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TESI DI LAUREA

UPFRONT SURGERY VERSUS NEOADJUVANT CHEMOTHERAPY FOLLOWED BY SURGERY FOR RESECTABLE GASTRIC CANCER. AN OBSERVATIONAL RETROSPECTIVE STUDY.

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ABSTRACT

Introduction

Gastric cancer represents a major global health concern, with over 1 million cases diagnosed worldwide each year. Surgical resection remains the only curative option available for gastric cancer and the oncologic outcomes strictly depend on the radicality of surgery. Thus, a multimodal approach involving the combination of preoperative chemotherapy with postoperative adjuvant therapy has been progressively adopted, with the purpose of reducing the lesion size before surgery. Few randomized trials documenting an actual superiority of multimodal approach over upfront surgery alone have been published. However, these studies have a significant underlying bias: the results of the chemotherapy scheme were compared to those of a surgical treatment that was not in conformity with the major international standards in terms of lymphadenectomy and surgical radicality.

Aim of the study

This retrospective study aims to demonstrate a non-inferiority of up-front surgical treatment (intended as total gastrectomy with D2 lymphadenectomy) alone over current neoadjuvant chemotherapy schemes followed by surgery, in terms of oncological outcomes.

Materials and Methods

Single high-volume center data of patients with adenocarcinoma of the stomach and of the cardia (Siewert types II and III) submitted either to upfront surgery (SURG group, n=72) or to neoadjuvant chemotherapy plus surgery (NAT group, n=35) were retrospectively analyzed.

Results

A total of 107 patients with adenocarcinoma of the stomach and of the cardia were included. No statistically significant difference was reported in the overall survival (OS) (80 months for the SURG group and 40 months for the NAT group, p=0.2613) between the SURG and the NAT group. Similarly, disease-free survival (DFS) was comparable between the two groups (10 months for the SURG group, 8 months for the NAT groups, p=0.1629). Patients with cTNM stage III did experience a benefit in terms of OS and DFS when receiving NAT, although the difference did not reach a statistical significance. In 18 patients (51.5%), NAT has led to a significant down staging of the tumor. A R0 resection was reported in 88 patients (82,2%).

Conclusion

Upfront radical gastrectomy might be considered for patients with early stages of gastric cancer, while neoadjuvant chemotherapy might be an alternative option for patients with resectable locally advanced disease, especially stage III.

Part I

State of the Art

1. INTRODUCTION

1.1. GASTRIC CANCER: AN OVERVIEW

1.1.1. INCIDENCE, MORTALITY AND GEOGRAPHICAL VARIABILITY

Although the incidence of gastric cancer (GC) is declining in the Western world due to appropriate interventions, it still constitutes a major global health problem, especially in East Asian countries. Globally, it appears to be the fifth most frequently diagnosed cancer, accounting for over 1,000,000 new cases each year. In 2020, It was responsible for over 768,000 deaths worldwide, making it the fourth leading cause of cancer-related deaths. (3) Compared to women, male rates are two times higher. Moreover, there is a significant geographic variation in the incidence of gastric cancer. (*Figure 1*) In many Western Asian nations, including Iran, Turkmenistan, and Kyrgyzstan, gastric cancer is the most frequently diagnosed cancer in men and the main cause of cancer mortality. Eastern Asian countries, including Mongolia, Japan and the Republic of Korea, have the highest incidence in men and women, respectively, while Northern America and Northern Europe often have lower rates that are comparable to those observed throughout all of Africa. (3)

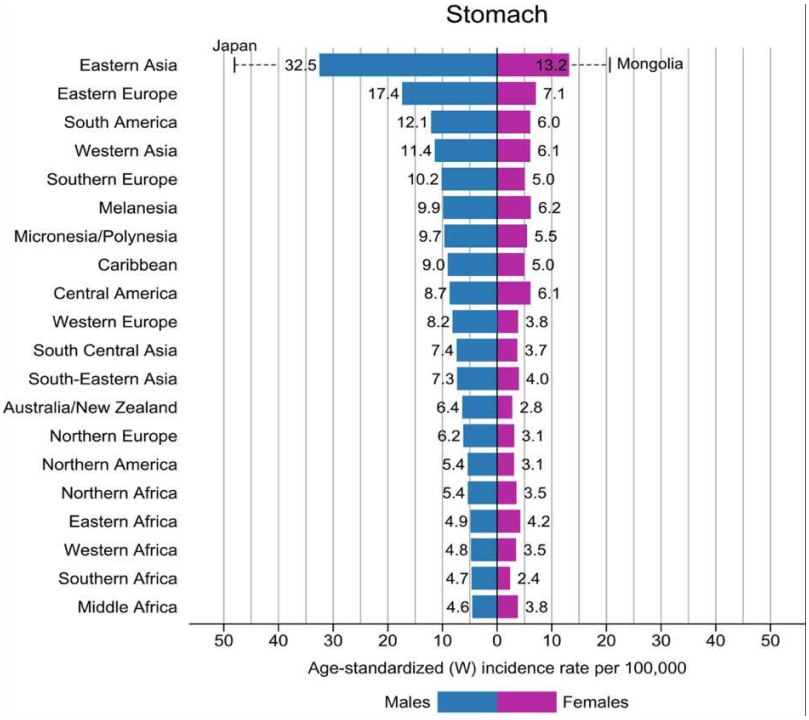

Figure 1: Region-specific incidence age-standardized rates by sex for stomach cancer in 2020. Rates are shown in descending order of the world (W) age-standardized rate among men, and the highest national rates among men and women are superimposed. Source: GLOBOCAN 2020.

The standard incidence rate in Italy is about 15-20 cases/100000 inhabitants per year with remarkable variability among the regions as well as among rural and industrial zones. In 2022, approximately 14,700 new diagnoses were estimated, including 8800 men and 5,900 women, respectively.

The reported overall survival rate at 5 years for AJCC Stage III is 44.5% in Japan, 59.5% in Taiwan, 63,7% in South Korea, 46.6% in Germany, 31.5% in United Kingdom, 47% in Norway, 35% in Hong Kong, 67% in South Africa, 47% in The Netherlands and more than 50% in some Italian series. (2)

1.1.2. RISK FACTORS

Stomach cancer can typically be divided into two major topographical subtypes, the cardia and noncardia gastric cancers, which have different risk factors, carcinogenesis, and epidemiologic patterns. (3) Chronic infection with *Helicobacter pylori* is considered the principal cause of

noncardia gastric cancer, being responsible for 89% of cases, and 78% of all gastric cancer cases, respectively. (4) The prevalence of this chronic infection is extremely high, infecting 50% of the world's population, and its geographical distribution correlates reasonably with that of stomach cancer, resulting in Asian countries having the highest rate. However, less than 5% of infected hosts will develop gastric cancer, likely because of variability in both bacterial and host genetics, age at the time of infection, and environmental factors. *Helicobacter pylori* is a Gram-negative bacterium that has been described as a class I carcinogen by the WHO since 1994. There are two main mechanisms by which the infection caused by this bacterium affects the oncogenesis process: an indirect inflammatory reaction on the gastric mucosa and a direct epigenetic outcome of H. pylori on gastric epithelial cells. (5) Intense tissue inflammation as well as premalignant and malignant lesions in the distal stomach seem to be associated with H. pylori expression of virulence genes such as cagA and vacA. Besides, H. pylori infection impairs the gastric tissue microenvironment, promoting epithelial–mesenchymal transition (EMT) and further gastric cancer progression. Similarly, the *Epstein-Barr Virus* infection is also responsible for an increased risk of cancer occurrence. About 10% of gastric carcinomas have been described to be EBV-positive and these all differ due to patients' characteristics, like sex, age, or anatomic subsite, and decrease with age among males.

Beyond *H. pylori* infection, various modifiable and nonmodifiable factors modulate the risk of gastric cancer (6), including genetic factors like family history and genetic talent, or environmental factors related to lifestyle and nutrition, such as low fruit and vegetables intake, foods preserved by salting, alcohol consumption, tobacco smoking. There is also strong evidence of increased risk caused by *Epstein–Barr virus* infection. (7)

Regarding genetic factors, gastric cancers are mostly sporadic and familial clustering is observed in about 10% of the cases. Hereditary gastric carcinomas include less than 3% of all cases. Hereditary diffuse gastric cancer (HDGC) is the most recognizable familial gastric carcinoma, and it results from a mutation in the CDH1 gene that encodes for E-cadherin, a transmembrane protein with an important role in establishing cell polarity and maintaining normal tissue morphology. A downregulation of this gene often correlates with strong invasive potential of human carcinomas and is demonstrated to be associated with about 70% and 56% lifetime risk in males and females respectively of developing gastric cancer. (8) CDH1 mutations account for 40% of HDGC families, but germline alterations of other genes, such as CTNNA1, are suggested to be responsible of remnant 60% of cases, with similar risk of developing gastric cancer.

Other familial cancer syndromes include Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, which is characterized by a mutation in 1 of 4 DNA mismatch repair genes (MLH1, MSH2, MSH6, and PMS2) and correlates with a lifetime risk up to 10% of developing gastric cancer along with colorectal and endometrial cancer, and familial adenomatous polyposis (FAP), a syndrome arising from a mutation in the APC tumor-suppressor gene, which causes formation of >100 synchronous colorectal adenomas at a younger age, resulting in about 100% risk of colon cancer, and is shown to increase the risk of gastric polyps. Another polyposis syndrome associated with higher risk of gastric cancer is MUTYH-associated polyposis (MAP), caused by mutations in MUTYH gene, a member of base-excision repair family, and being responsible of multiple adenomas in the colon and rectum. (8) Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) is a recently discovered syndrome characterized by >100 fundic gland polyposis with areas of

multifocal dysplasia, resulting from mutations in the APC gene and it correlates with a risk of 12-20% based to available literature. Lastly, patients affected by Juvenile polyposis syndrome (JPS), Peutz-Jegher syndrome (PJS) or Li-Fraumeni syndrome (LFS) have up to 21%, 29% and 2-5% lifetime risk respectively of being diagnosed with gastric carcinoma. (8) Ultimately, genetic susceptibility may be responsible for modifying the effect of environmental and dietary exposures, especially in nations where familial gastric cancer tends to have higher incidence.

Interestingly, many studies demonstrated that patients with group A blood type carry a higher relative risk of gastric cancer compared with other blood types and it is assumed that it may be caused by alterations in gastric secretion, intracellular signaling, inflammatory response to infections or increased susceptibility to pernicious anemia. (8)

Regarding dietary factors, according to The World Cancer Research Fund (WCRF), fruit and vegetables are acknowledged for being protectors against gastric carcinoma development. Fiber intake has also been inversely correlated to the risk of gastric cancer since dietary fibers may neutralize potentially carcinogenic nitrites and thus reduce their intragastric concentration. An increase of 10 g of dietary fiber per day is reported to be associated with a 44 % decreased risk of gastric cancer. (9) By contrast, the high consumption of processed or grilled meats high in nitrites and nitrosamines, salt-preserved or smoked foods can contribute to the development of gastric cancer, due to the interaction between food carcinogens and gastric epithelial cells that provokes changes in genes expression. N-nitroso compounds have been shown to significantly increase the risk of gastrointestinal cancer, mostly in cases of non-cardiac gastric carcinoma. (7)

Furthermore, the effects of smoking and alcohol have been taken into consideration as two habits that certainly affect the gastric cancer development. Studies show that smokers have approximately an 80% increased risk of developing cancer among non-drinkers. Besides, heavy drinkers have an around 80% increased risk of developing gastric cancer among smokers. (10) A Korean study demonstrates how the alcohol intake affects the risk of GC development among a group of patients with ALDH2 polymorphisms and the ALDH2*1/*2 genotype. (11)

Lastly, some studies found association between a rare disorder known as Ménétrier disease and increased cancer-related mortality, suggesting surveillance endoscopy is needed to early detect gastric cancer onset in this high-risk subgroup. In particular, this is a rare premalignant hyperproliferative gastropathy characterized by excessive mucosal hypertrophy and protein-losing enteropathy, along with hypochlorhydria, and massive foveolar hyperplasia as histopathologic finding. (12)

1.1.3. PRIMARY AND SECONDARY PREVENTION

Despite advancements in surgery and new therapeutic strategies in oncology, gastric cancer still has a very poor prognosis, and it tends to be detected at late stage mostly because it often does not cause specific symptoms. When symptoms do occur, they may be vague, including unexplained weight loss, vague abdominal pain, nausea, hyporexia, and fatigue. Therefore, measures are warranted focusing on prevention, surveillance of subjects with premalignant lesions and early diagnosis to reduce gastric cancer incidence and mortality.

H. pylori gastritis is the predominant risk factor and recent data suggest that its eradication - at any stage of gastritis - has a beneficial effect on the risk of developing gastric cancer and results in decreasing its incidence. In countries with high gastric cancer incidence, a population-based eradication seems a worthwhile intervention, while a more targeted approach consisting in treating only high-risk groups could be considered in moderate-to-low-incidence countries. In Western countries, the balance between benefits, harms and costs of H. pylori eradication is less clear-cut, since a larger number of people need to be tested for H. pylori for every gastric cancer death prevented.

Other prevention strategies for gastric cancer aim to identify patients with premalignant lesions either by endoscopic or serologic screening. Upper endoscopic screening is based on thorough examination of the stomach lining either by endoscopic evaluation alone (as it is frequently performed in Japan), or in combination with random and targeted biopsy sampling with the use of the OLGA scoring system. (13) Endoscopic examination has the highest accuracy for assessment of the gastric mucosa, but it could only be feasible in high-risk populations given the costs and the number of subjects needed to screen. Therefore, upper endoscopy for gastric cancer screening alone would not be cost-effective in Western countries. (4) Besides, serologic screening is potentially an elegant and more widely applicable alternative for endoscopic screening. It is based on pepsinogen I, II, and their ratio, sometimes combined with serum anti-*H. pylori* IgG antibody levels and measurement of fasting gastrin. Measurement of pepsinogen I and II offer a sensitivity of 69–70 % and a specificity of 88–97 % for the diagnosis of extensive chronic atrophic gastritis. (14) Subjects with a positive serology result must undergo endoscopy to assess the extent and

severity of the suspected lesions. On the other hand, pepsinogens perform better for detecting atrophic gastritis than for gastric neoplasms.

Although endoscopic screening doesn't seem to be cost-effective in low incidence countries, endoscopic surveillance of patients with precancerous lesions may be. (13) Surveillance would aim for timely diagnosis of cancer allowing for curative therapy and reduction of mortality. It's currently advocated in low-to-high incidence countries, and available data seem to support this practice.

Further preventive interventions aim at promotion of a healthy lifestyle with dietary advice (increased fruit and vegetables intake, salt restriction), limited alcohol consumption and smoking cessation. Several studies are also researching the impact of certain pharmacological interventions on gastric cancer incidence, including statins and non-steroidal anti-inflammatory drugs (NSAID). Statin use is shown to be correlated to a modest risk reduction and consequently, to prevent a single case of gastric cancer, a high number of subjects need to be treated long-term. (13) Moreover, Cyclooxygenase-2 is involved in H. pylori-associated gastric carcinogenesis (15), but Cox-2 inhibitors don't seem to have any additional beneficial effect after its eradication.

1.1.4. GASTRIC CARCINOGENESIS PATHWAY (CORREA'S CASCADE)

Gastric cancer is a multi-factorial disease that develops with a multi-step process, known as Correa cascade. (16) This consists of sequential events from nonactive (or chronic active) gastritis to precancerous lesions, and finally, gastric carcinoma. In summary, the Correa's cascade comprises:

1. Non-active or chronic active gastritis;

2. Precancerous lesions:
    i. atrophic gastritis;
    ii. intestinal metaplasia;
    iii. low-grade dysplasia;
    iv. high-grade dysplasia;
3. gastric adenocarcinoma.

H. pylori infection is a crucial trigger in carcinogenesis, leading to persistent inflammatory microenvironment and subsequent multiple phenotypic disorders. Correa cascade begins with a first inflammatory phase which damages the gastric mucosa. The primary preventive measures for this phase aim to eradicate H. pylori, reducing inflammation, and promoting the mucosal restoration. The second phase includes all types of gastric precancerous lesions, which is the turning point in Correa cascade for gastric carcinogenesis, and their regression is the secondary prevention strategy. Unfortunately, there is no specific drug able to reach a real *restitutio ad integrum* of gastric mucosa at this stage. The third - and last - phase consists in neoplastic proliferation, invasion and metastatization. Therefore, discovering new pharmacologic therapies that counteract this almost irreversible process of gastric carcinogenesis is the key to gastric cancer prevention and treatment.

1.1.5. HISTOPATHOLOGICAL CLASSIFICATION

Approximately 90% of gastric cancers are adenocarcinomas (ACs), but other rarer malignancies affecting the stomach include gastrointestinal stromal tumors (GISTs), lymphomas and neuroendocrine tumors (NETs). According to the stage at diagnosis, gastric cancer can be divided into two major subtypes: the early-stage cancer and the locally advanced one, respectively.

Based on macroscopic features, early gastric carcinomas are sub-classified into three main categories, according to the Endoscopic Classification Review Group (Paris classification): 0-I (protruded); 0-II (superficial); and 0-III (excavated). (17) Instead, locally advanced gastric carcinomas are macroscopically sub-classified according to the Borrmann classification into four types: polypoid/fungating without ulceration (type I), ulcerated with elevated borders and sharp margins (type II), ulcerated with diffuse infiltration at the base (type III) and diffusely infiltrative with thickening of the wall (type IV).

