes com cirurgias prévias sem ressecção (10%). No total, houve 51 ressecções após quimioterapia. Fatores independentes associados à sobrevida global em 60 meses foram: quimioterapia pré-operatória (57,3% vs. 40,7%, $p=0,029$), taxa de complicação, linfadenectomia D2 e estadiamento primário. Casos iniciais mostraram um melhor resultado no grupo neoadjuvante sem significância estatística ($p=0,447$), o que foi observado nos tumores mais avançados ($p=0,027$). A cirurgia ótima foi alcançada em 68,6% do grupo neoadjuvante e 51,9% do grupo de cirurgia de princípio ($p=0,030$), com sobrevida global semelhante (56,6% vs. 52,4%, $p=0,904$). **Conclusões:** Cirurgia de princípio ótima, seguida de terapia adjuvante, com dissecação D2, é eficaz e não foi estatisticamente inferior ao tratamento neoadjuvante.

Palavras-chave: Neoplasias gástricas. Gastrectomia. Terapia neoadjuvante. Obstrução da saída gástrica.

INTRODUCTION

Despite the recent increase in cardia tumors, the distal stomach remains an important site of gastric adenocarcinoma^{16,21,23,26}. Due to the high rate of late diagnoses, patients' nutritional status is commonly affected, sometimes with gastric outlet obstruction, which often requires intervention before systemic treatment^{5,6,14,17}. Patient morbidity, costs, side effects, and variable response rates also hinder the decision for neoadjuvant treatment. In this context, upfront surgery becomes an alternative. From 2013 to 2024, 85.7% of gastric cancer surgeries in the Brazilian public health system were performed

within 60 days of the diagnosis, whereas only 52.5% of patients referred for chemotherapy started the treatment within this period²⁴. The objective of this study is to compare upfront resection with neoadjuvant systemic therapy followed by surgery and to identify factors influencing their outcomes.

METHODS

The study is a retrospective analysis of patients with locally advanced gastric adenocarcinoma followed between 2012 and 2020 at a single center, comparing upfront surgery and preop-

¹Faculdade de Ciências Médicas da Santa Casa de São Paulo, Department of Surgery – São Paulo (SP), Brazil.

Correspondence: Augusto Canton Gonçalves. Email: cantonaugusto@gmail.com

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erative chemotherapy treatment. Patients with clinical diagnoses of early tumor (cT1N0), distant metastasis, and stump cancer were initially excluded. After staging laparoscopy or laparotomy, patients with unexpected carcinomatosis or other metastases were also excluded.

The treatment percentage in each group was calculated by dividing the total number of resections by the number of indicated patients, excluding cases with unexpected metastasis. Overall survival (OS) at 60 months was compared between the resections performed in an upfront (UPF) surgery setting and surgery following systemic treatment (neoadjuvant [NEO]), including resection cases with initial unsuccessful laparotomy attempts. The proposed treatment for each patient was chosen in routine tumor board meetings, considering tumor characteristics, patient clinical and social characteristics, such as conditions for regular transportation, family support, patient understanding and commitment to therapy. If possible, patients with more advanced tumors were intended to be referred for NEO treatment, but obstructive symptoms and social aspects frequently directed them to surgery. Lymphadenectomy D1 or D2 was defined by the surgeon based on intraoperative feasibility, where D1 was only performed when radical dissection was considered unsafe. Further postoperative analyses were performed, considering “true D2,” the cases with dissection of at least stations 8a, 9, and 11p on the pathology report, whereas “true D1” was considered when it involved only perigastric nodes and station 7. Resections with D2 dissection, no residual tumor (no R2), and no complications were considered optimal surgery. As a retrospective study, these analyses did not influence treatment decisions.

Tumor staging was based on the TNM (Tumor, Lymph Node, Metastasis) 8th edition³. For clinical staging of lymph nodes, the criteria used by Fukagawa et al.¹⁰ were applied. Nodes with a long axis=10 mm or a short axis=8 mm on tomography were considered positive. If the tumor depth was not defined by tomography, the endoscopic criteria of 6 cm size for more advanced lesions, used by Tanaguchi et al.²⁵, were applied. First, the entire cohort from both arms was compared, which was also adopted in prospective randomized studies^{8,27}. Second, to stratify the comparison between NEO and UPF by stage without the influence of systemic treatment, the clinical classification was used for NEO and the pathological classification for UPF, named the primary stage. NEO clinical stages cE I–II and UPF pathological stages pE IB–II were considered initial tumors. NEO clinical stages III–IVa and UPF pathological stage III were considered more advanced tumors.

