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RESEARCH ARTICLE

Staging I in a Gastric Adenocarcinoma Cohort: Description of Clinical, Imaging and Pathological Findings

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ABSTRACT

Background: Gastric cancer was the fourth cause of cancer related deaths in 2020 in the world. The aim of this study was to describe the characteristics of patients with gastric adenocarcinoma stage I by clinical, pathological, and neoadjuvant staging on a prospective cohort at single cancer center.

Methods: Sixty-three patients with stage I gastric adenocarcinoma treated at A.C.Camargo Cancer Center were evaluated for clinical, pathological, and clinical Stage. For the comparison between the clinical staging and the post-treatment one (surgical and neoadjuvant): tumor (T) and lymph nodes (N) were evaluated.

Results: Of the 63 patients, 29/63 (46%) were clinical stage I, and 34/63 (54%) were initially staged as clinical stage II and III that migrated to stage I after surgical and neoadjuvant treatment. As for the clinical aspects, 36/63 patients (57%) were men with average age of 58.7 years, 63% patients were caucasian and 83% (52) had private medical insurance. In the endoscopic reports, 68.3% (n=43) of the lesions were ulcerated and the histological type, 55.6% (n=35) were diffuse. Patients treated with neoadjuvant therapy, had 100% reduction of tumors T3/T4 to T1/T2 ($p<0.001$) and 78.5% of the regional lymph nodes, N+ to N0. ($p=0.001$).

Conclusion: The neoadjuvant therapy on patients with gastric adenocarcinoma led to significant tumor (T) and regional lymph nodes (N) regressions, thus, increasing the migration of cases from T3/T4 to T1/T2 and N+ to N0 in this cohort.

Keywords: Stomach Neoplasms; Neoadjuvant Therapy; Neoplasm Staging.

Introduction

The gastric cancer was the fifth most incident neoplasm worldwide in 2020, with 1,089,103 new cases and 684,996 deaths, representing 5.6% of incidence and 6.9% of cancer related deaths.¹ In Brazil, in the same year, the estimated number of cases were 20,139, being 12,961 men and 7,178 women, becoming the fourth neoplasm more frequent in men (4.3%) and eighth in woman (2.6%)¹.

About 95% of gastric cancer (GC) cases are adenocarcinomas, being more frequent in men and elderly², and in Asian and Latin American population. The most frequent associated risks to gastric cancer are the infection of *Helicobacter pylori*, sodium rich diet, high consumption of red meat, smoking, the consumption of alcohol (above 37 grams/day) and obesity³.

The therapeutic plan for patients with gastric adenocarcinoma depends, besides the patient's clinical performance, on the histological and clinical characteristics of the tumor and staging (AJCC)⁴. Staging is characterized by aggregating the characteristics according to the tumor (T), regional lymph nodes (N) and metastasis (M). Usually, patients are staged just after the diagnosis (clinical) and it again after treatment to verify its pathological details. Therefore, cancer staging is classified by three groups: clinical (cTNM), pathological (pTNM), referred to the patients that only underwent surgery and a third, (yTNM), referred to the patients that received neoadjuvant treatment and followed by a curative surgery⁴.

The clinical staging precedes treatment, and it is based on the patient's history and the imaging exams and histological diagnosis.⁴

The pathological staging is the macroscopic and microscopic exam of the surgical specimen (stomach) which describes the type of lesion (ulcerated, infiltrative, depressed, or elevated), the histological pattern, the safety margins and the presence of the regional lymph nodes infiltrated or not by the neoplasm. Regarding the neoadjuvant staging, the patient receives chemotherapy as before the main curative therapy (surgery), and the tumor is staged again through the surgical specimen, as to verify the local treatment response on the tumor and regional lymph nodes⁵.

Curative treatment for gastric cancer is surgery, including radical gastrectomy and postoperative chemotherapy, which are the standard treatments. However, surgery alone is not sufficient for the best survival outcomes^{6,7}. The MAGIC trial (2006) showed that neoadjuvant therapy, administered before surgery, has emerged as a promising strategy to enhance tumor response rates, downstage tumors, and potentially improve long-term outcome than the patients with standard treatment⁶. Neoadjuvant therapy (NAT) is a multimodal strategy developed to optimize prognosis and includes neoadjuvant chemotherapy (NACT), chemoradiotherapy (NACRT), targeted therapy and even immunotherapy⁷.