There are several pathohistological classification systems for the diagnosis of gastric cancer; the most used are the World Health Organization (WHO) and Japanese Gastric Cancer Association (JGCA) classifications, as well as that proposed by Laurén, which defines three main subtypes: intestinal, diffuse, and mixed. (18) The fifth edition of the WHO classification (published in 2019) is widely used in Western countries and recognizes five main histological subtypes: tubular, papillary, poorly cohesive (including signet ring cell and other subtypes), mucinous and mixed adenocarcinomas, with an addition of rare subtypes such as micropapillary carcinoma, gastric adenocarcinoma of the fundic gland type and undifferentiated carcinoma. (19)

1.1.6. ESOPHAGOGASTRIC JUNCTION ADENOCARCINOMA

Gastroesophageal junction (GEJ) adenocarcinoma is usually classified into three subtypes based on the Siewert classification (20), and they have different therapeutic implications:

- Siewert type I cancers: located between 1 and 5 cm above the GEJ; they are generally believed to develop in the context of lower esophageal Barrett's oesophagus;

- Siewert type II cancers: located between 1 cm above and 2 cm below the GEJ; they are true gastric cardia tumors;
- Siewert type III cancers: located between 2 and 5 cm below the GEJ, with invasion of the esophagus; they are subcardial gastric cancers.

The 8th edition of TNM classification included the redefinition for tumors located at the esophagogastric junction: cancers involving the gastroesophageal junction that have their epicenter < 2 cm into the proximal stomach (Siewert type I/II) are to be staged as esophageal carcinomas, whereas cancers whose epicenter is > 2 cm into the proximal stomach would be staged as gastric carcinomas. (21)

1.1.7. MOLECULAR BIOLOGY

The identification of new molecular patterns of gastric cancer allows a better understanding of its pathohistological sub-types and therefore may lead to identify new therapeutic targets. Since it is characterized by intratumoural and intertumoural heterogeneity, this entails both diagnostic and therapeutic challenges.

The Cancer Genome Atlas research network identified four different gastric cancer molecular pattern: EBV positive, microsatellite instability-high, genomically stable and tumours with chromosomal instability (CIN).(22) Specifically, amplification in key receptor tyrosine kinase oncogenes such as HER2, EGFR, FGFR2 and MET typically characterize the CIN sub-type. In patients with metastatic gastric cancer, HER2 expression status and PD-L1 combined positive score (CPS) should be investigated to customize first-line treatment in association with chemotherapy. Indeed, patients with HER2-positive gastric cancer benefit from treatment with the monoclonal antibody Trastuzumab, in addition to standard chemotherapy. The prevalence of HER2-overexpressing tumours is about 10%-20%, with higher prevalence in oesophagogastric junctional cancers and in the intestinal

subtype. (23) The intratumoural heterogeneity of HER2 expression hinders the effectiveness of this targeted treatment, therefore quantitative reporting of the percentage of tumour cells stained positively for HER2 by IHC has been suggested. Besides, immuno-therapies such as PD-1-inhibitors demonstrate efficacy in gastric cancer. The prevalence of PD-L1 CPS >1 (this cut-off would indicate positive PD-L1 expression) tumours is above 50%-60%. (24) A CPS cut-off >5 represents a validated threshold for overall survival benefit of treatment with Nivolumab in addition to standard first-line chemotherapy.

Microsatellite instability high/mismatch repair deficient (MSI-H/dMMR) are associated with better prognosis in resectable gastric cancer. (25) As MSI-H/dMMR are associated with an improved benefit from immunotherapy compared with chemotherapy in stage IV gastric cancer, MSI/MMR status should be assessed for patients with locally advanced and unresectable or metastatic gastric cancer to tailor treatment accordingly.

Other molecular markers, such as FGFR2 amplification/overexpression, MET amplification, claudin-18.2 overexpression and EBV are currently being investigated as potential predictive biomarkers.

1.1.8. CLINICAL PRESENTATION AND DIAGNOSIS

Early gastric cancer is often asymptomatic and about 80-90% of the patients are diagnosed at advanced stages and will likely have a poor outcome, especially in most Western countries, where no screening program in realized because of low gastric cancer incidence. In advanced disease, common signs and symptoms include dysphagia, asthenia, dyspepsia, vomiting, weight loss, hyporexia, early satiety and iron deficiency anemia. In many cases, these non-specific symptoms do not lead to urgent investigations, and this results in delayed diagnosis. Overall, 60% of people with gastric cancer are not eligible for curative treatment due to late

presentation or comorbidities. Additionally, nearly 80% of patients have regional lymph nodes involvement and the N staging parameter is known to profoundly influence survival rate. Instead, prognosis of patients with localized resectable disease depends on the surgical stage of the disease.

The gold standard method for diagnosing gastric cancer is upper-gastrointestinal endoscopic examination and multiple (5-8) biopsies should be carried out to provide adequately sized material for histological and molecular (including HER2 expression status and PDL1 CPS) interpretation, especially in the setting of ulcerated lesions. Endoscopic mucosal resection and endoscopic submucosal dissection may be curative and diagnostic for superficial lesions such as dysplasia or intramucosal carcinoma.

1.1.9. STAGING AND RISK ASSESSMENT

Currently, the American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis (TNM) staging system is the most common system used for gastric cancers. This system is based on the depth of tumour invasion (T), number of involved lymph nodes (N), and presence or absence of metastatic disease (M). The eighth edition of the AJCC Cancer Staging Manual specifies three different staging types (26):

- cTNM, clinical staging: it is based on physical examination, signs and symptoms, or the results of imaging tests and it's done before any surgical treatment is started,
- pTNM, pathologic staging: it results from histopathologic examination of a surgical specimen in patients undergoing resection without prior treatment,
- ypTNM, post-neoadjuvant pathologic staging: as for pTNM, in patients undergoing resection after preoperative therapy.

Clinical staging (cTNM) provides useful prognostic information for the development of an optimal treatment strategy for gastric cancer, and it has been significantly improved by the introduction of diagnostic modalities like endoscopic ultrasound (EUS), computed tomography (CT), 18-fluorodeoxyglucose-positron emission tomography/CT (18-FDG-PET/CT), and diagnostic laparoscopy.

Endoscopic ultrasound is recommended for assessing gastric wall involvement and presence of infiltrated perigastric lymph nodes. However, the diagnostic accuracy, which can range from 57% to 88% for T staging and 30%-90% for N staging, is operator-dependent. (27) The limited depth and visualization of the transducer represent a limit to distant lymph node evaluation. (28) Therefore, endoscopic ultrasound should be used if early-stage disease is suspected to define potential endoscopic approaches, or if early versus locally advanced disease (T3 or T4 tumour) needs to be determined. (27)

CT scanning, with an overall accuracy of 43–82% for measuring depth of invasion, is routinely used for preoperative staging. In contrast, 18-FDG-PET has improved specificity (92% vs. 62%), but significantly lower sensitivity (56% vs. 78%) when detecting local lymph node involvement than CT, and there is also low 18-FDG uptake in diffuse and mucinous subtypes. Furthermore, peritoneal involvement is often difficult to detect with FDG-PET. (29) As a result, combined FDG-PET/CT imaging seems to have higher accuracy rate in preoperative staging (68%) than FDG-PET (47%) or CT (53%) alone. (30)

Although EUS and CT currently represent the primary imaging modalities in clinical decision making, magnetic resonance imaging (MRI) showed great value in clinical application among patients with gastric cancer in refining preoperative staging and evaluating response to treatment, and providing more accurate information, particularly for patients who cannot

tolerate iodine contrast agents and those with peritoneal carcinosis or small hepatic metastatic lesions.

According to a recent metanalysis, sensitivity and specificity of MRI to diagnose T stage are about 93% and 91%, and N stage, 86% and 67%, respectively. However, the application value of MRI in patients with gastric cancer has not yet reached consensus. (31)

Diagnostic laparoscopy can be used to detect radiographically occult metastases in patients with T3 or N1 tumors before surgical resection or preoperative therapy. (30) However, laparoscopic staging is based on a bidimensional evaluation and has limited accuracy in the identification of hepatic metastases and perigastric lymph nodes. Besides, cytology testing of peritoneal fluid may be useful to identify occult carcinomatosis since its positive result is associated with a poor prognosis and high probability of recurrence following curative resection. (32) Therefore, even without macroscopic peritoneal implants, a positive peritoneal cytology should be regarded as M1 disease, requiring chemotherapy as the first line of treatment. Preoperative laparoscopy may be performed to assess the peritoneal cavity and analyze peritoneal washings in medically fit patients with potentially resectable stage cT1b or higher locoregional disease when considering preoperative therapy. Laparoscopy with cytology can also be considered for medically fit patients with surgically unresectable disease.

TNM Classification of Carcinoma of the Stomach

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ; intraepithelial tumor without invasion of the lamina propria
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures
T4	Tumor invades serosa (visceral peritoneum) or adjacent structures
T4a	Tumor invades serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures
Regional Lymph Nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
N3a	Metastasis in 7-15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Table 1 TNM classification of gastric carcinoma. From Edge S, Byrd D, Compton C, et al, editors: AJCC cancer staging manual, ed 7, New York, 2010, Springer.

ANATOMIC STAGE	PROGNOSTIC GROUP		
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
	T1	N1	M0
IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
IIIB	T4b	N0	M0
	T4b	N1	M0
	T4a	N2	M0
	T3	N3	M0
IIIC	T4b	N2	M0
	T4b	N3	M0
	T4a	N3	M0
IV	Any T	Any N	M1

Table 2 Anatomic stage and prognostic group for gastric cancer. From Edge S, Byrd D, Compton C, et al, editors: AJCC cancer staging manual, ed 7, New York, 2010, Springer

1.2. TREATMENT OF GASTRIC CANCER

1.2.1. GENERAL PRINCIPLES

Gastric cancer is generally classified as early gastric cancer, operable gastric cancer, and advanced gastric cancer as regards diagnosis and treatment management.

- **Early gastric cancer** is an invasive malignant tumour confined to the mucosa and submucosa (T1), regardless of the lymph node involvement (any N). Endoscopic resection is the gold standard for treatment of early gastric cancer, and this tumour is associated with an extremely good prognosis (> 90% 5-year survival).
- **Operable gastric cancer** is defined as resectable locally advanced (≥T2 N+) tumour.
- **Advanced gastric cancer** is inoperable locally advanced or metastatic disease.

Therapeutic decisions for patients with gastric cancer are usually made with a multidisciplinary team approach. Gastric cancer treatment is individualized and based on both tumour characteristics (endoscopic findings, histology, staging evaluation) and patients' clinical fitness and preference. Although a multimodal approach is mandatory, surgery is still considered the standard of care.

1.2.2. ENDOSCOPIC RESECTION

Endoscopic resection is a minimally invasive treatment strategy for premalignant gastrointestinal lesions, and it is a well-established first-line treatment modality for selected early-stage gastric cancer in East Asian and Western countries.

Recently, with improvements in the early detection of superficial neoplasia and advances in techniques used, endoscopic resection has become widely performed, having favorable clinical outcomes compared to those of surgical resection, such as greater safety and improvement of the patient's quality of life. Therefore, it has become the standard of care for tumors that have minimal risk of lymph node metastasis, based to the following inclusion criteria (33):

- intramucosal differentiated tumor without ulcers, size >2 cm;
- intramucosal differentiated tumor with ulcers, size ≤3 cm;
- intramucosal undifferentiated tumor without ulcers, size ≤2 cm;
- submucosal invasion less than 500 μm (sm1), differentiated tumor, size ≤3 cm.

These "expanded" criteria led to accomplishing large en bloc resections by using minimally invasive endoscopic submucosal dissection.

Basically, two different endoscopic procedures can be performed:

- **Endoscopic mucosal resection (EMR)**: using either suck and cut (suction) or lift and cut (nonsuction) technique, intramucosal tumours with a <2 cm diameter can be safely removed. (34) In the lift and cut technique, the lesion is separated from the muscularis propria by means of submucosal injection, and this will reduce the chances of perforation. In cases of invasive lesions, a nonlifting sign appears signaling the unsuitability of performing mucosal resection. Instead, trough the suction technique a pseudopolyp is formed by band ligation, which is then resected with a snare. However, in cases of the EMR cap technique, submucosal injection is used, and the lesion is sucked into the cap and resected using a prelooped snare.
- **Endoscopic submucosal dissection (ESD)**: using this technique, various types of endoscopic electrosurgical knives are used to dissect submucosal layer and remove tumors greater than 2 cm in diameter

with acceptable complication rates. Endoscopic submucosal dissection is superior than endoscopic mucosal resection for en bloc resection, complete resection, curative resection and local recurrence risk, while having an increased perforation risk and longer operation time. Therefore, this technique provides an alternative to surgical resection for early gastric cancer patients with ignorable risk of lymph node metastasis. (35)

1.2.3. SURGICAL RESECTION

Surgical options for gastric cancer are mainly subtotal or total gastrectomy, whereas limited resections (nonanatomic wedge-type resection or limited proximal gastrectomy) are infrequently considered since they are most likely to adversely impact oncologic outcomes. Indeed, approximately 75% of cases in Western countries are poorly differentiated gastric cancers and this requires wide resection to ensure negative margins. Moreover, T1a tumours have about 10% probability of lymph node involvement, whereas T1b and T2 tumours have 34% and 44% probability of involvement, respectively. (36) Since lymphatic spread is the main prognostic factor in patients undergoing curative resection for gastric cancer, a radical treatment is required to lower the risk of local and/or systemic relapse, by providing adequate longitudinal and circumferential resection margins and ensuring an adequate D2 lymph node dissection. (37)

The term *R status* defined by Hermanek et al (38) is used to describe the extent of resection, which directly influences gastric cancer patients' survival. Specifically, R0 refers to a microscopically margin-negative resection, R1 indicated removal of all macroscopic disease with remanence of microscopic disease, and R2 describes gross residual disease with gross residual tumor due to an inadequate resection of primary tumor, infiltration of regional nodes, and to macroscopic margin involvement). Long-term

survival can be expected only after an R0 resection with optimal lymphadenectomy. (38)

Furthermore, the development of laparoscopic and robotic-assisted surgery, along with endoscopic resection for early-stage gastric cancer, have had an important impact on the treatment strategies revolution in the last few decades. Minimally invasive surgery was originally limited to treat distal early gastric cancers, not requiring complete gastrectomy or extended lymphadenectomy. Both minimally invasive and robotic gastrectomies are considered to provide positive clinical outcomes, equivalent to those of open surgeries and, additionally, they present even lower rates of postoperative complications, such as incisional hernias or bowel obstructions, which frequently occur following gastrectomy via laparotomic access. (39–41)

1.2.3.1. SUBTOTAL AND TOTAL GASTRECTOMY

Nowadays, subtotal gastrectomy accounts for 23%-70% of all cancer resections performed in high-volume centers. It's usually defined as "2/3" or "4/5" gastrectomy based to the extent of gastric resection, but these don't have any oncological implication as long as the proximal margin of the resection is tumour-free and adequate lymphadenectomy is performed. Instead, the size of the remnant stomach pouch is essential for the following reconstruction phase; when it is of adequate size a tension-free gastroduodenal anastomosis can be obtained based to the Billroth I method, whereas other reconstruction methods (Billroth II or Roux-en-Y) are used in case of short remnant. Since long-term oncological outcome does not seem to be affected by the type of gastric resection or by the length of the proximal resection margin, in patients with middle-third (gastric body or antrum) advanced gastric cancer a subtotal gastrectomy with curative intent (when a >1 cm proximal free margin is guaranteed, according to the JCGC) can be

safely performed. (37) Such patients will benefit in terms of postoperative morbidity and mortality rates, as well as quality of life so this procedure is to be preferred in cases of patients with advanced age, malnutrition, and comorbidities.

On the other hand, total gastrectomy is indicated for tumors involving the proximal or entire stomach, or in selected cases such as signet ring cell gastric cancer, or hereditary diffuse gastric cancer (42).