Perioperative chemotherapy mainly consisted of protocols based on either Capecitabine or Epirubicin (XELOX or ECF). Most patients in the UPF group received postoperative MacDonald or XELOX protocol. Multivisceral surgery was defined by the resection of at least one of the following organs: colon, liver, pancreas, spleen, or diaphragm. The majority of patients (90%) were followed for at least 60 months, and the minimum period was 45 months. All data were obtained from the Esophagogastric and Bariatric Surgery Division of Santa Casa de São Paulo.

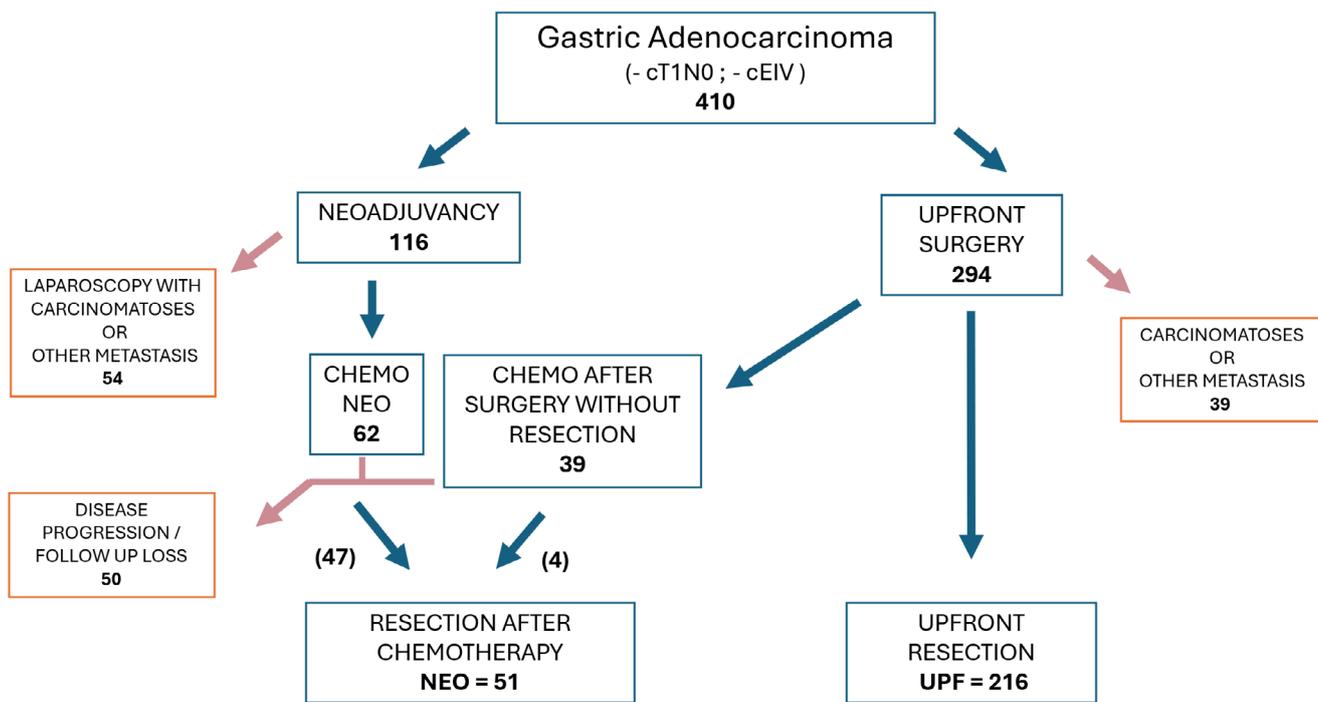
Patient characteristics were presented through frequencies and percentages for qualitative variables and by mean, median, standard deviation, minimum, and maximum values for quantitative variables. Association between qualitative variables was evaluated by Pearson's χ^2 test or Fisher's exact test (when 25% or more of the expected values were less than 5). The compari-

son between two groups for quantitative variables was assessed by Student's t-test or Mann-Whitney test (if the data did not follow a normal distribution). In the overall survival analysis, the time from surgery to death or last information was calculated; patients alive at the end of follow-up were considered “censored.” Survival curves were constructed using the Kaplan-Meier method and compared through the log-rank test. Additionally, Cox regression was used to calculate the hazard ratio (HR) and respective 95% confidence intervals. Finally, both unadjusted and adjusted HR values, according to variables of interest, were presented. Binary logistic regression was utilized to evaluate factors related to optimal surgery. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated for each variable of interest and presented through unadjusted and adjusted OR values. The analyses were performed using the statistical software SPSS for Windows v.25 and Stata v.14 for Windows. The study was approved by the Ethics Committee of the Institution (CAAE number 69680423.6.000).