The aim of the present study was to evaluate the sociodemographic, characteristics and clinical features regarding the impact of pTNM and yTNM in patients with stage 01. By assessing the impact of neoadjuvant chemotherapy on tumor downstaging, pathologic response, and long-term survival outcomes, clinicians and researchers can guide treatment decisions, refine prognostic

models, and identify patients who may require additional or alternative therapeutic interventions. This knowledge can aid in optimizing treatment protocols, reducing unnecessary surgeries, and improving overall patient outcomes.

Methods

This is a prospective cohort composed of sixty-three patients with gastric adenocarcinoma stage I, including pre and post treatment. This study is part of the case-control project named "Epidemiology of Gastric Adenocarcinomas in Brazil" conducted at the A.C. Camargo Cancer Center (ACCCC).

The cases were patients with diagnose of gastric adenocarcinoma recruited from march of 2016 to august of 2019 at a single cancer center (ACCCC), of both genders and ages between 18 and 75 years. The patients with clinical or pathological stages II, III and IV were excluded from the analysis.

The variables included in this study was: gender (male and female), age as continuous variable and stratified variables ≥ 60 or < 60 years old, self-assigned ethnicity as Caucasian, African-descendent, brown, and Asian, the infection of *H. pylori* in endoscopic and pathological exams were characterized as positive and negative or not evaluated. Cases were staged according to the AJCC 8th edition⁴ and the histological classification applied was Lauren's (1965)⁹. All cases were analyzed by relative and absolute frequencies in the program SPSS. To compare of pre- and post-treatment of T and N variables was utilized the chi-squared test.

Results

In this prospective cohort of sixty-three patients in clinical, pathological, and neoadjuvant stage I, 36/63 (57%) were men with average age of 58.7 years with Caucasian self-identification ethnicity (63%). (Table 01)

Table 01. Sociodemographic and characteristics of 63 patients with gastric adenocarcinoma stage I at A.C.Camargo cancer center

Variable	Frequency (N)	Percentage (%)
Gender		
Male	36	57%
Female	27	43%
Age		
Average (in years) \pm SD	58.7(\pm 10.61)	
≤ 60 years	33	52%
> 60 years	30	48%
Ethnicity		
Caucasian	40	63%
Brown	13	21%
Asian	6	10%
Afro-descendant	4	6%
Total	63	100%

SD= Standard Deviation.

Regarding the access to treatment, 52/63 (83%) had medical insurance. The H. pylori infection was positive in 22% of cases (14/46) with the Giemsa diagnostic method more frequent 52% (33). Regarding to the Lauren's histological classification, the diffuse type was the more frequent 55.6% (n=35). (Table 02)

Table 02. Clinical characteristics of sixty-three patients with gastric adenocarcinoma stage I at A.C.Camargo Cancer Center

Variable	Frequency (N)	Percentage (%)
Access to Treatment		
Private Medical Insurance	52	83%
Public Health System - SUS	11	17%
H pylori*test		
Negative	32	51%
Positive	14	22%
Diagnostic Method		
Giemsa (Pathology)	33	52%
Urease (Endoscopy)	12	19%
Not researched	18	29%
Lauren's Classification		
Diffuse	35	55.6%
Intestinal	22	34.9%
Mixed	6	9.5%

*46/63 patients had researched H.pylori

Of the sixty-three patients, 29 were clinical Stage I at diagnosis and 34/63 (54%) migrated to Stage I after surgery (9/34) and (25/34) preceded of neoadjuvant treatment. The most frequent lesions found on endoscopic exams were ulcerated 68.3% (n=43). The information found on CT scan and virtual gastroscopy was gastric wall thickness. (Table 03)

Table 03. Endoscopic characterization and imaging description of sixty-three patients with gastric adenocarcinoma Stage I.

Characteristic	Frequency	Percentage
Lesion in the Endoscopy (n=63)		
Ulcerated	43	68.3%
Depressed	8	12.7%
Elevated	8	12.7%
Infiltrative/ Plane/Polyp	4	6.3%
Average lesion size (cm)	2.3 cm	
Computed Tomography SCAN (n=52)		
Gastric Wall Thickness	26	41.3%
Lesion*	6	9.5%
No evidence of disease	20	31.7%
Virtual Gastroscopy - CT (n=13)		
Gastric Wall Thickness	12	19.0%
Lesion*	1	1.6%
Positive Lymph nodes - CT (N)		
Yes	7	11.1%
No	6	9.5%
Lesion in the echo-endoscopy (n=15)		
Ulcerated	8	12.7%
Depressed	3	4.8%
Elevated	2	3.2%
Infiltrative/ Plane	2	3.2%
Positive Lymph nodes – Echo (N)		
Yes	3	4.8%
No	12	19.0%

* Ulcerated, infiltrated, plane depressed or elevated lesions or polyps

Of twenty-nine patients of clinical Stage I, 18/29 were men with ages below 60 years old (15/29). The most frequent lesion type found in the endoscopy was ulcerated and in the echo-endoscopy was depressed, with average size of 1.94cm. The intestinal histological type was the most found. In the CT SCAN there was not seen evidence of disease on 14/29 cases. In virtual gastroscopy,

the gastric wall thickness of the gastric wall was found in all the cases. The presence of regional lymph nodes was not identified in this imaging exams. (Table 04)

Table 04. Clinical, histological, endoscopic, and imaging characterization of twenty-nine patients with gastric adenocarcinoma Clinical Stage I.