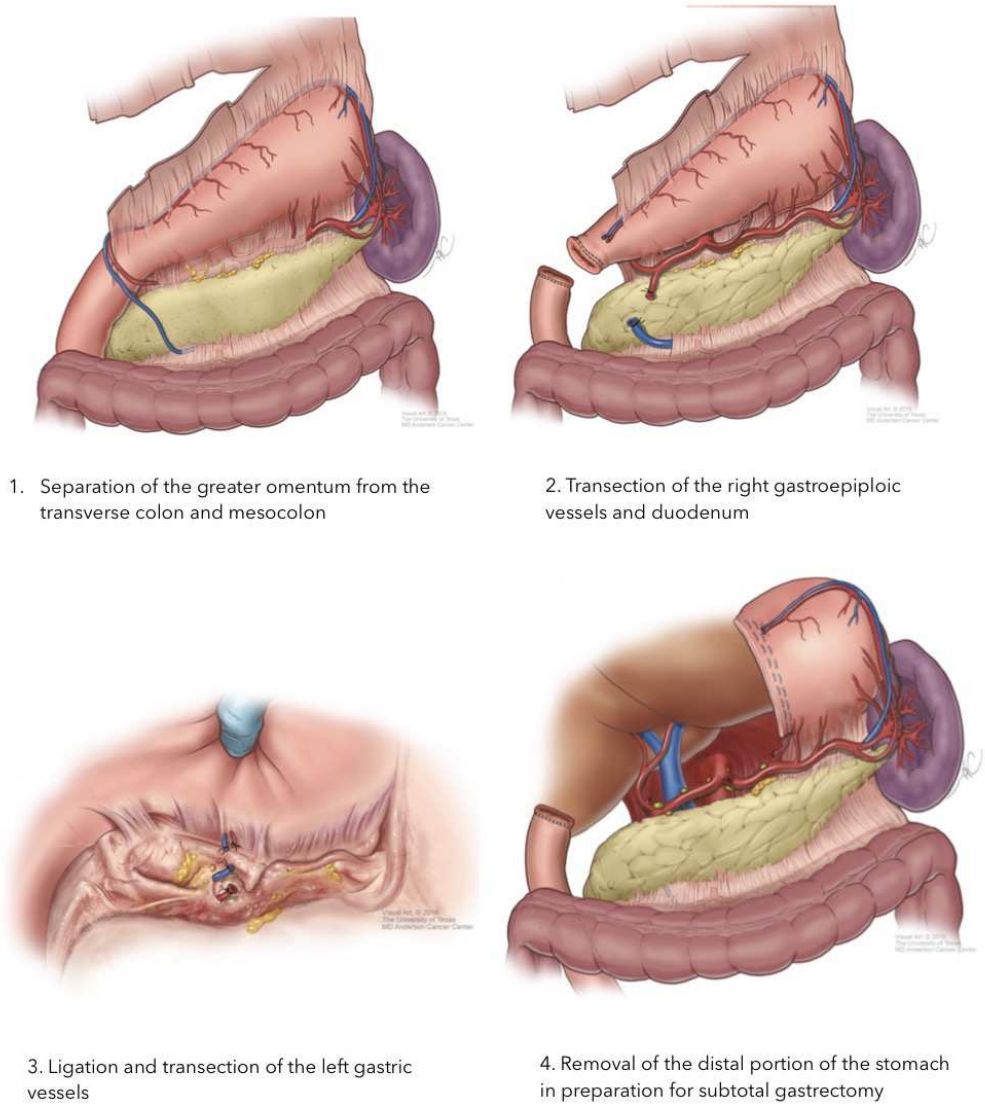

Figure 2. Operative steps in subtotal gastrectomy for gastric cancer. The greater omentum is separated from the transverse mesocolon (1), then follows the transection of the right gastroepiploic and gastric vessels and duodenum (2). The left gastric vessels are cut (3) before transection of the stomach for subtotal gastrectomy (4) and final reconstruction (Figure 3). In cases of tumors that extend more proximally, the short gastric vessels are also transected, and reconstruction is performed. Source: CA CANCER J CLIN 2021; 71:264–279

1.2.3.2. ONCOLOGICAL PRINCIPLES OF D2 LYMPH NODE DISSECTION

There has not been a wide consensus about the proper type of lymph node dissection that should be performed between Eastern and Western surgeons, until the publication of the latest studies. (43) In Eastern countries, the D2 lymphadenectomy has been considered the standard of care. On the contrary, in Western countries, the D2 lymphadenectomy was traditionally considered as an over-treatment for gastric cancer patients since its increased perioperative morbidity and mortality rate without significant survival benefits, therefore total or distal gastrectomy was usually accompanied by a more limited dissection.

Furthermore, three major randomized controlled trials which compared D1 and D2 lymphadenectomy performed within gastric resection have drastically influenced the guidelines for gastric cancer surgical treatment. These include the notorious "Dutch trial" (1989-1993) by the Dutch Gastric Cancer Group (44), the MRC trial performed by Cuschieri et al (45), and a study conducted by the Italian Gastric Cancer Study Group. (43) As the MRC and the Dutch trial reported higher postoperative morbidity and mortality for D2 lymphadenectomy, the authors of the latter study concluded that the postoperative complications in the D2 arm were not as high as previously reported and it should be considered the best option for patients with advanced disease and lymph node metastases. (46) They also recommend a D2 lymphadenectomy in clinically early carcinomas that are not suitable for endoscopic treatment. Indeed, a more limited lymphadenectomy in patients with co-morbidities, not eligible for endoscopic treatment, would be a good compromise between the risks of an extensive operation in a fragile patient and optimal oncological results. In clinical practice, D2 standard lymph node dissection becomes mandatory in most patients, whereas a less extensive lymphadenectomy can be

performed in 10-20% of cases. Results of trials on gastric cancer multidisciplinary management reported higher survival rates of D2 surgery alone compared to those of less extensive surgery plus adjuvant therapy. (37)

Also, it is now clear that the higher rate of morbidity and mortality associated to D2 lymphadenectomy are mostly related to distal pancreatectomy and/or splenectomy which were routinely performed along with proper D2 lymphadenectomy. According to 15-year survival data by Dutch trial, patients with lymph nodal invasion who undergo D1 gastrectomy are likely to show early local recurrence because of inadequate dissection. In conclusion, spleen and pancreas preserving D2 dissections are recommended for patients with resectable gastric cancer, as they are performed by adequately trained surgeons in high-volume centers.

In general, as the survival benefit has been widely demonstrated, the global consensus on D2 lymphadenectomy has significantly increased. On the contrary, it is still controversial whether to perform an extended lymphadenectomy beyond the usual D2 dissection provide any advantage in treating advanced gastric cancer. The routine D2 plus the para-aortic nodes dissection is currently no more indicated since a Japanese trial showed no survival benefit compared to D2 lymphadenectomy alone in the absence of clinical suspicion of para-aortic node metastases.

1.2.3.3. CLASSIFICATION OF GASTRIC LYMPH NODE STATIONS

Lymph node dissection in gastric cancer had firstly been standardized in 1973 by recognizing 16 distinct anatomic lymph node stations and then revised in 2011 with the JGCA classification where a detailed description of the regional lymph nodes of the stomach is provided. *(Table 3)* According to this classification, the lymphatic drainage of the stomach is drained via lymphatics and filtered through lymph nodes which are mainly classified

into regional stations (stations 1-12 and station 14v) plus distant stations (13-20, 110-112). Metastasis to any other node is staged as M1. To determine the N status, the total number of lymph nodes (the examination of 16 or more regional lymph nodes is recommended) and the number of involved lymph nodes at each nodal station are recorded. When a malignant nodule is found in the lymphatic drainage area of the primary tumor, it is counted as a metastatic lymph node in the N status determination.

The JGCA defined the extent of systematic lymphadenectomy according to the type of gastrectomy performed. For total gastrectomy, D1 lymphadenectomy requires the dissection of stations from No.1 to 7; D1+ includes D1 stations plus stations No.8a, 9, and 11p, and D2 includes D1 stations plus stations No.8a, 9, 10, 11p, 11d, and 12a. (46) For distal gastrectomy, the lymph nodes stations to be dissected in D1 lymphadenectomy are stations No.1, 3, 4sb, 4d, 5, 6 and 7; D1+ includes D1 stations plus stations No.8a, and 9, and D2 includes D1 stations plus stations No.8a, 9, 11p, and 12a. (46)

1.2.3.4. LYMPH NODE DISSECTION FOR EARLY GASTRIC CANCERS

Early gastric cancer was thought to have an excellent prognosis with survival rates of 98-100% after treatment, but some threatening subgroups have lower survival rates (about 70%) due to an increased lymph node metastases incidence (14-20%). The most important prognostic factors for early gastric cancer are:

- The depth of invasion in the gastric wall: the 5-year survival rate is 100% for mucosal lesions and 90% for lesions penetrating the submucosa.
- The morphological growth patterns of the lesions. According to Kodama classification of morphological growth patterns,

penetrating A type is associated with a 31.7% risk of lymph nodes disease.

- The lymphovascular invasion status: the mean incidence of lymph node metastases is 53% in the presence of lymphovascular invasion compared to 9% in the absence of invasion.
- The tumour grade of differentiation: well-differentiated tumors have lymph node involvement in 13% of the cases compared to 34% when a poorly differentiated tumor is the case.
- The histopathologic lesion type: diffuse type (sec. Lauren) and tumor size >2 cm significantly increases the risk of lymph node involvement. The probability of lymph node metastases is about 2.3 times higher for depressed lesions compared to elevated lesions, according to Paris classification.

No	Nodal station	No	Nodal station
1	Right paracardial LN	12p	LN in the hepatoduodenal ligament (behind the portal vein)
2	Left paracardial LN	13	LN on the posterior surface of the pancreatic head
3	LN along the lesser curvature	14v	LN along the superior mesenteric vein
4sa	LN along the short gastric vessels	14a	LN along the superior mesenteric artery
4sb	LN along left gastroepiploic vessels	15	LN along the middle colic vessels
4d	LN along right gastroepiploic vessels	16a1	LN in the aortic hiatus
5	Suprapyloric LN	16a2	LN around the abdominal aorta (from the upper margin of the celiac trunk to the lower margin of the left renal vein)
6	Infrapyloric LN	16b1	LN around the abdominal aorta (from the lower margin of left renal vein to upper margin of the inferior mesenteric artery)
7	LN along the left gastric artery	16b2	LN around the abdominal aorta (from the upper margin of the inferior mesenteric artery to the aortic bifurcation)
8a	LN along the common hepatic artery (Antero-superior group)	17	LN on the anterior surface of the pancreatic head
8p	LN along the common hepatic artery (Posterior group)	18	LN along the inferior margin of the pancreas
9	LN around the celiac artery	19	Infradiaphragmatic LN
10	LN at the splenic hilum	20	LN in the esophageal hiatus of the diaphragm
11p	LN along the proximal splenic artery	110	Paraesophageal LN in the lower thorax
11d	LN along the distal splenic artery	111	Supradiaphragmatic LN
12a	LN in the hepatoduodenal ligament (along the hepatic artery)	112	Posterior mediastinal LN
12b	LN in the hepatoduodenal ligament (along the bile duct)		

Table 3 Lymph node station numbers as defined by the Japanese Gastric Cancer Association. (From Japanese Gastric Cancer Association: Japanese Classification of Gastric Carcinoma, 2nd English edition. Gastric Cancer 1:10–24, 1998.)

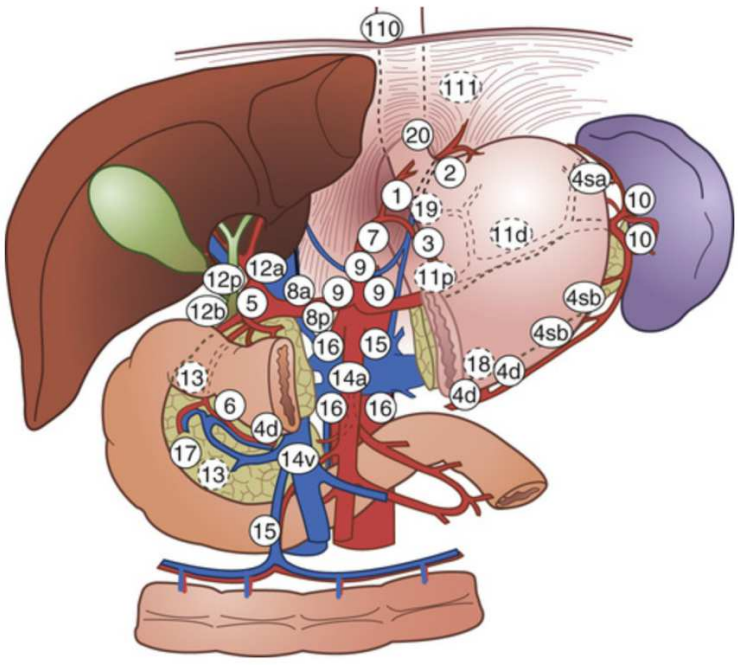

Figure 3 Lymph node station numbers as defined by the Japanese Gastric Cancer Association. (From Japanese Gastric Cancer Association: Japanese Classification of Gastric Carcinoma, 2nd English edition. Gastric Cancer 1:10–24, 1998.)

1.2.3.5. RECONSTRUCTION AFTER SUBTOTAL GASTRECTOMY

There are multiple reconstruction methods after subtotal gastrectomy, such as Billroth I gastroduodenostomy, Billroth II gastrojejunostomy (with or without Braun anastomosis), Roux-en-Y gastrojejunostomy, uncut Roux-en-Y gastrojejunostomy and jejunal interposition. Generally, the proper reconstruction procedure should be chosen based on surgical results, as well as the functional outcome and postoperative quality of life.

Symptomatic bile reflux esophagitis is the most important factor influencing postoperative quality of life, but various reconstruction methods help to prevent it; however, this complication occurs in 5% of patients, regardless of the type of reconstruction. (47) Billroth I and II reconstructions are the preferred method of anastomosis across Japan, whereas Roux-en-Y anastomosis is routinely performed by Western surgeons, with a view to preventing symptomatic gastroesophageal reflux disease, reducing the risk of cancer of the gastric stump, and improving the functional outcome.

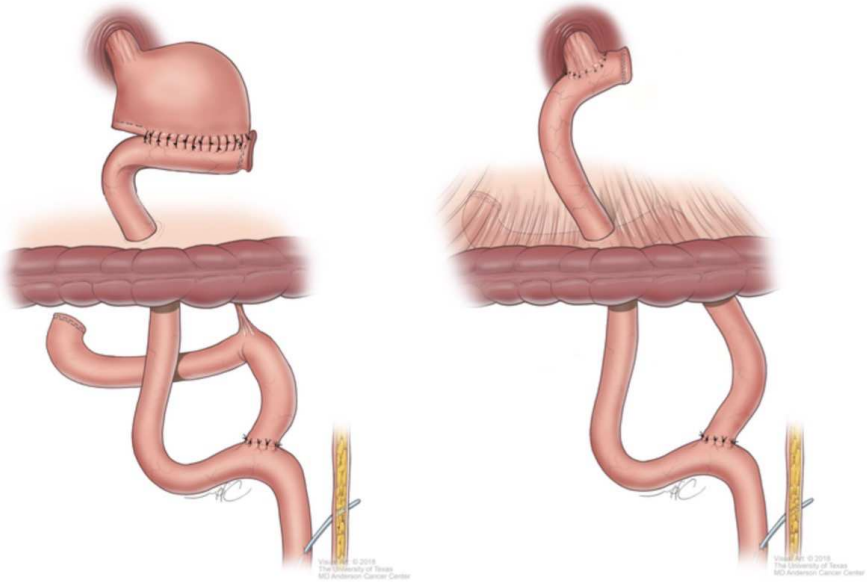

Figure 4. Types of reconstruction following subtotal or total gastrectomy for gastric cancer. Source: CA CANCER J CLIN 2021; 71:264–279

1.2.3.6. RISK OF CANCER OF THE GASTRIC STUMP

Cancer of the gastric stump is typically detected 5-10 years after subtotal gastrectomy. (48) A gastric stump cancer detection within 5 years from gastrectomy probably results from understaged disease or from non-curative gastrectomy due to the choice to perform partial gastrectomy instead of total gastrectomy. On the other hand, true primary cancer of the gastric stump occurs more than 5 years postoperatively, with a less than 1% incidence in the long-term. (49) In Eastern countries it accounts for two thirds of all cancer gastrectomies, with early carcinoma affecting 60% of all patients, regardless of the reconstruction procedure. Therefore, ~~a~~ lifelong endoscopic monitoring to detect early gastric cancer is recommended. (37)

1.2.3.7. FUNCTIONAL OUTCOME

When considering the surgical management of gastric cancer patients, the postoperative quality of life is an essential aspect that cannot be ignored. The most frequent disorders affecting gastrectomized patients include reflux esophagitis, alkaline gastritis, as well as symptoms determining functional dyspepsia, such as the dumping syndrome, the delayed gastric emptying and malabsorption. Bile reflux into the gastric remnant following Billroth I and II reconstruction is recognized to be a major cause of postoperative disorder. On the other hand, Roux-Y reconstruction seems to be effective in reducing duodenogastric reflux although having frequent complications, including Roux-Y stasis syndrome or increased susceptibility to form gallstones. (50) A study on the endoscopic evaluation of the remnant stomach showed that less than 5% of patients reported signs of reflux esophagitis, thus confirming that other functional disorders (e.g.,

the decrease in lower esophageal sphincter pressure, or the accommodation of the remnant stomach to a meal) are involved in post-gastrectomy functional dyspepsia.

1.2.4. SYSTEMIC THERAPY FOR LOCALIZED GASTRIC CANCER

Multimodality treatment is shown to be effective for patients with localized gastric cancer, according to various randomized clinical trials results. In Europe and many Western countries, perioperative chemotherapy has become the standard of care, since it leads to tumour downsizing, allowing for more curative resections, whereas postoperative chemotherapy alone might be considered in patients receiving a radical surgery plus a D2 lymphadenectomy; however, a peri-operative approach is preferred since adjuvant chemotherapy is less well tolerated. (51) Moreover, adjuvant chemoradiotherapy might be an option for patients who have not undergone an appropriate lymph nodes dissection and have not received preoperative therapy. (51) Preoperative treatment has been increasingly introduced into current guidelines, however there is no sufficient evidence proving an actual superiority of neoadjuvant therapy with adequate D2 gastrectomy over a surgery-upfront approach, due to a lack in standardization of proper D2 lymphadenectomy procedure in all trials.

1.2.4.1. PERIOPERATIVE CHEMOTHERAPY

For potentially resectable patients with >cT1 (any cN, cM0) disease, perioperative therapy has been increasingly administered rather than adjuvant therapy following upfront surgery, especially in Western countries. (36) Neoadjuvant chemotherapy is preferred over postoperative therapy since it may lead to tumour downstaging, lowering the risk of micrometastases and it is better tolerated. Despite all the theoretical

advantages of adding systemic therapy to upfront surgery, there's a non-negligible risk of chemotherapy unresponsiveness and progression of the disease, therefore delaying vital local treatment.