RESULTS

During the study period, 410 patients with locally advanced gastric cancer attended our institution. Two-hundred and ninety-four patients were referred directly to surgery, and 39 of them had unexpected metastasis. Of the remaining 254, upfront resection (UPF) was performed in 216 (85%). In the NEO group with 116 patients, the staging laparoscopy detected metastasis in 54. Out of 62 patients, 47 (76%) underwent gastrectomy after neoadjuvancy, and another four were resected among 39 previous unsuccessful resection attempts (10%). In total, there were 51 resections after chemotherapy (NEO) (Figure 1).

UPF and NEO had similar mean ages of 61.8 and 58.0 ($p=0.05$). In both groups, male patients were more frequent. More advanced primary stage (pEIII) corresponded to 72.5% of UPF cases, and in NEO (cEIII and IVa), they were 63.9% of the patients, without statistical significance ($p=0.242$). The tumor size distribution, based on the number of affected stomach segments, was similar in UPF and NEO. The frequency of subtotal gastrectomies was 79.2% in UPF, with 65.3% of lower-centered tumors, whereas in NEO, subtotal resections represented 47.1% of cases ($p<0.001$), with 35.3% of the main portion of lesions in the distal stomach. There was no statistically significant difference in Lauren's histological type, but NEO had 63.9% of diffuse cell adenocarcinoma, more than UPF with 47.1% ($p=0.086$). Complete pathological response corresponded to 9.8% of NEO patients, and ypN0 was observed in 60.8% of cases. The percentage of D2 lymphadenectomy was 62.0% in UPF and 74.5% in NEO, with no statistically significant difference ($p=0.094$). Among D2 surgeries, D2 with 8a/9/11p dissection was also similar in UPF and NEO, with 89.6% and 92.1% ($p=0.767$), as was D1 without 8a/9/11p among D1 surgeries, with 86.6% and 76.9% ($p=0.400$), respectively. The mean number of resected lymph nodes had no statistically significant difference between the two groups, with 29.1 in UPF and 32.4 in NEO ($p=0.066$, $p>0.05$). When analyzed separately by type of lymphadenectomy, numbers were also similar for both D1 (UPF with 20.2 vs. NEO with 20.4 resected nodes, $p=0.918$, $p>0.05$), and D2 (UPF with 34.5 vs. NEO with 36.6, $p=0.205$). Patients, main characteristics are presented in Table 1, and the complete data are presented in Tables 2, 3, and 4.



cT1N0: early gastric cancer; cEIV: distant metastasis, stump cancer, and carcinomatosis; chemo=chemotherapy; NEO: neoadjuvant.

Figure 1. Study flowchart.

Considering all resected patients, the independent prognostic factors for overall survival at 60 months (OS) were: preoperative treatment, where NEO had better outcomes, with 57.3% compared to 40.7% in the UPF group (HR=0.60, $p=0.029$, $p<0.05$); complication rate (HR=1.99, $p=0.001$, $p<0.05$); D2 lymphadenectomy (HR=0.63, $p=0.006$, $p<0.05$); and primary stage (HR=1.62, $p=0.010$, $p<0.05$). Table 5 and 6 show the main variables associated with OS. UPF and NEO groups demonstrated no statistically significant difference in the survival curves for initial tumors ($p=0.447$, $p>0.05$), which was observed in the more advanced tumors group ($p=0.027$, $p<0.05$).

The UPF group had a lower bleeding rate and shorter procedures, but it demonstrated higher complication rates of 17.1% vs. 7.8% without a statistically significant difference ($p=0.098$, $p>0.05$). Among all UPF patients, the complications were characterized by 7.9% of anastomotic or stapler leaks and a 10.2% rate of Clavien-Dindo III or higher, including a 6% mortality rate, which was not seen in NEO (0%). Both UPF and NEO had around 10% of multivisceral resections, but with different distributions of affected organs. UPF had more R2 surgeries, with 6.9% vs. 2.0%, without statistical significance ($p=0.322$, $p>0.05$).

Lymphadenectomy showed different outcomes in UPF, as in this group, D1 dissection had an OS of 28.3 vs. 48.3% with D2 dissection ($p<0.001$). The difference was not as large in the NEO group, with OS of 68.4% for D1 and 57.5% for D2 surgeries ($p=0.369$, $p>0.05$). Consequently, UPF and NEO had similar survival curves with D2 dissection ($p=0.586$, $p>0.05$) and different curves with D1 dissection ($p=0.011$, $p<0.05$). Optimal surgery represented 68.6% of NEO and 51.9% of UPF ($p=0.030$, $p>0.05$) and had similar OS curves in both groups ($p=0.904$, $p>0.05$).