Numerous studies assessed the survival benefit of perioperative chemotherapy versus upfront surgery in patients with resectable gastric cancer, such as the UK-based phase III MAGIC trial. This study compared perioperative chemotherapy with the ECF regimen (epirubicin, cisplatin, and 5-fluorouracil) to surgery alone, resulting in a 36% 5-year survival (vs 23%). (52) The anthracycline epirubicin is no longer used in modern perioperative regimens due to additional toxicity without benefit, whereas the combination of cisplatin and fluorouracil seems to be equally effective, according to a French trial. (53)

A further study (FLOT4-AIO) comparing perioperative FLOT (fluorouracil plus leucovorin, oxaliplatin, and docetaxel) with ECF resulted in median OS of 50 months (vs. 35 months) and a 9% improvement in 5-year OS rates (45% vs 36%). Although there are concerns over the comparative arm including epirubicin, which has doubtful efficacy in gastric cancer, FLOT is a new standard of care. In less fit patients, perioperative therapy with a fluoropyrimidine plus platinum doublet is to be preferred.
Ultimately, peri-operative chemotherapy (pre- and post-operative) is routinely administered for resectable gastric cancer (stage > IB); the FLOT regimen is the standard of care for patients fit for triplet chemotherapy, whereas a combination of fluoropyrimidine with cisplatin/oxaliplatin is preferred for unfit patients.

1.2.4.1.1. RESPONSE EVALUATION AFTER NEOADJUVANT CHEMOTHERAPY FOR RESECTABLE GASTRIC CANCER

Different approaches for response evaluation following preoperative chemotherapy are available: a histopathological one, provided by tumor regression grading (TRG) systems including the Mandard or Becker scores, or a radiological one, based on CT findings. (54) Metabolic studies such as FDG PET-CT are promising, but not routinely used in clinical setting. Histopathological methods provide information about the primary tumor only, discarding information from lymph nodes or metastatic deposits, and patients submitted to neoadjuvant chemotherapy and rendered medically unfit for surgery are not evaluated. TRG systems categorize the quantity of regressive changes after perioperative chemotherapy, such as the percentage of residual tumor related to the original tumor site or the estimation of the chemo-induced fibrosis in relation to residual tumor. (55)

Regression grade	Relation between tumor and fibrosis			Proportion of residual tumor	
	Mandard	Dworak	Ryan	Becker	JGCA
Complete	TRG1; no residual cancer cell, total fibrosis	TRG4; no tumor cells, only fibrotic mass		TRG1a; 0% residual tumor	TRG3; 0% residual tumor
Subtotal	TRG2; rare residual cancer cells, scattered through the fibrosis	TRG3; difficult to find tumor cells microscopically, which scattered in fibrotic tissue	TRG1; no or rare residual cancer cells	TRG1b; <10% residual tumor	TRG2; 1–33% residual tumor
Partial	TRG3; more residual cancer cells, but outgrown by fibrosis	TRG2; easy to find tumor cells microscopically, with dominantly fibrotic changes	TRG2; more residual cancer cells	TRG2; 10–50% Residual tumor	TRG1b; 34–66% residual tumor
No response	TRG4; residual cancer cells outgrowing fibrosis TRG5; absence of regressive changes	TRG1; dominant tumor mass with obvious fibrosis TRG0; no regression	TRG3; residual cancer cells outgrowing fibrosis or no regression	TRG3; >50% residual tumor	TRG1a; >67% residual tumor TRG0; 100% residual tumor

TRG, tumor regression grade; JGCA, Japanese Gastric Cancer Association.

Table 4 Summary of TRG systems. Source: Garbarino GM, Mainardi F, Berardi E, Zerunian M, Polici M, Campanelli M, et al. Tumor regression grade (TRG) for gastric cancer and radiological methods on predicting response to perioperative chemotherapy: a narrative review. Digestive Medicine Research

Radiologic response evaluation is typically determined by measuring any change in tumor size, according to the "Response Evaluation Criteria In Solid Tumors" (RECIST v1.1) (56):

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. The sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Downstaging is also possible, comparing the radiological stage at diagnosis (rTNM) to the pathological stage following chemotherapy (ypTNM).

1.2.4.2. ADJUVANT CHEMOTHERAPY AND CHEMORADIOTHERAPY

Some Asians trials established the benefit of adjuvant therapy in patients with pT3-T4 or >N0 stage gastric cancer who undergo upfront surgery. According to the CLASSIC trial, 3-year disease-free survival rate of adjuvant capecitabine and oxaliplatin in patients who undergo curative-intent D2 gastrectomy was 74% (vs 59% for surgery alone). (57) Adjuvant oral fluoropyrimidine S-1 monotherapy or S-1 plus docetaxel can also be considered, where available. (58)

Regarding the role of adjuvant chemoradiation, it can be given to patients who have not undergone an appropriate D2 gastrectomy, resulting in R1 (microscopic residual cancer) or R2 (macroscopic residual cancer) resection. In current regimens, it should preferably be given as a concomitant fluoropyrimidine-based chemoradiotherapy to a total dose of 45 Gy in 25 fractions by intensity-modulated radiotherapy techniques. Additionally, some Korean studies did not demonstrate a survival benefit for the addition of postoperative radiotherapy in patients who had undergone gastrectomy with D2 lymphadenectomy. (59) Furthermore, for patients with MSI-H resected gastric cancer, adjuvant chemotherapy should be avoided due to no added benefit, but if a downstaging response is required, the FLOT regimen is to be preferred. (25)

1.2.5. SYSTEMIC THERAPY FOR METASTATIC AND UNRESECTABLE GASTRIC CANCER

Systemic therapy for management of unresectable disease has typically a palliative intent and aims at providing symptom relief, delaying disease progression, and extending life. HER2, PD-L1, and MSI/MMR testing is essential for a tailored therapeutic approach. The decision to offer palliative care alone or along with systemic therapy is dependent on the patient's performance status, based on the ECOG and the Karnofsky Scales, which are routinely used for oncologic patients. (60) Patients with higher ECOG PS/lower KPS scores tend to have poor prognosis for most serious illnesses. Specifically, patients with a Karnofsky score <60% or an ECOG score >3 should be offered best supportive care only, whereas systemic therapy can be added for patients with better performance status. According to several randomized trials, the addition of systemic therapy to best supportive care is demonstrated to prolong survival in patients with advanced gastric cancer, regardless of the chemotherapy agent utilized; e.g., the addition of

chemotherapy with irinotecan to best supportive care was found to significantly improve overall survival compared with best supportive care alone (4 months vs. 2,4 months). (61) The choice of proper treatment depends on the toxicity profile of the regimen; combination regimens are to be preferred as for higher response rates and lower toxicity compared with single-agent therapy.

Standard first-line therapy is a fluoropyrimidine-platinum (oxaliplatin/cisplatin) doublet regimen. In fit patients, a triplet regimen combining a fluoropyrimidine, oxaliplatin, and docetaxel can be considered for higher response rates, whereas for patients who do not tolerate platinum compounds, Irinotecan-5-FU may be an alternative option. (62) HER2-overexpression status assessment is also important to define whether the addition of Trastuzumab to cytotoxic first-line chemotherapy is required. Furthermore, the addition of Nivolumab to first-line chemotherapy in patients with a PD-L1 CPS ≥5 is demonstrated to significantly improve overall survival and progression-free survival.

The selection of proper regimens for second-line treatment is dependent on prior therapy and performance status. Cytotoxic chemotherapy agents non previously administered in the first line can be attempted. Docetaxel, Paclitaxel, or Irinotecan monotherapy are preferred treatment options with different toxicity profiles. (63,64) Additionally, 5-FU-Leucovoirin-Irinotecan (FOLFIRI) is an effective second-line treatment option for gastric cancers refractory to docetaxel-based chemotherapy. (65) In the phase 3 REGARD trial, anti-VEGFR-2 monoclonal antibody Ramucirumab has been shown to have limited response rates but improved overall survival compared with placebo in the second-line setting. (66) A subsequent study (phase III RAINBOW trial) demonstrated that second-line treatment with paclitaxel plus ramucirumab was superior to paclitaxel plus placebo with an overall survival of 9.6 versus 7.4 months. (67) Ultimately, paclitaxel plus

ramucirumab regimen is a preferred option after progression on a fluoropyrimidine and platinum doublet for eligible patients. Otherwise, single-agent chemotherapy can be considered.

In the third-line setting, the oral cytotoxic agent trifluridine-tipiracil (combination of an antimetabolite with a thymidine phosphorylase inhibitor), is demonstrated to have a survival benefit over placebo (5.7 vs 3.6 months) in patients with chemorefractory gastric cancer, based on the phase III TAGS trial. (68)

1.2.6. TARGETED THERAPY AND IMMUNOTHERAPY

Molecular characterization of gastric adenocarcinoma has led to a progressive tailoring of systemic therapy in the last decade. The Cancer Genome Atlas project first categorized gastric cancer into four major molecular subtypes (22): tumours characterized by chromosomal instability (CIN, >50%) and amplification of genes encoding tyrosine kinase receptors, microsatellite instability (MSI, 22%) tumours, presenting a very high mutation rate and DNA methylation, genomically stable (MSS, 20%) tumours, and EBV positive tumours (9%), characterized by DNA hypermethylation, high frequency of PIK3CA mutations and PDL1/PDL2 overexpression. Therefore, biomarkers (including MSI status, HER2 amplification, TMB, and MMR deficiency) testing allows for identification of patients with advanced gastric cancer who are most likely to benefit from immunotherapy and targeted therapy. Specifically, treatment with Trastuzumab is based on the presence of HER2 overexpression (23), whereas treatment with Pembrolizumab/Nivolumab depends on testing for MSI, MMR, PD-L1 expression or TMB. (24,69,70) Regarding treatment of HER2-overexpressing advanced gastric cancer, the phase III ToGA trial first evaluated the efficacy and safety of Trastuzumab. Results demonstrated

significant improvement in median overall survival with the addition of Trastuzumab to standard chemotherapy scheme in patients with HER2-overexpressing cancer (13.8 vs 11 months, respectively). This study assessed Trastuzumab in combination with chemotherapy agents (cisplatin and a fluoropyrimidine) as the standard treatment for patients with HER2-overexpressing advanced gastric cancer. (23)

The Asian Cancer Research Group provided a further classification based on molecular characteristics of gastric adenocarcinoma by its categorization into two main groups which have different prognostic value: the microsatellite instable (MSI) and microsatellite stable (MSS) tumors. (71) The latter group was categorized based on evidence of epithelial-mesenchymal transition or TP53 status (wild type/inactivated). Interestingly, the MSI subtype showed the best prognosis, while the MSS/EMT subtype was correlated with higher risk of recurrence.
Overall, these two classifications have led to better understanding of the molecular basis of gastric cancer and to identification of new molecular targets and design of new therapeutic approaches to significantly improve these patients' survival.

Beyond molecular targeted therapies, immune checkpoint inhibitors combined with standard chemotherapy regimens also represent a valid strategy in the treatment of advanced or metastatic gastric cancer and numerous clinical trials has assessed their efficacy. (72) A variety of immune checkpoint inhibitors to different targets expressed by either tumoral or immune cells is currently being investigated: anti-PD-1 (primarily expressed on T-cells) antibodies, such as Nivolumab, Pembrolizumab, as well as anti-PD-L1 (primarily expressed on cancer cells) antibodies, including Atezolizumab, Avelumab, Durvalumab, and the anti-

CTLA-4 (expressed on T-cells) antibody Ipilimumab. (72) In particular, the combination of immunotherapy with standard chemotherapy regimens is the object of current research, based on the rationale of a possible synergistic effect of T-cell recruitment and activation.

Currently, the main prognostic/predictive biomarkers for immunotherapy effectiveness are PD-L1 expression along with MSI status. (73) The humanized anti-PD-1 monoclonal antibody Pembrolizumab is already the subject of great excitement thanks to promising preliminary overall survival data which suggest that immuno-oncology may play a significant role in gastric cancer.

The phase I KEYNOTE-012 trial investigated Pembrolizumab in pretreated patients with PD-L1 positive advanced gastric cancer and showed sustained antitumor responses in 22% of patients. (74)

In the phase II KEYNOTE-059 trial Pembrolizumab monotherapy demonstrated durable responses in patients with advanced gastric cancer that progressed after second-line treatment, regardless of tumour PD-L1-expression status and with better safety profile compared with standard chemotherapy agents. (75)

In the randomized trial, phase III KEYNOTE-061 Pembrolizumab did not significantly improve overall survival compared with paclitaxel as second-line therapy for advanced gastric or gastro-oesophageal junction cancer with PDL-1 CPS>1, despite favourable safety profile. (76)

The Asian phase III ATTRACTION-2 trial investigated treatment with Nivolumab and it resulted in clinically meaningful improvements in survival, thus indicating that it might be a new treatment option for heavily pretreated patients with advanced gastric or gastro-oesophageal junction cancer patients. (70)

Preliminary data from the phase I/II CheckMate-032 study of Nivolumab monotherapy in advanced/metastatic gastroesophageal cancer patients

showed promising results in heavily pretreated patients, with overall response rate 12%, and 21% stable disease, regardless from PD-L1 expression. (77)
Combination of Nivolumab plus standard cytotoxic agents was also effective as first-line therapy in CheckMate-649 trial. (78)

Ultimately, the range of treatment options for advanced or metastatic gastric adenocarcinoma is constantly expanding, and combinations of immune checkpoint inhibitors with either standard chemotherapy drugs or molecular-targeted agents can be considered, resulting in lower toxicity profile. Design of new immunotherapies is needed, as well as improved biomarkers for selecting patients mostly likely to benefit from anti-PD-1 or PD-L1 inhibitors in earlier treatment lines or combination therapies, and molecular targeted drugs for therapy-refractory tumours should also be established in the near future. This is intended to enhance survival outcomes and patient selection for immunochemotherapy, considering that only a fraction of patients experiences real clinical benefit from immunotherapy. (79)

1.2.7. BEST SUPPORTIVE CARE

The goals of palliative care are to prevent, reduce, and relieve suffering and improve the quality of life for gastric cancer patients regardless of the tumour stage or treatment schedule. In patients with advanced or metastatic gastric cancer, it aims at providing symptom relief, improvement in overall quality of life, such as providing nutritional support, and may result in prolongation of life. (80) A multimodality interdisciplinary approach to best supportive care of gastric cancer patients is recommended. Indeed, in a recent randomized phase III trial, patients who received

multidisciplinary supportive had an increase in survival (3 months) compared to those who received chemotherapy. (81)

Weight loss represents a significant prognostic factor in gastric cancer patients and may have different causes, such as obstruction of the gastrointestinal tract, hyporexia, malabsorption, hypermetabolism or it may also be direct consequence of chemotherapy and surgical treatment. According to various phase III studies, weight loss of >10% before treatment and >3% during the first cycle of treatment seems to be associated with reduced overall survival. (82)

Dysphagia due to proximal gastric tumours may be relieved by radiotherapy or stent placement. (83) Stenting is warranted in patients with short life expectancy and severe dysphagia, since the relief of dysphagia is immediate, whereas radiotherapy (both brachytherapy and external beam) is effective around 4-6 weeks after treatment. (84) Acute bleeding is common in patients with gastric cancer and may be tumor-related or a consequence of therapy. Patients with acute severe bleeding (hematemesis or melena) should undergo prompt endoscopic assessment and therapy (through injection, clip placement, ablation with argon plasma coagulation or other laser therapy, or a combination of modalities), despite a high rate of recurrent bleeding. (80,85) Interventional radiology with angiographic embolization techniques may be a useful alternative to endoscopy. (86) Additionally, external beam radiation therapy has been shown to effectively manage acute and chronic gastrointestinal bleeding. (87) Malignant gastric obstruction requires a palliative therapy to reduce nausea and vomiting and, when possible, allow resumption of an oral diet and therapy selection should be individualized. Treatment options used to alleviate or bypass obstruction include surgery (gastrojejunostomy or gastrectomy), chemo- or radiotherapy, and endoscopic placement of a self-expanding metal

enteral/esophageal stent in patients with luminal obstruction. The choice between enteral stenting or gastrojejunostomy should be based on patient's life expectancy and obstruction severity, since stenting is associated with more rapid relief and tolerance to oral intake and shorter hospital stays, whereas gastrojejunostomy is preferable in patients with higher life expectancy. (88–90) In patients with gastric outlet obstruction, the primary goal is to reduce nausea and vomiting via venting gastrostomy (that has endoscopic, radiologic, or surgical placement) pyloric stenting or bypass surgery. (91) Enteral feeding using nasojejunal or nasogastric tubes, or percutaneous feeding tubes may be necessary for patients who cannot tolerate an oral diet.

1.3. FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

Gastric cancer is an aggressive disease commonly associated with very poor prognosis even in the setting of resectable disease, but survivorship is beginning to evolve thanks to introduction of targeted therapies. However, surgery and systemic treatments frequently cause side-effects that adversely affect health-related quality of life. Therefore, gastric cancer patients have follow-up visits every 3 to 6 months for the first few years along with radiological investigations for monitoring of symptoms, and to early detect disease recurrence or progression before significant clinical deterioration. (51)

Part II

Our Study

2. AIM OF THE STUDY

This is a local center observational retrospective study which is part of an observational retrospective multicenter study with matched treatment comparison ("SNAC protocol", version 01, date of first writing: 1.2.2022, promoter: University of Torino, Department of Oncology). The study aims at assessing a non-inferiority of upfront surgery alone with optimal D2 dissection compared to neoadjuvant regimens followed by surgery for gastric cancer.

The present study retrospectively analyses a subgroup of patients with adenocarcinoma of the stomach and of the cardia (Siewert type II and III) submitted either to neoadjuvant chemotherapy or to upfront surgery with optimal lymphadenectomy, with the primary objective to assess overall survival.

Secondary objectives of the study are:

- estimation of disease-free survival (DFS)
- estimation of perioperative morbidity and mortality (up to 2 months after surgery);
- determination of R0-resection rate.

3. MATERIALS AND METHODS

3.1. STUDY DESIGN AND COHORT SELECTION

In this observational retrospective study, we recruited patients with adenocarcinoma of the stomach and of the cardia submitted to radical surgery between January 2012 and January 2023 at the 1rst Surgical Clinic of the Padua University Hospital.

We included adult and older adult patients (age > 18 years), of both genders, with resectable histologically proven adenocarcinoma of the stomach or the cardia (Siewert type II and III), without distant metastases (M0), submitted either to preoperative (or perioperative) chemotherapy and D2 gastrectomy (partial or total gastrectomy plus D2 lymphadenectomy, according to *Japanese Gastric Cancer Treatment Guideline*), or to upfront D2 gastrectomy, followed by adjuvant treatment when recommended.

Exclusion criteria were as follows: distant metastases (cM+) and all primarily not resectable stages; relapsed gastric cancer; malignant secondary disease, dated back <5 years (exception: In-situ-carcinoma of the cervix uteri, adequately treated skin basal cell carcinoma); other types of lymphadenectomy lower than D2 or other types of gastric surgery non included in the previous types (e.g. wedge resections).

Patients not presenting a gastric adenocarcinoma were excluded in order to avoid possible bias coming from the different prognosis associated with others and less common histological types of the tumor (such as neuroendocrine tumors, GISTs, sarcomas, lymphomas, melanomas).

3.2. COLLECTED VARIABLES

3.2.1. PREOPERATIVE WORK UP AND CANCER STAGING

The following data, when available, were collected and analyzed: basic demographics, preexisting gastroesophageal condition, presenting symptoms, radiological and laboratory tests, comorbidities, previous thoracic/abdominal surgery, alcohol and tobacco use; data of diagnosis, initial tumor stage, tumor location, tumor histology, tumor grading, type of neoadjuvant treatment, restaging after neoadjuvant treatment, toxicity linked to neoadjuvant (NAT), type of surgical resection.

Comorbidities and fitness of patients before surgery were classified according to the Charlson Comorbidity index (CCI) and the American Society of Anesthesiologists (ASA) classification, respectively.

The Karnofsky Performance Status (KPS) (60) was used to express the functional ability status of patients in our database and the Charlson Comorbidity Index (92) was estimated for every patient based on their clinical history and comorbidities. The ASA (American Society of Anesthesiology) classification (93) was estimated before surgery and used to assess the operative risk of patients in the study.

All patients underwent EGDS and biopsy to obtain histological diagnosis and to assess tumor length. CT scans of the chest and abdomen (and neck in selected cases) were obtained in all patients to rule out any metastatic disease and to assess the local extension of the disease.

EUS was used to provide additional information on tumor depth and lymph node status. The 18F-FDG-PET/CT was performed in selected cases of suspected metastatic foci. In some patients, an abdominal MRI was performed, in order to rule out the presence of hepatic metastatic foci. Some

cases required a staging laparoscopy plus peritoneal cytology prior to any treatment, in order to exclude a secondary localization of cancer.

Tumors were staged according to the 8th edition of the TNM criteria proposed by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC/UICC) (26).

3.2.2. MULTIDISCIPLINARY BASED CHOICE OF TREATMENT

All cases were discussed at the Multidisciplinary Team Meeting for esophago-gastric cancer at our Center with the participation of surgeons, oncologists, radiologists, radiation therapists and anesthesiologists. The decisions to treat the patients with neoadjuvant therapy plus surgery or surgery alone was made considering not only the cancer features and the initial stage of the disease, but also the patients' characteristic, comorbidities, and preferences. Patients with stage disease that could be eligible for neoadjuvant therapy (clinical stages greater or equal to T2N0 with risk factors or more advanced stages, excluding metastatic disease) who had contraindications to Chemotherapy and Chemoradiation (presence of contraindication as well as history of cardiac, respiratory, or vascular disease) underwent primary surgical resection.

3.2.3. NEOADJUVANT THERAPY

All patients underwent a multidisciplinary evaluation and neoadjuvant therapy was considered for each patient. Preoperative treatments were indicated according to cancer stage, location, histological type and patient's performance status and comorbidities. The preferred chemotherapy regimen involved a combination of docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil (FLOT). In selected patients, neoadjuvant radiotherapy was also administered (41.4-54 Gy in fractions of 1.8 to 2 Gy per day (94). After

completion of neoadjuvant therapy all patients underwent a restaging process that included at least an EGDS and a CT scan with an iodinated contrast medium, unless contraindicated. Clinical response to neoadjuvant therapy was assessed according to the Post-neoadjuvant Therapy TNM Staging (ypTNM) according to the 8th edition of the TNM criteria proposed by the AJCC/UICC (26).

Neoadjuvant therapy response was evaluated according to RECIST criteria (56) and surgical indication was discussed by our multidisciplinary team.

We collected the data about Toxicity linked to NAT. Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. (95)

3.2.4. SURGERY

For the current study, only patients who underwent surgical resection were considered. Patients who underwent palliative surgery (esophageal stent placement, ablation, feeding gastrostomy or jejunostomy) were excluded.

The surgical approach was based on the cancer location and extent. Surgical techniques performed for resection of the disease were laparotomic partial (subtotal (4/5) gastrectomy) and total gastrectomies. All patients received a D2- lymph node dissection. An initial exploratory laparoscopy to exclude a peritoneal involvement or the presence of a metastatic disease was performed in selected cases. Reconstruction of digestive tract by esophagojejunal Roux-en-Y anastomosis was generally performed with a circular stapler. In selected cases, the placement of a jejunostomy was required.

Surgical radicality was defined as R0 (complete resection) in case of absence of microscopic or macroscopic residual cancer, R1 or R2 in case of presence

of microscopic or macroscopic residual cancer, respectively. The lymph nodes (LNs) stations to be dissected in D2 lymphadenectomy were stations 1, 3, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, and 12a, as illustrated in *Table 3* (right paracardial LNs, lesser curvature LNs, left greater curvature LNs along the left gastroepiploic artery, rt. greater curvature LNs along the 2nd branch and distal part of the right gastroepiploic artery, suprapyloric LNs, infrapyloric LNs, left gastric artery LNs, anterosuperior LNs along the common hepatic artery, celiac artery LNs, proximal splenic artery LNs, hepatoduodenal ligament LNs along the proper hepatic artery). The details regarding the surgical procedures were abstracted from the surgical reports.

After surgical resection, the specimen has been analyzed by a pathologist who restaged the disease according to the 8th edition of the TNM criteria. Data regarding pathological staging of the tumor (pTNM and ypTNM) were collected. Additional pathologic data, including the total number of removed lymph nodes, the total number of involved lymph nodes, the peritumoral lymphocytic infiltrate, the presence or absence of lymphovascular invasion, and molecular details (including TP53, EBER, HER-2, BRAF…) were recorded from reports given by the pathologist.

3.2.5. POST-OPERATIVE COURSE

Patients were monitored postoperatively, and a water-soluble contrast medium swallow was performed on postoperative day 7th. If any complication at the anastomosis site was suspected, further investigations, such as upper digestive tract endoscopy or an enhanced CT scan, were performed.

All postoperative morbidities were recorded and classified according to the Gastrectomy Complications Consensus Group (*Table 5*) (96). The severity of

each complication was labeled according to the Clavien-Dindo classification *(Table 6)* (97) and grouped into complications requiring treatments not under general anesthesia (<3b) and those requiring it (≥3b). We considered the complications developed in the first 90 postoperative days. Perioperative mortality was considered as in-hospital (all deaths occurring at the hospital) and 90-day mortality (all deaths occurring within 90 days of surgery).

Table 5 Gastrectomy Complications Consensus Group.

INTRAOPERATIVE COMPLICATIONS
- Unintended intraoperative damage to major vessels and/or organs requiring reconstruction or resection - Intraoperative bleeding requiring urgent treatment - Unexpected medical conditions interrupting or changing the planned procedure
POSTOPERATIVE SURGICAL COMPLICATIONS
- Postoperative bleeding requiring both urgent transfusions and invasive treatment - Postoperative bowel obstruction (clinical/radiological signs of obstruction, inability to enteral feed, longer need for NG suction) - Postoperative bowel perforation or necrosis requiring surgical treatment (or cause of death) - Duodenal leak (irrespective of presentation, method of identification, clinical consequences, and treatment) - Anastomotic leak (irrespective of presentation, method of identification, clinical consequences, and treatment) - Postoperative pancreatic fistula - Postoperative pancreatitis diagnosed both clinically and radiologically - Other postoperative abnormal fluid from drainage and/or abdominal collections without gastrointestinal leak(s) preventing drainage removal or requiring treatment - Delayed gastric emptying (by 10th postoperative day) requiring treatment or delaying discharge - Other major complications requiring re-intervention or other invasive procedures
POSTOPERATIVE GENERAL COMPLICATIONS
- Stroke causing patient's permanent deficit - Need for CPR - Myocardial infarction with patient's transfer to CCU/ICU/other critical care facility - Cardiac dysrhythmia requiring invasive treatment - Acute myocardial failure with acute pulmonary edema or drop in EF >50% - Pulmonary embolism with symptoms confirmed by urgent CT scan - Need for prolonged intubation (>24 hours after the surgical procedure) - Respiratory failure requiring reintubation - Need for tracheostomy - Pleural effusion requiring drainage - Pneumothorax requiring treatment - Acute liver dysfunction (the Child-Pugh score >8 for longer than 48 hours) - Acute renal insufficiency (postoperative creatinine twice its preoperative value)/renal failure requiring CVVH or dialysis - Infections (gastrointestinal, respiratory, urinary, or other) with both symptoms and germ isolation

Table 6: Clavien-Dindo classification of Postoperative complications

Degree	Definitions
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
III	Requiring surgical, endoscopic or radiological intervention
IIIa	Intervention not under general anesthesia
IIIb	Intervention under general anesthesia
IV	Life-threatening complication (including CNS complications)* requiring IC/ICU-management
IVa	single organ dysfunction (including dialysis)
IVb	multiorgan dysfunction
V	Death of a patient

3.2.6. FOLLOW-UP

The patients were followed-up after surgery with clinical and radiological appointments at 1-3-6-12 months for the first year; every 6 months for the next 5 years and then yearly. All patients were observed until death or were censored at their last confirmed contact with the healthcare system. Any recurrence of disease and its location was also recorded together with the date of its detection. Overall survival (OS) was calculated from the date of surgery until the date of death or last follow-up, which was on the 10th of June, 2023. Disease Free Survival (DFS) was calculated from the date of diagnosis until the recurrence or last follow-up or the date of death.

Patients' death causes were divided into two groups: cancer-related and non cancer-related.

3.3. STATISTICAL ANALYSIS

Data are expressed as medians (interquartile range—IQR) or means (±standard deviation—SD) for quantitative variables, and as absolute frequencies (percentages) for categorical variables. Quantitative variables were compared using the *Mann-Whitney test* or the *Kruskal-Wallis test*, as appropriate. Categorical variables were analyzed with the *Chi-square test* or *Fisher's exact test* in the case of absolute frequencies < 5. We considered statistical test findings significant for p-values of less than 0.05. p-values for multiple comparisons were corrected for alpha inflation using the *Bonferroni method*. Overall and recurrence-free survival estimates were calculated using the *Kaplan-Meier method*. The survival curves were compared using the *log-rank test* or the *Gehan-Breslow-Wilcoxon test*, as appropriate. Univariate and multivariate analyses were run to identify potential risk factors for overall survival. Variables showing a p-value < 0.1 on univariate analysis were included in the multivariate logistic regression to identify independently associated risk factors. We performed the statistical analysis using JMP® Statistical Discovery LLC, version 17.1.0 (SAS Institute srl, ITA).

4. RESULTS

4.1. COHORT SELECTION

We retrospectively reviewed data of 107 patients with adenocarcinoma of the stomach and of the esophago-gastric junction (Siewert type 2 and 3) submitted to surgery at 1st Surgical Clinic of the University Hospital of Padova from January 2012 to January 2023.
As stated in Materials and Methods, we included patients with resectable gastric cancer and categorized them into two main groups, according to the pre-operative treatment: patients who underwent upfront surgery (SURG group, n=72) and patients who received neoadjuvant treatment (NAT) plus surgery (NAT group, n= 35).

A total of 72 patients were excluded from the study, due to the following reasons: 11 patients had an oligometastatic disease; 20 patients did not have complete clinical data; 6 patients underwent degastro-gastrectomy; 4 patients were Siewert type I; 31 patients had different histologies of gastric cancer (NETs, GISTs, NHLs…).

4.2. PATIENTS' CHARACTERISTICS

Patients' characteristics are summarized in *Table 7*.
The cohort included 107 patients with gastric adenocarcinoma, 66 males (61,7%) and 41 females (38,3%), with a mean age at diagnosis of 67,29 years ± 11,26.
Cardiovascular, metabolic, endocrine, and respiratory comorbidities were comparable between the two groups of patients. The results for the two groups were substantially similar also for alcohol consumption and tobacco

smoking, gastroesophageal reflux disease (GERD) or Barrett's esophagus, and previous abdominal, thoracic, and other type of surgery.

Regarding patients' performance status, no differences were noted between the two groups in terms of Eastern Cooperative Oncology Group performance status (ECOG PS) score, Karnofsky Performance Status (KPS) score and American Society of Anesthesiologists (ASA) score. Mean Charlson Comorbidity Index (CCI) was 4,91 ± 1,82: patients submitted to upfront surgery had a higher CCI when compared to patients who were given NAT (p=0,0466).

Forty-two patients (39,3%) had a cardia cancer: 22 patients (20,6%) had a Siewert 2 tumor and 20 (18,7%) had a Siewert 3 lesion. Sixty-four patients (59,8%) had a lesion located either in the upper part of the stomach (body/fundus, n=31, 29,0%) or in the gastric antrum and lower body (n= 33, 30,8%). No differences were noted between SURG and NAT in the tumor location.

Twenty-six patients (24,3%) presented with dysphagia at diagnosis and four patients (3,74%) required the placement of a nutritional jejunostomy prior to any treatment. Mean weight before surgery was 25,66 kg/m^2 ± 4,07. Mean BMI at the hospital admission was 25,66 kg/m^2 ± 4,07. Mean weight loss at diagnosis was 9,14 kg ± 4,20.

All patients underwent staging EGDS and CT Scans of the chest and abdomen (and neck in selected case). Twenty-five (23,4%) patients underwent EUS and 23 (21,5%) underwent 18F-FDG-PET/CT. In particular, mean maximum standardized uptake value (SUVmax) calculated on 19 patients resulted 9,64 ± 7,06. In five more cases (4,7%), an abdominal MRI was performed, in order to rule out the presence of hepatic metastatic foci (in all cases it resulted negative for metastatic disease).

In 9 patients (8,4%) a staging laparoscopy was performed before any treatment. No patient included in this study had a positive peritoneal citology.

Considering the clinical stage of the tumor, 28 patients (26,2%) had a cTNM stage I, 54 (50,1%) had a stage II, 25 (23,4%) had a stage III, and none had stage IV *(see Table 8)*. Patients of the NAT group tended to present with tumors with higher T stage (p=0,0087) and with a higher proportion of lymph nodal metastases (p <0,0001) when compared to patients of the SURG group. Consequently, patients who received NAT presented with a higher clinical stage when compared to patients submitted to upfront surgery (p <0,0001).

Table 7: Patients' characteristics.

	COHORT (n=107)	**SURG (n=72)**	**NAT (n=35)**	**P value**
Age at diagnosis (years), mean ± SD	67,29 ± 11,26	69,54 ± 11,98	64,26 ± 8,70	0,0112
Gender				n.s.
M, n (%)	66 (61,7%)	41 (56,9%)	25 (71,4%)	
F, n (%)	41 (38,3%)	31 (43,1%)	10 (28,6%)	
Weight before surgery*(kgs), mean ± SD *calculated on 97 patients	72,84 ± 13,47	71,43 ± 12,78	75,41 ± 14,49	n.s.
BMI at hospital admission* (kg/m^2), mean ± SD *calculated on 90 patients	25,66 ± 4,07	25,51 ± 4,09	25,91 ± 4,09	n.s.
ECOG PS	(n=74)	(n=49)	(n=25)	n.s.
0, n (%)	48 (64,9%)	33 (67,4%)	15 (60,0%)	
1, n (%)	22 (29,7%)	13 (26,5%)	9 (29,7%)	
2, n (%)	3 (4,1%)	2 (4,1%)	1 (4,0%)	
3, n (%)	1 (1,4%)	1 (2,0%)	0 (0)	
Karnofsky PS	(n=71)	(n=49)	(n=22)	n.s.
≤ 80, n (%)	23 (32,3%)	14 (28,6%)	9 (40,9%)	
> 80, n (%)	48 (67,6%)	35 (71,4%)	13 (59,1%)	
Charlson Comorbidity Index, mean ± SD	4,91 ± 1,82	5,13 ± 1,96	4,46 ± 1,40	0,0466
ASA cl.	(n=103)	(n=68)	(n=35)	n.s.
1, n (%)	3 (2,9%)	3 (4,4%)	0 (0)	
2, n (%)	53 (51,5%)	35 (51,5%)	18 (51,4%)	
3, n (%)	44 (42,7%)	27 (39,7%)	17 (48,6%)	
4, n (%)	3 (2,9%)	3 (4,4%)	0 (0)	
Comorbidities				
Cardiovascular, n (%)	67 (62,6%)	48 (44,9%)	19 (17,8%)	n.s.
Metabolic, n (%)	29 (27,1%)	18 (16,8%)	11 (10,3%)	n.s.
Endrocrine, n (%)	9 (8,4%)	7 (6,5%)	2 (1,9%)	n.s.
Tumoral, n (%)	22 (20,6%)	17 (15,9%)	5 (4,7%)	n.s.
Other types, n (%)	79 (73,8%)	52 (48,6%)	27 (25,2%)	

Table 8: Patients' clinical staging characteristics.