We analyzed a UPF group of 210 patients, examining preoperatively predictable variables in relation to optimal surgery. Independent associated variables were age (less than 62 years),

total gastrectomy, no multivisceral surgery, no three-segment tumor, and diffuse type (Table 7). Additionally, we assessed variables linked to increased complications in patients who underwent radical surgery (D2 lymphadenectomy without R2 resection, $n=130$) (Table 8).

DISCUSSION

Since the publication of the MAGIC trial in 2006⁸, preoperative chemotherapy for gastric adenocarcinoma has improved, and its benefit in Western countries was further confirmed by FLOT trial in 2019^{1,2}. Other Brazilian studies were compatible with our analysis, and they have also shown the advantage of preoperative chemotherapy in those patients that complete treatment, despite problems with patients' poor conditions and health care systems^{7,11,18}. Gastric outlet obstruction is one of the most important factors leading to the decision for upfront surgery in gastric cancer^{5,6,14,17}, and it has been described as a worse prognostic factor for non-metastatic cases^{6,14,17}. Unsurprisingly, our study identified more distal tumors, reflecting the necessity of intervention in patients with gastric outlet obstruction. The response to NEO therapy, considering the ypN0 rate and the absence of residual tumor percentage, was comparable to the literature, ranging from 31%⁸ to 59%¹ and from 3.0%²⁶ to 16%¹ respectively. As expected, this response to preoperative chemotherapy was more beneficial for more advanced tumors, which contributes to validate the adopted stratification criteria.

In our study, UPF presented a higher complication rate than NEO, including Clavien-Dindo III or higher, which was not seen in other studies^{8,11,20,27}. Although not all preoperative data were available, UPF patients might have had a worse clinical condition and nutritional status, due to obstructive disease. This may also be caused by the selection effect of neoadjuvancy. Patients operated on in the NEO group

Table 1. Patients main characteristics.

Characteristics	UPF	NEO	p-value
	n=216	n=51	
Age (years)			
Mean (SD)	61.8 (12.8)	58.0 (10.9)	0.05
Median (min–max)	63 (24–92)	57 (30–78)	
Lauren's type (%)			
Diffuse	138 (63.9)	24 (47.1)	0.086
Intestinal	72 (33.3)	25 (49.0)	
Mixed	6 (2.8)	2 (3.9)	
Primary stage (pUPF x cNEO) (%)			
Initial	78 (36.1)	14 (27.5)	0.242
More advanced	138 (63.9)	37 (72.5)	
Lymphadenectomy (%)			
D1	82 (38.0)	13 (25.5)	0.094
D2	134 (62.0)	38 (74.5)	
Lymphadenectomy D2—8a/9/11p dissection (%)			
Absent	14 (10.4)	3 (7.9)	0.767
Present	120 (89.6)	35 (92.1)	
Lymphadenectomy D1—8a/9/11p dissection (%)			
Absent	71 (86.6)	10 (76.9)	0.4
Present	11 (13.4)	3 (23.1)	
D1 resected lymph nodes			
Mean (SD)	20.3 (10.2)	20.2 (9.2)	0.918
Median (IQR)	20 (12–27)	18 (14–22)	
D2 resected lymph nodes			
Mean (SD)	34.5 (14.9)	36.5 (11.9)	0.205
Median (IQR)	31 (24–43)	34 (29–48)	
(y)pN (%)			
(y)pN0	45 (20.8)	31 (60.8)	<0.001
(y)pN+	171 (79.2)	20 (39.2)	
Surgery (%)			
Subtotal gastrectomy	171 (79.2)	24 (47.1)	<0.001
Total gastrectomy	45 (20.8)	27 (52.9)	
Multivisceral surgery (%)			
No	193 (89.4)	46 (90.2)	0.86
Yes	23 (10.6)	5 (9.8)	
Residual tumor (R2) (%)			
No	201 (93.1)	50 (98.0)	0.322
Yes	15 (6.9)	1 (2.0)	
Complications (%)			
No	179 (82.9)	47 (92.2)	0.098
Yes	37 (17.1)	4 (7.8)	
Complications – Leaks (%)			
No	199 (92.1)	51 (100)	0.05
Yes	17 (7.9)	0	
Clavien-Dindo (%)			
No complication	179 (82.9)	47 (92.2)	0.265
I/II	15 (6.9)	2 (3.9)	
III/IV/V	22 (10.2)	2 (3.9)	
Optimal surgery (%)			
No	104 (48.1)	16 (31.4)	0.03
Yes	112 (51.9)	35 (68.6)	

UPF: upfront; NEO: neoadjuvant; SD: standard deviation; min: minimum value; max: maximum value; IQR: interquartile range (Q1–Q3); UPF: upfront; NEO: neoadjuvant; ypN0: negative lymph nodes; ypN1: positive lymph nodes.

had already managed to overcome chemotherapy toxicity to be fit for surgery, representing a less vulnerable population, which is suggested by the lower percentage of patients reaching surgery in this group. This difference was also present in prospective trials^{8,27}.