	COHORT (n=107)	SURG (n=72)	NAT (n=35)	P value
cT				0,0087
cT1, n (%)	1 (0,9%)	1 (1,4%)	0 (0)	
cT2, n (%)	39 (36,5%)	33 (45,8%)	6 (17,1%)	
cT3, n (%)	54 (50,5%)	33 (45,8%)	21 (60,0%)	
cT4, n (%)	13 (12,2%)	5 (6,9%)	8 (22,9%)	
cN				<0,0001
cN0, n (%)	48 (44,9%)	41 (56,9%)	7 (20%)	
cN1, n (%)	33 (30,8%)	22 (30,6%)	11 (31,4%)	
cN2, n (%)	22 (20,6%)	9 (12,5%)	13 (37,1%)	
cN3, n (%)	4 (3,7%)	0 (0)	4 (11,43%)	
cM				.
cM0, n (%)	107 (100%)	72 (100%)	35 (100%)	
Clinical stage				<0,0001
I, n (%)	28 (26,2%)	26 (36,1%)	2 (5,7%)	
II, n (%)	54 (50,5%)	38 (52,8%)	16 (45,7%)	
III, n (%)	25 (23,4%)	8 (11,1%)	17 (48,6%)	

4.3. NEOADJUVANT THERAPY

Thirty-five (32,7%) patients received neoadjuvant treatment before surgical intervention: 29 patients (27,1%) underwent chemotherapy alone, while six patients (5,6%) received concurrent chemoradiotherapy. The main chemotherapy regimens used are reported in *Table 9.*

One patient was treated with a targeted therapy, consisting in 5 cycles of Trastuzumab in addition to chemotherapy. One patient required a dose reduction of the chemotherapy due to a renal and liver impairment. Ten patients (28,6%) experienced a clinically significant toxicity due to neoadjuvant treatments which led to the discontinuation of NAT in one case. A grade 3 toxicity was registered in 5 patients (14,3%).

After restaging, 4 patients (11,4%) showed a complete response according to RECIST criteria, 22 patients (62,9%) showed a partial response and 9 (25,7%) had either stable disease or disease progression.

4.4. SURGERY AND POSTOPERATIVE COURSE

Operative and post-operative course characteristics are summarized in *Table 10*.

All 107 patients underwent either total gastrectomy (n=79, 73,8%) or partial gastrectomy (n=28, 26,2%). All patients received a D2-lymph node dissection.

All patients underwent a laparotomic resection. An initial exploratory laparoscopy to exclude a peritoneal involvement or the presence of a metastatic disease was performed in 18 patients (this approach was more frequent in the NAT group, p=0,0235), followed by a laparotomic resection.

For patients undergoing total gastrectomy, reconstruction of digestive tract by esophagojejunal Roux-en-Y anastomosis was generally performed with a circular stapler. Mean stapler's diameter was 26,09 mm ± 3,34.

The placement of a jejunostomy during surgery occurred in 8 cases (7,5%).

Intraoperative blood loss and intraoperative complications were comparable among the two groups.

Sixty-seven patients (62,6%) required a post-operative assistance in the ICU with a mean ICU stay of 1,18 days ± 0,65 (with no significant differences between the two groups). The majority of patients received an immediate extubation after surgery.

Table 9: Neoadjuvant therapy characteristics.

	n (%)	**N° of cycles, media ± DS (min-max)**
Type of Neoadjuvant Therapy		
	(n=35)	
Chemotherapy alone	29 (82,9%)	
Chemoradiotherapy	6 (17,1%)	
CT scheme	(n=35)	
FLOT	17 (48,6%)	4,06 ± 1,09 (2-6)
FOLFOX	1 (2,9%)	6
EOX	2 (5,7%)	5 ± 1,53 (4-6)
Other regimens or combinations of antitumoral drugs:	11 (31,4%)	4,56 ± 1,01 (3-8)
Cisplatin + 5FU + Taxane	1	
Cisplatin + 5FU	1	
MK3475-585 study (Sper/Pembro/Placebo+Cisplatin+Capecitabine)	1	
FOLFOx + xELOx + Capecitabine	1	
CROSS	1	
(FLOT + Pembrolizumab)/placebo	1	
Carboplatin + Taxane	4	
Cisplatin + Capecitabine + Trastuzumab	1	
Not specified	4 (11,4%)	4 (4-4)
Immunotherapy		
(Mk3475-585 study) sper-pembro/placebo+cispl+cape	1	3
(FLOT + pembrolizumab)/placebo	1	8
Targeted Therapy		
Trastuzumab + chemotherapy	1	5

No differences in postoperative morbidity were noted between the two groups. *(Table 11)* Fifty-two patients (49,5%) had at least one complication. Nine patients (17%) experienced an anastomotic leak, which required a surgical intervention in one case. No differences in the severity of the complications were noted between the two groups.

Mean length of hospital stay (LOS) was 15,93 days ± 8,38, while the overall postoperative mortality rate for the entire cohort of the patients was 4.7 % (once again, there were no differences between patients submitted to upfront surgery or to NAT).

Table 10: Operative and post-operative course characteristics.

	COHORT (n=107)	SURG (n=72)	NAT (n=35)	P value
Tumour location				n.s.
Siewert II, n (%)	22 (20,6%)	13 (18,1%)	9 (25,7%)	
Siewert III, n (%)	21 (19,6%)	11 (15,3%)	10 (28,6%)	
Body-fundus, n (%)	31 (29,0%)	25 (34,7%)	6 (17,1%)	
Antrum, n (%)	33 (30,8%)	23 (31,9%)	10 (28,6%)	
Type of Gastrectomy				0,0156
Total Gastrectomy, n (%)	79 (73,8%)	48 (66,7%)	31 (88,6%)	
Partial Gastrectomy, n (%)	28 (26,2%)	24 (33,3%)	4 (11,4%)	
P.O Assistance	(n=94)	(n=60)	(n=34)	n.s.
ICU, n (%)	67 (71,3%)	40 (66,7%)	27 (79,4%)	
Return to ward, n (%)	27 (28,7%)	20 (33,3%)	7 (20,6%)	
ICU stay (days), mean ± SD* *Calculated on 71 patients	1,18 ± 0,65	1,25 ± 0,81	1,07 ± 0,27	n.s.
P.O. complications	(n=105)	(n=70)	(n=35)	n.s.
No, n (%)	53 (50,5%)	36 (51,4%)	17 (48,6%)	
Yes, n (%)	52 (49,5%)	34 (48,6%)	18 (51,4%)	
Complication with highest Clavien Dindo score	(n=51)	(n=34)	(n=17)	n.s.
CD < 3b, n (%)	42 (82,4%)	27 (79,4%)	15 (88,2%)	
CD ≥ 3b, n (%)	9 (17,7%)	7 (20,6%)	2 (11,8%)	
Mortality at 90 days				n.s.
No, n (%)	102 (95,3%)	70 (97,2%)	32 (91,4%)	
Yes, n (%)	5 (4,7%)	2 (2,8%)	3 (8,6%)	
Lenght of hospital stay (days), mean ± SD	15,93 ± 8,38	16,28 ± 9,20	15,23 ± 6,45	n.s.

4.5. PATHOLOGICAL CHARACTERISTICS

Final histological report characteristics are reported in *Table 12*. When looking to the pathological stage, pT stage tended to be higher in the SURG group (p=0,0392). There were no differences in the N stage, in the total number of retrieved lymph nodes and in the rate of positive lymph nodes (LNR). The final pathological stage was different between the two groups, with NAT having more advanced cancers (p=0,0234) *(Table 14)*.

Pathological tumor regression (TRG), according to *Mandard et al* was graded as TRG-1 in 3 patients (8,6%), TRG-2 in 2 patients (5,7%), TRG-3 in 8 patients (22,9%), TRG-4 in 14 (40%). In the remaining 6 patients (17,1%), the pathological tumor regression was evaluated with *Becker* grading system: 3 patients (8,6%) had a score equal to 3, 2 patients (5,7%) equal to 2, and one

patient (2,9%) a score equal to 1. A pathological complete response after neoadjuvant therapy was present in 3 patients (8,6%).

Table 11: Postoperative complications

	COHORT (n=107)	**SURG (n=72)**	**NAT (n=35)**	**P value**
Postoperative Surgical Complications	(n=39)	(n=29)	(n=10)	n.s
Postoperative bleeding	8 (20,5%)	7 (24,1%)	1 (10,0%)	n.s
Postoperative bowel obstruction	2 (5,1%)	2 (6,9%)	0 (0)	n.s
Postoperative bowel perforation or necrosis	0 (0)	(0)	(0)	n.s
Duodenal leak	3 (7,7%)	2 (6,9%)	1 (10,0%)	n.s
Anastomotic leak	9 (23,1%)	7 (24,1%)	2 (20,0%)	n.s
Postoperative pancreatic fistula	0 (0)	0 (0)	0 (0)	n.s
Postoperative pancreatitis	0 (0)	0 (0)	0 (0)	n.s
Intra-abdominal collections	16 (41,0%)	10 (34,5%)	6 (60,0%)	n.s
Postoperative biliary leak	0 (0)	0 (0)	0 (0)	n.s
Ascitis	0 (0)	0 (0)	0 (0)	n.s
Lymphorrhea	1 (2,6%)	1 (3,5%)	0 (0)	n.s
Gastroparesis	0 (0)	0 (0)	0 (0)	n.s
Other major complications	0 (0)	0 (0)	0 (0)	n.s
Postoperative General Complications	(n=38)	(n=24)	(n=14)	
Stroke	1 (2,6%)	1 (4,2%)	0 (0)	n.s
Myocardial infarction	2 (5,3%)	2 (8,3%)	0 (0)	n.s
Cardiac dysrhythmia	5 (13,2%)	3 (12,5%)	2 (14,3%)	n.s
Pulmonary embolism	1 (2,6%)	1 (4,2%)	0 (0)	n.s
Need for prolonged intubation (> 24 hours after the surgical procedure)	0 (0)	0 (0)	0 (0)	n.s
Respiratory failure	1 (2,6%)	1 (4,2%)	0 (0)	n.s
Need for tracheostomy	0 (0)	0 (0)	0 (0)	n.s
Pleural effusion	14 (36,8%)	9 (37,5%)	5 (35,7%)	n.s
Pneumothorax	4 (10,5%)	2 (8,3%)	2 (14,3%)	n.s
Acute liver dysfunction	0 (0)	0 (0)	0 (0)	n.s
Acute renal insufficiency	0 (0)	0 (0)	0 (0)	n.s
Infections (gastrointestinal, respiratory, urinary, or other)	27 (71,1%)	19 (79,2%)	8 (57,1%)	n.s
Other general complications	9 (23,7%)	5 (20,8%)	4 (28,6%)	n.s
Late Complications of gastrectomy procedure	(n=10)	(n=4)	(n=6)	
Early dumping (30 minutes after eating)	7 (70,0%)	3 (75,0%)	4 (66,7%)	n.s
Late dumping (>2 hours after eating)	3 (30,0%)	1 (25,0%)	2 (33,3%)	n.s.

A R0 resection was reported in 88 patients (82,2%). Proximal resection margins were positive for tumor infiltration in eleven patients (10,3%), and distal resection margins in nine patients (8,41%).

Six patients (5,6%) had an HER2-overexpressing disease. Thirty-seven patients (34,6%) had a PDL-1 combined positive score (CPS) higher than 5. Microsatellites instability-high (MSI-H) GC was found in 15 patients (14,0%).

Table 12: Final histological report characteristics.

	COHORT (n=107)	**SURG (n=72)**	**NAT (n=35)**	**P value**
Ist. sec Bormann, n (%)	(n=63)	(n=46)	(n=17)	n.s.
Type 1, polypoid, n (%)	11 (17,5%)	8 (17,4%)	3 (17,7%)	
Type 2, fungating, n (%)	18 (28,6%)	14 (30,4%)	4 (23,5%)	
Type 3, ulcerated, n (%)	26 (41,3%)	19 (41,3%)	7 (41,2%)	
Type 4, diffuse (*Linitis Plastica*), n (%)	8 (12,7%)	5 (10,9%)	3 (17,7%)	
Ist. sec. Lauren	(n=73)	(n=52)	(n=21)	n.s.
Intestinal, n (%)	40 (54,8%)	30 (57,7%)	10 (47,6%)	
Diffuse, n (%)	23 (31,5%)	15 (28,9%)	8 (38,1%)	
Mixed, n (%)	10 (13,7%)	7 (13,5%)	3 (14,3%)	
Signet ring	(n=102)	(n=70)	(n=32)	n.s.
Not signet ring, n (%)	64 (62,8%)	48 (68,6%)	16 (50,0%)	
Signet ring, n (%)	38 (32,3%)	22 (31,4%)	16 (50,0%)	
Vascular-lymphatic invasion	(n=104)	(n=70)	(n=34)	n.s.
No, n (%)	28 (26,9%)	19 (27,1%)	9 (26,5%)	
Yes, n (%)	76 (73,1%)	51 (72,9%)	25 (73,5%)	
Perineural invasion	(n=103)	(n=69)	(n=34)	n.s.
No, n (%)	44 (42,7%)	29 (42,0%)	15 (44,1%)	
Yes, n (%)	59 (57,3%)	40 (58,0%)	19 (55,9%)	
Grading, n (%)	(n=93)	(n=68)	(n=25)	0,0390
G1, n (%)	14 (15,1%)	13 (19,1%)	1 (4,0%)	
G2, n (%)	20 (21,5%)	17 (25,0%)	3 (12,0%)	
G3, n (%)	59 (63,4%)	38 (55,9%)	21 (84,0%)	
Resection margins				
Proximal m.	(n=104)	(n=69)	(n=35)	n.s.
Negative, n (%)	93 (89,4%)	64 (92,8%)	29 (82,9%)	
Positive, n (%)	11 (10,6%)	5 (7,3%)	6 (17,1%)	
Distal m.	(n=104)	(n=69)	(n=35)	0,0283
Negative, n (%)	95 (91,4%)	66 (95,7%)	29 (82,9%)	
Positive, n (%)	9 (8,6%)	3 (4,4%)	6 (17,1%)	
Surgical margins	(n=103)	(n=68)	(n=35)	0,0299
R0, n (%)	88 (85,4%)	62 (91,2%)	26 (74,3%)	
R1, n (%)	14 (13,6%)	5 (7,4%)	9 (25,7%)	
R2, n (%)	1 (1,0%)	1 (1,5%)	0 (0)	
LNR (%), media ± DS	13,14 ± 21,88	11,32 ± 19,18	16,83 ± 26,47	n.s.
HER-2	(n=88)	(n=61)	(n=27)	n.s.
HER-2 -, n (%)	82 (93,2%)	56 (91,8%)	26 (96,3%)	
HER-2 +, n (%)	6 (6,8%)	5 (8,2%)	1 (3,7%)	
PDL-1	(n=52)	(n=30)	(n=22)	n.s.
CPS ≤ 5, n (%)	15 (28,9%)	6 (20%)	9 (40,9%)	
CPS > 5, n (%)	37 (71,2%)	24 (80%)	13 (59,1%)	
MSI-H	(n=50)	(n=28)	(n=22)	0,0206
MSI-H, n (%)	6 (12,0%)	6 (21,4%)	0 (0)	
MSS, n (%)	44 (88,0%)	22 (78,6%)	22 (100%)	
EBER/EBV	(n=43)	(n=26)	(n=17)	n.s.
EBER –, n (%)	41 (95,4%)	25 (96,2%)	16 (94,1%)	
EBER+, n (%)	2 (4,6%)	1 (3,8%)	1 (5,9%)	
P53 expression	(n=45)	(n=25)	(n=20)	n.s.
P53 WT, n (%)	21 (46,7%)	14 (56,0%)	7 (35,0%)	
P53 -/- or +/+, n (%)	24 (53,3%)	11 (44,0%)	13 (65,0%)	

Table 13: Adjuvant therapy characteristics.

	n (%)	Number of cycles, media ± DS (min- max)
Type of Adjuvant Therapy	(n=49)	
Chemotherapy alone	44 (89,8%)	
Chemoradiotherapy	3 (6,1%)	
Radiotherapy alone	2 (4,1%)	
CT scheme	(n=49)	
FLOT	15 (30,6%)	4,07 ± 2,55 (3-6)
XELOX	8 (16,3%)	4,83 ± 3,18 (3-8)
FOLFOX	7 (14,3%)	9,8 ± 2,79 (6-12)
Capecitabine mon.	3 (6,1%)	7,67 ± 3,68 (7-8)
EOX	1 (2,0%)	4
ECF	1 (2,0%)	6
Other regimens or combinations of antitumoral drugs:	8 (16,3%)	8,4 ± 2,89 (3-12)
Capecitabine+Cisplatin	1	
Cisplatine+De Gramont	4	
De Gramont	1	
Mk3475-585 study (sper-pembro/placebo+cispl+cape)	1	
(FLOT + pembrolizumab)/placebo	1	
Not specified	4 (8,2%)	6
Immunotherapy		
(Mk3475-585 study) sper-pembro/placebo+cispl+cape	1	3
(FLOT + pembrolizumab)/placebo	1	

Table 14: Patients' pathological staging characteristics

	COHORT (n=107)	SURG (n=72)	NAT (n=35)	P value
pT				0,0392
pT0, n (%)	3 (2,8%)	0 (0)	3 (8,6%)	
pT1, n (%)	23 (21,5%)	18 (25,0%)	5 (14,3%)	
pT2, n (%)	16 (15,0%)	12 (16,7%)	4 (11,4%)	
pT3, n (%)	32 (29,9%)	18 (25,0%)	14 (40,0%)	
pT4, n (%)	33 (30,8%)	24 (33,3%)	9 (25,7%)	
pN	(n=106*)	(n=72)	(n=34)	n.s.
pN0, n (%)	49 (46,2%)	36 (50,0%)	13 (38,2%)	
pN1, n (%)	26 (24,5%)	17 (23,6%)	9 (26,5%)	
pN2, n (%)	8 (7,6%)	4 (5,6%)	4 (11,8%)	
pN3, n (%)	23 (21,7%)	15 (20,8%)	8 (23,5%)	
	*in one patient the data is not available			
pM				.
pM0, n (%)	107 (100%)	72 (100%)	35 (100%)	
Pathological stage	(n=106)	(n=72)	(n=34)	0,0234
0, n (%)	3 (2,8%)	0 (0)	3 (8,8%)	
I, n (%)	31 (29,3%)	23 (31,9%)	8 (23,5%)	
II, n (%)	35 (33,0%)	27 (37,5%)	8 (23,5%)	
III, n (%)	37 (34,9%)	22 (30,6%)	15 (44,2%)	

Table 15: Adjuvant therapy, disease recurrence and death characteristics.