D2 dissection was an important prognostic factor in the UPF group, which was not seen in the NEO. The equivalent quality of lymphadenectomy was verified by the similar proportion of nodes resected during D1 and D2 surgeries in both groups, and they also had a similar percentage of D2 with 8a/9/11p and D1 without 8a/9/11p, which was adopted to verify more precisely “true” D1 and D2 lymphadenectomy postoperatively. Previous studies have contributed to this discussion in the upfront surgery setting^{9,12,22}, but there are few studies concerning surgery radicality after the rise of preoperative chemotherapy.

The parameters used for optimal surgery are contemplated in the study of benchmarks for adenocarcinoma gastrectomies¹⁹. When patients underwent optimal surgery, there were no statistical survival differences between UPF and NEO, which contributes to the discussion about the selection of patients who benefit from preoperative chemotherapy. In addition, the lower percentage of patients reaching surgery in NEO is also relevant, pointing out the importance of the upfront alternative. It may be considered in a high incidence of obstructive distal tumors scenario, but also in the context of primary initial tumors, where UPF was also demonstrated to be not statistically inferior to NEO. This reflects the need for more prospective studies with primary stage stratification. Nevertheless, upfront surgeries had more morbidity, and together with the necessity of D2 dissection, they might become riskier.

Table 2. Patient characteristics².

General characteristics	UPF	NEO	p-value
	n=216	n=51	
Age (years)			
Mean (SD)	61.8 (12.8)	58.0 (10.9)	0.050*
Median (min–max)	63 (24–92)	57 (30–78)	
Sex (%)			
Female	88 (40.7)	17 (33.3)	0.330 [†]
Male	128 (59.3)	34 (66.7)	
Tumor center gastric segment (%)			
Low centered	141 (65.3)	18 (35.3)	<0.001 [†]
Middle centered	45 (20.8)	12 (23.5)	
Upper centered	30 (13.9)	21 (41.2)	
Number of affected segments (%)			
1	132 (61.1)	37 (72.5)	0.291 [†]
2	68 (31.5)	12 (23.5)	
3	16 (7.4)	2 (3.9)	
Lauren's type (%)			
Diffuse	138 (63.9)	24 (47.1)	0.086 [†]
Intestinal	72 (33.3)	25 (49.0)	
Mixed	6 (2.8)	2 (3.9)	
Primary stage (pUPF x cNEO) (%)			
Initial	78 (36.1)	14 (27.5)	0.242 [†]
More advanced	138 (63.9)	37 (72.5)	
Pathological stage			
Complete response	0	5	0.001 [†]
IA	0	9	
IB	17	9	
IIA	25	5	
IIB	36 (36.1%)	4 (62.7%)	
Initial			
IIIA	62	11	
IIIB	54	6	
IIIC	22 (63.9%)	2 (37.3%)	

UPF: upfront; NEO: neoadjuvant; SD: standard deviation; min: minimum value; max: maximum value.

*Student t-test; [†]Pearson χ^2 test.

The analysis of preoperatively predictable variables within the UPF group reveals which patients had a better chance of optimal upfront surgery. While tumor location and stage were not statistically significant, three-segment tumors showed a worse outcome. Total gastrectomy, the absence of multivisceral surgery, and age were also independent factors for optimal surgery. It is important to consider that performing radical surgery (D2 lymphadenectomy without R2 resection) involves the surgeon's intraoperative decisions. Objectively, we also analyzed the variables related to complication rate exclusively in patients who underwent radical surgery. The only independent factor that remained statistically significant in both analyses was age younger than 62 years. This suggests a greater relevance of the patient's clinical condition over the tumor characteristics themselves for the likelihood of optimal procedures when focusing solely on the upfront surgery setting. However, this must be interpreted carefully, as larger lesions may indirectly affect a patient's overall status, and older patients may also have poorer conditions for receiving chemotherapy, necessitating a tailored decision-making process. In the literature, more advanced stages and total gastrectomies are associated with a higher incidence of complications^{4,15}, while middle segment tumors are linked with better prognoses, though the association with complications is not widely described¹³. These dif-

ferences from our results warrant further investigation with a larger patient cohort and more comprehensive preoperative factors, but this certainly provides a promising direction for future research.