	COHORT (n=107)	SURG (n=72)	NAT (n=35)	P value
Adjuvant therapy	(n=101)	(n=68)	(n=33)	0,0342
No, n (%)	52 (51,5%)	40 (58,8%)	12 (36,4%)	
Yes, n (%)	49 (48,5%)	28 (41,2%)	21 (63,6%)	
Recurrence	(n=84)	(n=57)	(n=27)	n.s.
No, n (%)	52 (61,9%)	36 (63,2%)	16 (59,3%)	
Yes, n (%)	32 (38,1%)	21 (36,8%)	11 (40,7%)	
Death	(n=45)	(n=32)	(n=13)	n.s.
Cancer related, n (%)	20 (44,4%)	13 (40,6%)	7 (53,8%)	
Surgery related, n (%)	2 (4,4%)	1 (3,1%)	1 (7,7%)	
Other, n (%)	2 (4,4%)	2 (6,3%)	0 (0)	
Cause of death not available, n (%)	21 (46,8%)	16 (50,0%)	5 (38,5%)	

In 18 patients (51.5%), NAT has led to a significant down staging of the tumor *(Table 16)*. In particular, 7 patients (20%) had a significant response on the T, 6 patients (17,1%) had a significant response on the N and 6 patients (17.1%) on both parameters. Sixteen out of 18 patients (88,9%) who had a down staging of at least one parameter had a clinical stage II or III disease; of these, 8 patients (50%) had a stage II and the remaining 8 (50%) had a stage III adenocarcinoma. Considering proportions of patients with T0-2 and T3-4 before and after NAT plus surgery, 29 patients (82,9%) had cT3-4 (Any N) and 6 (17,1%) had cT0-2 (Any N) before treatment; after receiving chemotherapy and surgery, 22 patients (62,9%) had ypT3-4 (Any N) and 12 patients (34,3%) had ypT0-2 (Any N), thus emphasizing a down staging effect of NAT on advanced gastric tumours.

Forty-nine patients (45,8%) received adjuvant treatment following radical surgery, and 14 of these patients (28,6%) experienced a toxicity related to chemotherapy.

Table 16 Pathological downstaging in patients receiving NAT before surgery.

Clinical stage	n (%)	Pathological stage	n (%)
cN0	7 (20,0%)	**ypN0**	13 (37,1%)
T1 N0 M0	0 (0)	T0-1 N0 M0	7 (20%)
T2 N0 M0	2 (5,7%)	T2 N0 M0	3 (8,6%)
T3 N0 M0	5 (14,3%)	T3 N0 M0	3 (8,6%)
T4 N0 M0	0 (0)	T4 N0 M0	0
cN+	28 (80%)	**ypN+**	21* (60%)
T1 AnyN M0	0	T1 AnyN M0	1 (2,9%)
T2 AnyN M0	4 (11,4%)	T2 AnyN M0	1 (2,9%)
T3 AnyN M0	16 (45,7%)	T3 AnyN M0	10 (28,6%)
T4 AnyN M0	8 (22,9%)	T4 AnyN M0	9 (25,7%)
cM+	0	ypM+	0

* in one patient the data is missing

4.6. SURVIVAL ANALYSIS

The median follow-up for the entire cohort was 23 months (range 1-122). Forty-five patients (42,1%) died: 2 (4,4%) out of these patients died during the hospitalization and 43 (95,6%) during the follow-up period. Thirty-two patients (29,9%) experienced a disease recurrence and 28 (87,5%) out of 32 died for the disease. Patients had single or multiple sites of recurrence, and these were: esophago-jejunal anastomosis (2 patients), gastro-jejunal anastomosis (1 patient), peritoneum (15 patients), distant lymph nodes (8 patients), liver (3 patients), lungs or pleura (4 patients), bone (2 patients). In two patients, the site was not specified.

The 1-yr, 3-yr and 5-yr survival rates for the SURG group were 88, 61 and 52 months, respectively. The 1-yr, 3-yr and 5-yr survival rates for the NAT group were 76, 56 and 47 months, respectively. There was no statistically significant difference in the overall survival (OS) (80 months for the SURG group and 40 months for the NAT group, p =0.2613) between the SURG and the NAT group *(Figure 5)*. Similarly, disease-free survival (DFS) was similar between the two groups (10 months for the SURG group, 8 months for the NAT groups, p =0.1629) *(Figure 6)*. When looking to the tumor staging, OS did not significantly differ between the two groups of patients with clinical stages II-III (36 months for the SURG group, 40 months for the NAT group,

p=0.8788) *(Figure 7)*. We further subcategorized patients according to their final pathological stage into patients with cTNM stage II and III, and patients with cTNM stage III experienced a survival benefit when receiving NAT (17,5 months for the SURG group, 23 for the NAT group, p=0,2363), although the difference did not reach a statistical significance *(Figure 9)*. The same benefit is reported in DFS of patients with clinical stage III receiving NAT (11 months for the SURG group, 39 for the NAT group, p=0,4575) *(Figure 12)*.

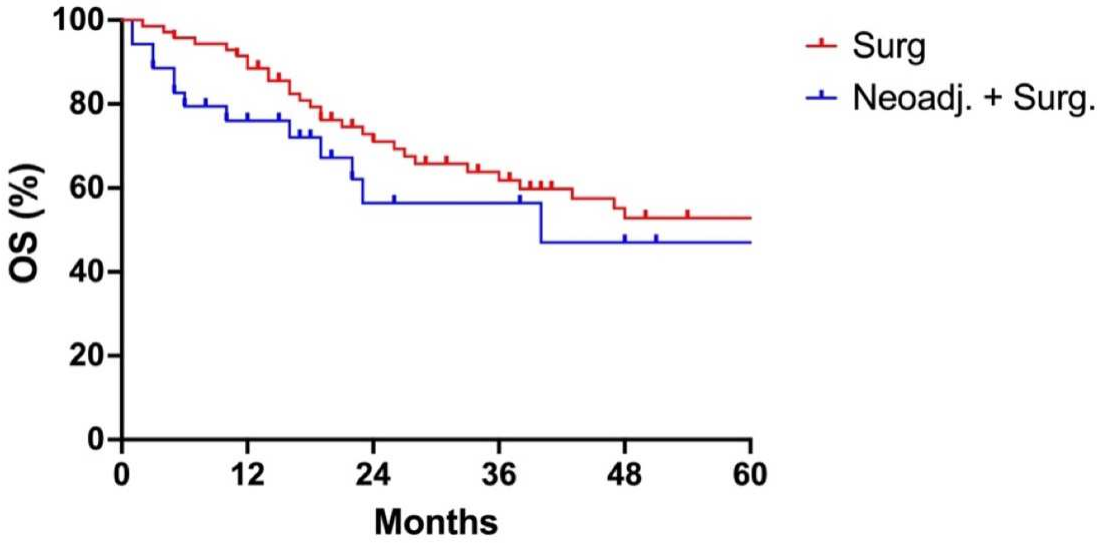

Figure 5: OS for the entire cohort of patients (80 months for the SURG group vs 40 months for the NAT group, p=0.2613).

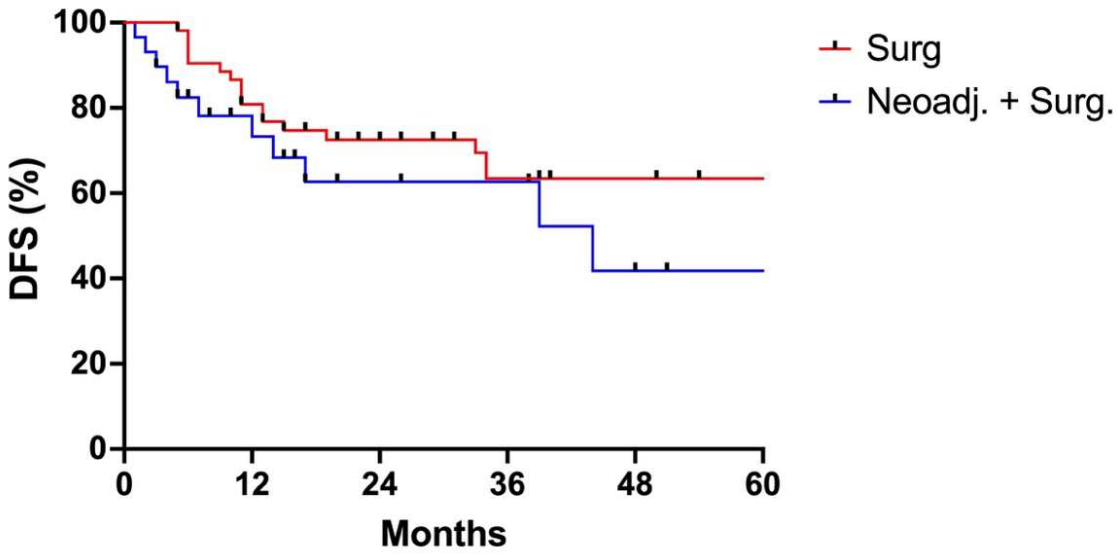

Figure 6: DFS for the entire cohort of patients (10 months for the SURG group, 8 months for the NAT groups, p=0.1629).

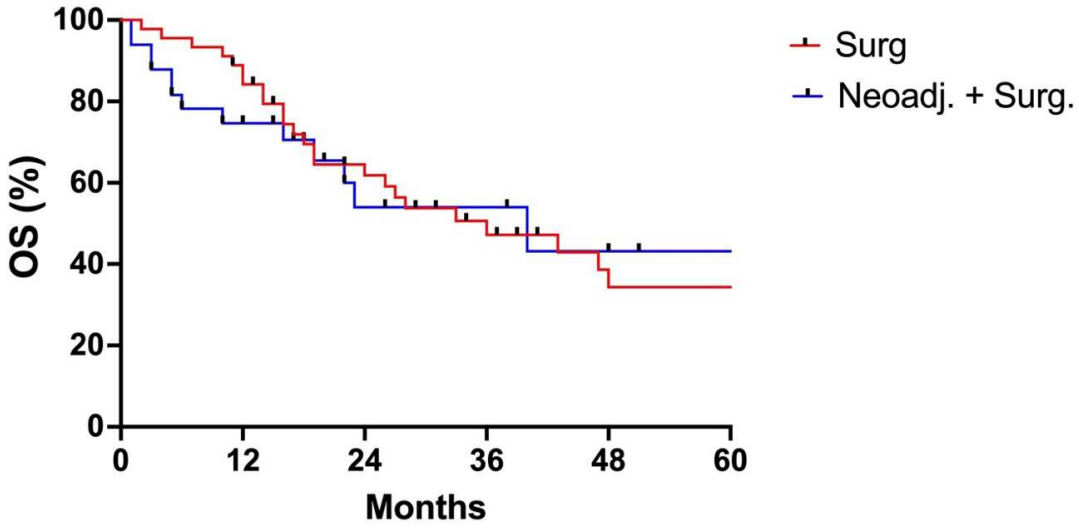

Figure 7: OS for a subgroup of patients presenting clinical stage II-III tumours (36 months for the SURG group, 40 for the NAT group, p=0,8788).

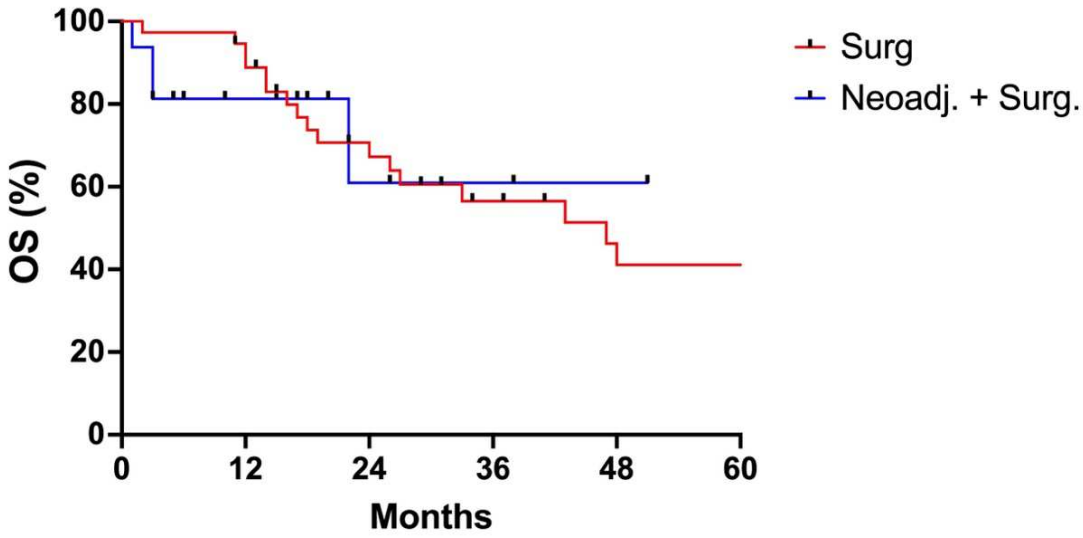

Figure 8: OS for a subgroup of patients presenting clinical stage II only (24 months for the SURG group, 19 for the NAT group, p=0,9951)

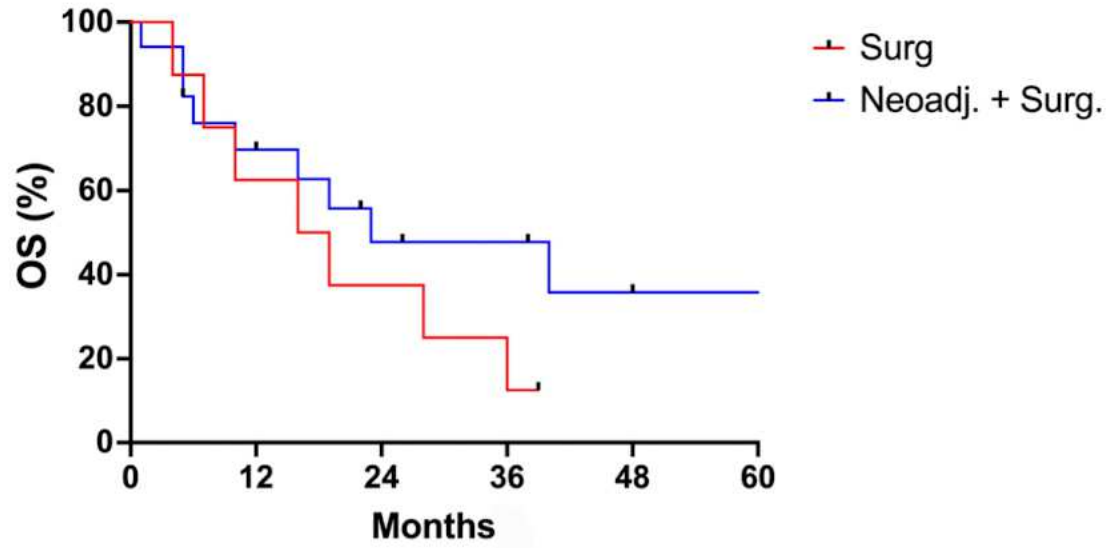

Figure 9: OS for a subgroup of patients presenting clinical stage III only (17,5 months for the SURG group, 23 for the NAT group, p=0,2363).

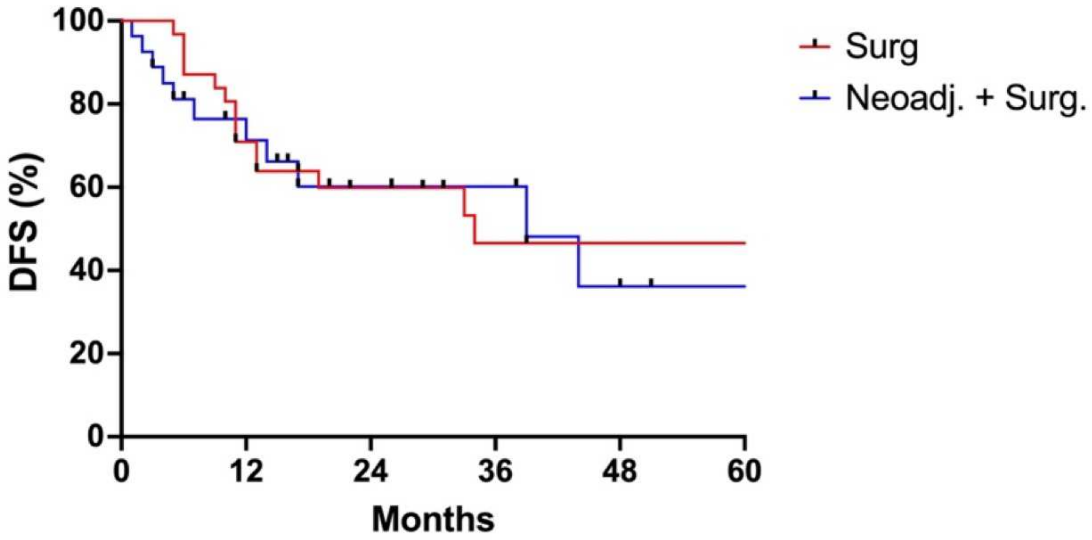

Figure 10: DFS for a subgroup of patients presenting clinical stage II-III tumours (34 months for the SURG group, 39 for the NAT group, p=0,728).