Regarding the implications for practice, we acknowledge that the current standard in many Western countries favors NEO treatment for advanced tumors when feasible. However, the reality of needing to perform upfront surgery, whether due to obstructive symptoms or patients' poor clinical and support conditions for receiving chemotherapy, necessitates a deeper understanding of this approach. Our study aimed to explore these scenarios, and our conclusions about optimal surgery point out that by verifying its likelihood preoperatively, it might be possible to better select patients for systemic treatment to avoid the risk of progression and side effects. Conversely, another practical conclusion is the need to identify unexpected intraoperative findings that hinder safe, optimal surgery. In this situation, surgeons may consider not advancing to resections, evaluating nutritional procedures, such as gastroenterostomies or jejunostomies, and directing the patient to NEO treatment.

As a retrospective study, our analyses had some limitations. Imprecise clinical staging, which is a major concern in gastric cancer treatment decisions, is also expected in our study, and some staging exams were performed at different institutions

Table 3. Patient characteristics of lymphadenectomy and lymph nodes.

Lymphadenectomy characteristics	UPF	NEO	p-value
	n=216	n=51	
Resected lymph nodes			
Mean (SD)	29.1 (15.0)	32.4 (13.3)	0.066*
Median (min–max)	27 (2–86)	32 (8–56)	
Affected lymph nodes			
Mean (SD)	5.9 (7.5)	2.8 (5.5)	<0.001*
Median (min–max)	4 (0–51)	0 (0–25)	
Lymphadenectomy (%)			
D1	82 (38.0)	13 (25.5)	0.094†
D2	134 (62.0)	38 (74.5)	
Lymphadenectomy D2 – 8a/9/11p dissection (%)			
Absent	14 (10.4)	3 (7.9)	0.767‡
Present	120 (89.6)	35 (92.1)	
Lymphadenectomy D1 – 8a/9/11p dissection (%)			
Absent	71 (86.6)	10 (76.9)	0.400‡
Present	11 (13.4)	3 (23.1)	
D1 resected lymph nodes			
Mean (SD)	20.3 (10.2)	20.2 (9.2)	0.918*
Median (IQR)	20 (12–27)	18 (14–22)	
D2 resected lymph nodes			
Mean (SD)	34.5 (14.9)	36.5 (11.9)	0.205*
Median (IQR)	31 (24–43)	34 (29–48)	
(y)pN (%)			
(y)pN0	45 (20.8)	31 (60.8)	<0.001†
(y)pN+	171 (79.2)	20 (39.2)	

UPF: upfront; NEO: neoadjuvant; SD: standard deviation; min: minimum value; max: maximum value; IQR: interquartile range (Q1–Q3); ypN0: negative lymph nodes; ypN1: positive lymph nodes.

*Mann-Whitney test; †Pearson χ^2 test; ‡Fisher's exact test.

before the patients were referred to our service. The preoperative chemotherapy started mainly in 2017 in our institution, leading to a smaller group of these patients. During the study period, systemic protocols were changed, with variable complete treatment rates, which corresponds to a bias. Comorbidities and body mass index information were frequently missing and could not be used.

We debated the use of propensity score matching, and we concluded that it might not be the most suitable approach given the smaller number of patients in the NEO arm, which could limit statistical power. Key baseline characteristics (age, primary stage, histological type, lymphadenectomy, multivisceral surgery, and residual tumor rate) were not statistically different between the groups. The higher incidence of distal tumors and subtotal gastrectomies in the UPF group, within a context of more advanced stages, might suggest a higher proportion of obstructive tumors and patients with poorer base-

line status. However, even in this context, the outcomes of optimal upfront surgery were similar to those of NEO treatment.

CONCLUSIONS

Optimal upfront surgery followed by adjuvant therapy, particularly with D2 dissection, is effective and was not statistically inferior to NEO treatment.

AUTHORS' CONTRIBUTIONS

ACG: Conceptualization, Data analysis, Investigation, Literature review, Methodology, Writing – original article. RSR: Data analysis, Investigation, Literature review. ACHM: Investigation. BGDC: Investigation. CCZ: Investigation. WRFJ: Conceptualization. OAPC: Conceptualization, Data analysis, Methodology. PK: Conceptualization, Data analysis, Investigation, Methodology.

Table 4. Patients surgical characteristics.