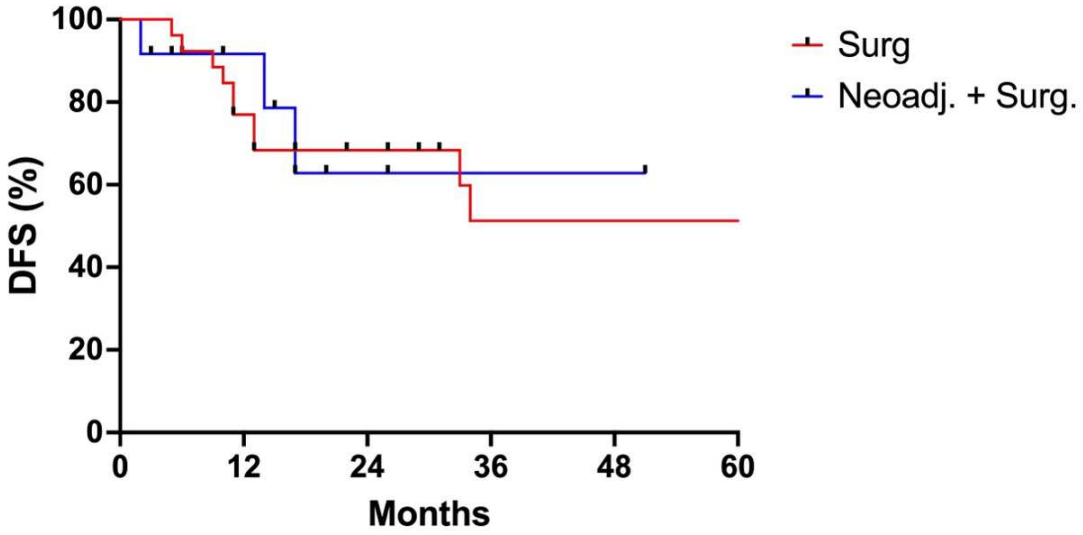

Figure 11: DFS for a subgroup of patients presenting clinical stage II only (9,5 months for the SURG group, 9 for the NAT group p=0,8891)

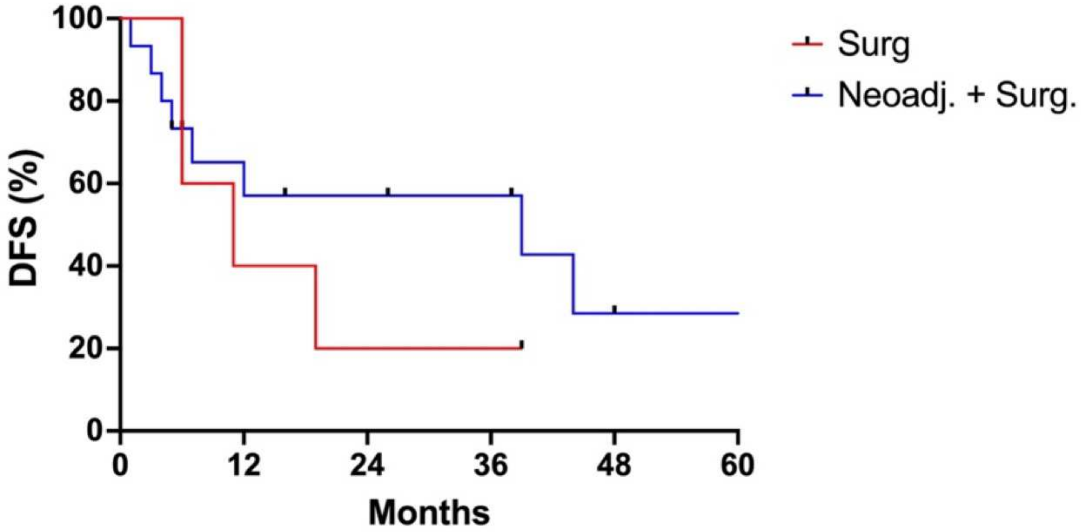

Figure 12: DFS for a subgroup of patients presenting clinical stage III only (11 months for the SURG group, 39 for the NAT group, p=0,4575).

Part III

Conclusion

5. DISCUSSION

In this observational study a population of 107 adult patients with adenocarcinoma of the stomach and of the cardia was retrospectively analyzed and subcategorized accordingly to the treatment they received: they either underwent upfront gastrectomy (SURG, n=72) or received neoadjuvant chemotherapy before surgery (NAT, n=35). The decision whether to treat selected patients with neoadjuvant therapy plus surgery or upfront surgery was made by a multidisciplinary team that considered all patients' and disease's characteristics (including clinical stage of the tumor, patient's fitness and comorbidities), as well as patients' preferences.

According to the results of our study, the upfront surgery approach for curative treatment of gastric adenocarcinoma was shown to be non-inferior to neoadjuvant therapy (NAT) plus radical surgery. In fact, the two approaches didn't show a statistically significant difference in terms of OS (80 months for the SURG group and 40 months for the NAT group, p=0.2613) and DFS (10 months for the SURG group, 8 months for the NAT groups, p=0.1629) when considering the entire cohort.

A similar result was reported in a RCT by Schuhmacher et al (111), which included a cohort of 144 patients with locally advanced adenocarcinoma of the stomach or esophagogastric junction (type II and III). Patients were randomly assigned to preoperative chemotherapy followed by surgery (consisting in two 48-day cycles of cisplatin plus infusion of fluorouracil) or to surgery alone. The estimated median survival was 64.62 months (95% CI) in the neoadjuvant arm versus 52.53 months (95% CI) in the surgery alone arm, with HR=0.84 (95% CI, 0.52 to 1.35; P=0.466). The authors concluded that preoperative chemotherapy might not have a beneficial impact on patients treated in that trial.

Moreover, our results showed that, considering a subgroup of patients presenting clinical stage II-III gastric adenocarcinoma, OS did not significantly differ between the two groups (36 months for the SURG group vs 40 months for the NAT group, p=0.8788). Instead, patients with cTNM stage III alone did experience a survival benefit when receiving NAT, although the difference did not reach a statistical significance. The same benefit was reported in DFS of patients with pathological stage III receiving NAT.

Furthermore, when analyzing postoperative outcomes, we observed a 49,5% postoperative morbidity rate, and a 4,4% postoperative mortality rate, considering the entire cohort. Additionally, no significant differences were reported between the SURG and the NAT groups, nor in the severity based on their Clavien-Dindo score. These results compare favorably with those of the MAGIC trial, where a 45% morbidity rate and 5% mortality rate were assessed, as well as with those of the FFCD trial, where postoperative morbidity was comparable between the surgical and the perioperative chemotherapy arm (21% vs 28%, respectively), with a 5% surgical mortality rate. A further RCT by Biffi et al (112) showed a 28.5% morbidity rate without registering any mortality.

Considering surgical margins, we reported an 82,2% R0 resection rate (91,2% vs 74,3% for the SURG group and the NAT group, respectively) and a tumor infiltration rate of 10,3% for the proximal resection margins and 8,41% for distal resection margins. Comparable results are found in the FNCLCC/FFCD RCT, R0 resection rate was 84% in the perioperative chemotherapy and surgery group versus 74% in the surgery alone group (P=0.04).

According to the previously presented results, patients who underwent radical D2 gastrectomy without prior treatment reported similar long-term

outcomes to the subjects eligible for neoadjuvant therapy, with comparable rate of perioperative complications. These results seem to confirm the hypothesis that upfront surgery for gastric cancer is non-inferior to neoadjuvant treatment plus surgery, when principles of surgical radicality are observed, along with extended lymph node dissection.

Interestingly, when focusing on the group of patients receiving NAT plus surgery, 51.5% of patients had to a significant down staging of the tumor, of which 20% had a significant response on the "T" parameter, 17,1% had a significant response on the "N" and 17.1% on both parameters, respectively. Furthermore, 88,9% of patients who had a down staging of the tumour had a clinical stage II or III disease, with 50% of patients having a stage II and the remaining half having a stage III adenocarcinoma. When comparing proportions of patients with T0-2 and T3-4 before and after NAT plus surgery, we observed a reduction from 82,9% to 62,9% of patients having c/ypT3-4 (Any N) and an increase from 17,1% to 34,3% of patients having c/ypT0-2 (Any N).

A meta-analysis (113) on neoadjuvant chemotherapy for advanced gastric cancer seems to have comparable findings, showing a significant down-staging effect on advanced gastric cancer: an higher rate of pT0-2 was reported for NAC group than for control group (49.9% vs 37.5%), with an OR of 1.71 (95% CI: 1.26-2.33). Thus, NAT might be considered as first line treatment for patients with locally advanced gastric adenocarcinoma considering the significantly high probability of down staging of the tumour. However, further studies are needed to better define and standardized characteristics of patients who might have the highest benefit from NAT with the lowest post-treatment morbidity rate, to better perform a tailored treatment for all GC patients.

Lastly, we reported a 38,1% rate of disease recurrence for the general cohort, with no statistically significative differences between the SURG and the NAT group (36,8% vs 40,7%). One of the most frequently reported sites of recurrence was peritoneum (46,9%). Similar results were obtained in the FFCD RCT, where the reported rates of recurrence were 55% for the group pf patients receiving NAT and 64% for patients who underwent upfront surgery. In the MAGIC RCT local recurrence was confirmed in 14.4% of patients in the perioperative-chemotherapy group and 20.6% in the surgery group, with distant metastases confirmed in 24.4% and 36.8% of patients, respectively.

In conclusion, despite significant advances in the management of gastric adenocarcinoma, this malignancy still represents a therapeutic challenge. Delayed clinical manifestation and high risk of metastatic lesions at diagnosis make it the fourth leading cause of cancer-related death worldwide. (98) Nonspecific symptoms consent its identification usually at advanced pathological stages, especially in Western countries, where a population-wide cancer-screening program does not seem to be cost-effective due to low incidence rate of the disease. (4) In Asian countries, instead, high prevalence of risk factors, such as *H. pylori* infection, and gastric preneoplastic lesions, have led to the establishment of screening endoscopy along with surveillance programs for high-risk subgroups of patients. In the last decades there has been a significant expansion of our understanding of the genomics of gastric cancer with the identification of many potentially targetable mutations and the consequent development of new target therapies. (99) Although this considerable progress, radical surgery remains the only available treatment with curative intent for gastric cancer and surgical options include subtotal or total gastrectomy, whereas limited surgical approaches (pylorus-preserving gastrectomy, proximal

gastrectomy and local resection) are infrequently performed since they may not guarantee equal oncologic outcomes. (7) Moreover, the development of laparoscopic and robotic-assisted surgery, along with endoscopic resection for early-stage gastric cancer, have had an important impact on the treatment strategies in the last few decades. Minimally invasive surgery was originally limited to treat distal early gastric cancers, in cases not requiring complete gastrectomy or extended lymphadenectomy. Both minimally invasive and robotic gastrectomies are considered to provide positive clinical outcomes, equivalent to those of open surgery and, additionally, they present even lower rates of postoperative complications, such as incisional hernias or bowel obstructions, which frequently occur following gastrectomy via laparotomic access. (39–41)

Lymphatic spread is the main prognostic factor in patients undergoing curative resection for gastric cancer, therefore a radical treatment is required to lower the risk of local and/or systemic relapse, by providing negative longitudinal and circumferential resection margins and by ensuring an adequate D2 lymph node dissection. (37) Total gastrectomy along with optimal lymphadenectomy is shown to guarantee a 5-year survival rate of about 25–35% on average for resectable gastric cancer. These poor outcomes are motivated by high risk of local recurrence after surgery, likely due to lymph nodes infiltration, and the chance of developing nodal metastases increases with tumoral stage. Survival rate is about 70% in Japan and in other Eastern Asian countries, where diagnosis at early stages consents adequate radical surgery, along with extended lymph node dissection. Although surgical resection is the standard therapy for gastric cancer, the need for radical lymphadenectomy for curative treatment of gastric cancer is controversial (100). Two randomized trials from the Netherlands (101) and the UK (45) have shown no survival benefits, but

high morbidity and mortality, after D2 gastric dissection compared with D1 dissection, likely due to limited experience in D2 dissection of participating surgeons and difficulty in ensuring adequate standards of local control. Nevertheless, a Taiwanese randomized controlled trial reported survival benefit for patients with gastric cancer when a D2 (based on second edition of Japanese classification of gastric cancer) nodal dissection is performed by experienced surgeons. (100)

To improve the loco-regional control of gastric adenocarcinoma, by assuring surgical radicality with the lowest risk of micrometastases, some randomized clinical trials suggested the introduction of a perioperative chemotherapy to surgery, or the adoption of chemo-radiotherapy, in the adjuvant setting. Moreover, a conversion therapy may be considered with application of either chemotherapy or radiotherapy to surgical treatment in cases of originally unresectable tumour at advanced stages. (102) Systemic treatment modalities for advanced gastric adenocarcinoma have significant geographic variation and perioperative chemotherapy, which consists in giving half cycles of chemotherapy before and half cycles after surgery, is the standard treatment in Europe. (98) Publication of the MAGIC and the FNCLCC-FFCD randomized clinical trials (52,53) has led to the introduction of neoadjuvant chemotherapy into several guidelines in Western countries, since they showed how perioperative chemotherapy does significantly improve the overall survival (OS) and the disease-free survival (DFS) of patients with adenocarcinoma of the stomach and esophagogastric junction. However, there's no strong evidence of its superiority as compared to a radical D2 gastrectomy for locally advanced gastric cancer, considering patients' overall survival. In the MAGIC trial (52) 503 patients with clinical stage II or III adenocarcinoma of the stomach (75%) or gastro-oesophageal junction/lower oesophagus were enrolled and

subdivided accordingly to the received treatment: they were treated with either pre- and post-operative chemotherapy (consisting of three cycles of Epirubicin, Cisplatin, and Fluorouracil (ECF)) or with upfront surgery. Patients in the chemotherapy group showed a significant benefit in 5-year overall survival compared with surgery alone (36% *vs* 23%; p=0·009). Nevertheless, about 60% of these patients did not have a controlled D2 dissection, and this results in limited surgery. The phase 3 FNCLCC/FFCD 9703 study (53) enrolled 224 patients with gastro-oesophageal junction/lower oesophageal (75%), or stomach adenocarcinoma. Patients received either two to three cycles of cisplatin and fluorouracil before and after surgery or surgery alone. Patients in the chemotherapy group had significant increase in 5-year overall survival compared with surgery alone (38% *vs* 24%; p=0·02), but the type of dissection performed was not reported. Furthermore, these studies enrolled patients with adenocarcinomas located in different upper-gastrointestinal sites (lower esophagus, cardias, stomach cancers) regardless of their differences in prognosis and response to chemotherapy. In both studies, a subgroup analysis showed that cancer of the lower esophagus/cardia had the best response to neoadjuvant chemotherapy, while proper gastric cancer had lower response.

Lastly, overall survival rates of patients with locally advanced cancers after upfront surgery and D2 dissection reported from referral centers are significantly high, with reported rates higher than 50-55% (100,103–110), as compared to those reported after both surgery alone (23-24%) and neoadjuvant chemotherapy + surgery (36-38%) arms in the MAGIC and French trials respectively. These poor overall survival rates result from countries with no standardized surgery. Besides, a recent worldwide systematic review on neoadjuvant chemotherapy analyzed publications

from 1990 to date; they were mainly single centers low volume reports and took in consideration mixed populations of cardia and gastric cancer patients. When reported, there was no significant benefit of neoadjuvant chemotherapy. Just 4 out of these 14 articles analyzed the type of lymphadenectomy performed. Out of these, only in the EORTC trial a standardized D2 dissection was reported in almost all cases (111) and despite significant tumour downstaging in the neoadjuvant chemotherapy arm, no survival benefit was assessed. In addition, in most of these publications, the regimen adopted in the neoadjuvant chemotherapy was either experimental or abandoned, except for the ECF scheme.

In conclusion, there is still a limited number of randomized clinical trials published in the last decades, therefore larger studies are needed to investigate the best treatment option that might revolution these patients' prognosis, in light of the recent introduction of targeted antitumoral therapies.

LIMITS OF THE STUDY

The limitations of the study are its observational retrospective design, the small number of patients involved, and the unavailability of some patients' data considering that an historical cohort was analyzed. Despite its limitations, this study was conducted in a high-volume center and therefore its results add an interesting perspective on the treatment of gastric cancer.

6. CONCLUSION

In conclusion, upfront radical gastrectomy might be considered for patients with early stages gastric cancer, while neoadjuvant chemotherapy might be an alternative option for patients with resectable locally advanced disease, especially stage III. However, additional studies are needed to better investigate the beneficial aspects of neoadjuvant treatment when compared to radical surgery.

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