Surgical characteristics	UPF	NEO	p-value
	n=216	n=51	
Surgery (%)			
Subtotal gastrectomy	171 (79.2)	24 (47.1)	<0.001*
Total gastrectomy	45 (20.8)	27 (52.9)	
Multivisceral surgery (%)			
No	193 (89.4)	46 (90.2)	0.860*
Yes	23 (10.6)	5 (9.8)	
Pancreas	0	3 (5.9)	0.007 [†]
Liver	2 (0.9)	2 (3.9)	0.166 [†]
Colon	7 (3.2)	3 (5.9)	0.409 [†]
Spleen	11 (5.1)	2 (3.9)	0.999 [†]
Diaphragm	3 (1.4)	0	0.999 [†]
Residual tumor (R2) (%)			
No	201 (93.1)	50 (98.0)	0.322 [†]
Yes	15 (6.9)	1 (2.0)	
Bleeding (ml)			
Mean (SD)	263.9 (149.3)	371.3 (263.2)	0.001 [‡]
Median (min-max)	220 (50–780)	350 (50–1500)	
Surgery duration (min)			
Mean (SD)	209.9 (67.0)	238.0 (65.3)	0.016 [‡]
Median (min-max)	210 (45–390)	240 (140–480)	
Complications (%)			
No	179 (82.9)	47 (92.2)	0.098*
Yes	37 (17.1)	4 (7.8)	
Complications – Leaks (%)			
No	199 (92.1)	51 (100)	0.050 [†]
Yes	17 (7.9)	0	
Clavien-Dindo (%)			
No complication	179 (82.9)	47 (92.2)	0.265 [†]
I/II	15 (6.9)	2 (3.9)	
III/IV/V	22 (10.2)	2 (3.9)	

UPF: upfront; NEO: neoadjuvant; SD: standard deviation; min: minimum value; max: maximum value.

*Pearson χ^2 test; [†]Fisher's exact test; [‡]Mann-Whitney test.

Table 5. Patients' complications and postoperative staging.

Variable	HR non-adjusted (95%CI)	p-value	HR adjusted (95%CI)	p-value
Conduct				
Upfront	1		1	
Neoadjuvancy	0.57 (0.36–0.90)	0.017	0.60 (0.38–0.95)	0.03
Primary stage				
Initial	1		1	
More advanced	1.65 (1.14–2.37)	0.007	1.62 (1.12–2.34)	0.01
Lymphadenectomy				
D1	1		1	
D2	0.60 (0.43–0.83)	0.002	0.63 (0.45–0.87)	0.005
Complications				
No	1		1	
Yes	2.19 (1.47–3.25)	<0.001	2.04 (1.37–3.03)	<0.001
Pathological stage				
0–II	1			
III	2.25 (1.58–3.20)	<0.001		
Angiolymphatic invasion				
No	1			
Yes	2.12 (1.37–3.28)	0.001		
Perineural invasion				
No	1			
Yes	1.79 (1.23–2.61)	0.002		
Age (years)	1.02 (1.01–1.04)	<0.001		
Variable	HR non adjusted (95%CI)	p-value		
Gastrectomy				
Subtotal	1			
Total	1.39 (0.99–1.97)	0.059		
Lauren's type				
Diffuse	1			
Intestinal	0.79 (0.56–1.11)	0.171		
Mixed	0.97 (0.36–2.62)	0.944		
Multivisceral surgery				
No	1			
Yes	1.29 (0.78–2.13)	0.328		
Tumor center				
Lower	1			
Middle	1.06 (0.72–1.58)	0.76		
Upper	0.93 (0.60–1.43)	0.733		
Bleeding (mL)	1.001 (1.000–1.002)	0.207		
Surgery duration (min)	0.998 (0.996–1.001)	0.149		
Sex				
Female	1			
Male	0.94 (0.68–1.31)	0.728		

HR: hazard ratio; 95%CI: 95% confidence interval; yPN0: negative lymph nodes; yPN1: positive lymph nodes.

Table 6. Patients characteristics of upfront surgery and neoadjuvancy.

Variable	Mean survival time (months)	Overall survival probability			p-value
		1 year	3 years	5 years	
Upfront (n=216)					
Lymphadenectomy (%)					
D1	27	63.10	30.90	28.30	<0.001
D2	39.5	80.60	58.00	48.30	
Gastrectomy (%)					
Subtotal	36.5	78.30	51.00	43.30	0.043
Total	28.4	57.80	35.60	30.80	
Complications (%)					
No	37.7	78.70	52.60	43.90	<0.001
Yes	20.8	51.40	24.30	24.30	
pN (%)					
pN0	43.4	82.20	71.10	59.50	0.008
pN+	32.5	71.80	41.50	35.60	
Primary stage (pathological) (%)					
IB-II	41	79.50	64.10	54.20	0.005
III	31.2	70.80	38.40	33.00	
Optimal surgery (%)					
No	26.1	60.40	30.20	28.10	<0.001
Yes	42.9	86.60	64.00	52.40	
Neoadjuvancy (n=51) (%)					
Lymphadenectomy					
D1	47.8	92.30	76.90	68.40	0,369
D2	42.3	81.60	65.70	57.50	
Gastrectomy (%)					
Subtotal	48.2	91.70	79.20	65.20	0,239
Total	39.7	77.80	59.30	47.60	
Complications (%)					
No	43.6	85.10	68.00	59.00	0,81
Yes	45	75.00	75.00	37.50	
ypN (%)					
ypN0	52.5	90.30	87.10	83.70	<0,001
ypN+	29.9	75.00	39.40	15.00	
Primary stage (clinical) (%)					
I*/II	47.6	92.90	71.40	64.30	0,532
III/IVa	42.3	81.10	67.60	54.30	
Optimal surgery (%)					
No	46.4	87.50	75.00	60.60	0,646
Yes	42.5	82.90	65.60	56.60	
Pathological stage (%)					
0-II	52.5	90.60	90.60	73.20	<0,001
III	29	73.70	30.70	30.70	

ypN0: negative lymph nodes ; ypN1: positive lymph nodes ; pN: postoperative lymph nodes.

Table 7. Preoperative predictable variables related to upfront optimal surgery.

Variable	OR non-adjusted (95%CI)	p-value	OR adjusted (95%CI)	p-value
Age (ref.>62 years)*	1		1	
≤62 years	3.53 (2.00–6.24)	<0.001	3.73 (2.00–6.97)	<0.001
Sex (ref. Male)	1			
Female	1.31 (0.76–2.28)	0.337		
Stage (ref. More advanced)	1		1	
Initial	1.47 (0.84–2.59)	0.182	1.66 (0.88–3.12)	0.118
Gastrectomy (ref. Subtotal)	1		1	
Total	1.79 (0.90–3.56)	0.095	3.40 (1.28–9.08)	0.014
Multivisceral (ref. Yes)	1		1	
No	1.68 (0.68–4.11)	0.259	3.38 (1.06–10.73)	0.039
Main segment (ref. L)	1			
Segment M	1.42 (0.72–2.83)	0.314		
Segment U	1.06 (0.47–2.35)	0.894		
Number of segments (ref. 1)	1		1	
2	1.65 (0.91–3.02)	0.102	1.27 (0.64–2.49)	0.497
3	0.82 (0.29–2.32)	0.703	0.20 (0.05–0.84)	0.028
Histology (ref. Intestinal)	1		1	
Diffuse	1.93 (1.08–3.44)	0.026	2.04 (1.07–3.91)	0.031
Angiolymphatic inv. (ref. Yes)	1			
No	1.22 (0.61–2.46)	0.579		
Perineural inv. (ref. Yes)	1			
No	0.75 (0.40–1.39)	0.355		

N: 210 (six cases with mixed Lauren's type were excluded); OR: odds ratio; 95%CI: 95% confidence interval.

*Median age=62.

Table 8. Preoperative predictable variables related to absence of complications in radical upfront surgery (D2 lymphadenectomy without R2 resection).

Variable	OR non-adjusted (95%CI)	p value	OR adjusted (95%CI)	p value
Age (ref.>62 years)*	1		1	
≤62 years	7.28 (2.28–23.30)	0.001	9.57 (2.76–33.20)	<0.001
Sex (ref. Male)	1			
Female	3.21 (1.01–10.23)	0.048		
Stage (ref. More advanced)	1			
Initial	1.62 (0.58–4.52)	0.361		
Gastrectomy (ref. Subtotal)	1			
Total	1.37 (0.42–4.43)	0.604		
Multivisceral (ref. Yes)	1			
No	3.74 (1.10–12.68)	0.034		
Main segment (ref. L)	1		1	
Segment M	0.34 (0.12–0.96)	0.042	0.22 (0.07–0.71)	0.012
Segment U	0.58 (0.14–2.45)	0.458	0.62 (0.13–2.82)	0.533
Number of segments (ref. 1)	1			
2	1.59 (0.52–4.84)	0.102		
3	0.45 (0.10–2.00)	0.703		
Histology (ref. Intestinal)	1			
Diffuse	1.78 (0.66–4.76)	0.254		
Angiolymphatic inv. (ref. Yes)	1			
No	4.81 (0.61–37.87)	0.136		
Perineural inv. (ref. Yes)	1			
No	0.93 (0.31–2.80)	0.895		

N: 130 (three cases with mixed Lauren's type were excluded); OR: odds ratio; 95%CI: 95% confidence interval.

*Median age=62.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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