Clinical Stage (cTNM) I (n=29)				
Staging T	T1a	T1b	T2	Total
Age				
≤60 years	4	6	5	15
>60 years	8	3	3	14
Gender				
Male	6	6	6	18
Female	6	3	2	11
Lesion in the Endoscopy				
Ulcerated	8	5	4	17
Depressed	2	0	2	4
Elevated	0	3	2	5
Plane/ Polyp	2	1	0	3
Computed tomography (n=25)				
No evidence of disease	6	5	3	14
Gastric Wall Thickness	2	3	2	7
Lesion	2	1	1	4
Lauren's Classification				
Intestinal	8	4	2	14
Diffuse	3	3	5	11
Mixed	1	2	1	4

In 22 patients with pathological staging I (pTNM), it was observed the same age distribution under and above 60 years old (11/22). For the patients with neoadjuvant staging I (yTNM), it was most frequent in patients above 60 years old (25/38). Regarding the histological classification, the intestinal type was more found on the pTNM

I group, and the diffuse type on the yTNM patients. (Table 05).

Table 05. Pathological (pTNM) and neoadjuvant (yTNM) staging of 60 patients with gastric adenocarcinoma.

	Pathological (pTNM) I (n=22)					Neoadjuvant (yTNM) I (n=38)					
	T0	T1a	T1b	T2	Total	T0	T1a	T1b	T2	Tis	Total
Number of cases	4	9	7	2	22	1	10	21	5	1	38
Age											
≤60 years	-	5	5	1	11	-	2	10	1	-	13
>60 years	4	4	2	1	11	1	8	11	4	1	25
Lauren's Classification											
Diffuse	-	5	3	1	9	1	6	15	4	-	26
Intestinal	4	4	3	-	11	-	2	5	1	1	9
Mixed	-	-	1	1	2	-	2	1	-	-	3

When compared the clinical Stage of gastric adenocarcinoma with the pathological Stage, the anatomopathological examination of the surgical specimen identified that 12/16 patients continued to be T1/T2 staging, and 4/16 were T0. Regarding the T3/T4 staging,

100% (n=6), after surgery were found T1/T2. In relation to the presence of positive regional lymph nodes, 17/20 patients after surgery remained N0 and 3/20 (15%) clinically Staged N0 were N positive. (Table 06)

Table 06. The comparison between clinical (cTNM) and pathological (pTNM) Stage I of patients with gastric adenocarcinoma

	Clinical (cTNM)	Total	Pathological (pTNM)		p
			T1/T2	T0	
		n (%)	n (%)	n (%)	
Tumor (T)	T1/T2	16 (100)	12 (75)	4 (25)	0.754 ^a
	T3/T4	6 (100)	6 (100)	0	
Lymph nodes (N)	N0	20 (100)	17 (85)	3 (15)	1.000 ^a
	N+	2 (100)	1 (50)	1 (50)	
Total		22 (100)	18 (82)	4 (12)	

a: chi-squared test

When compared the clinical and neoadjuvant Stage, the histopathological exam revealed that 12/13 patients continued to be T1/T2

after treatment and 1 patient was T0. All the T3/T4 tumors (25) migrated to T1/T2. Regarding to the lymph nodes, 79% (19/24)

continued N0 post-treatment, and 21% (5/24) became positive (N+). Of the 14 patients that were N positive on the clinical Stage, post-treatment 11 cases were N0 and 3 continued

to be positive N+. Therefore, after neoadjuvant treatment, there was a significant reduction of tumor and lymph nodes. (Table 07)

Table 07. The comparison of clinical (cTNM) and neoadjuvant (yTNM) staging in 38 patients of gastric adenocarcinoma

Clinical (cTNM)		Total	Neoadjuvan (yTNM)		p
			T1/T2	T0	
		n (%)	n (%)	n (%)	
Tumor (T)	T1/T2	13 (100)	12 (92)	1 (8)	<0.001 ^a
	T3/T4	25 (100)	25 (100)	0	
			N0	N+	
Lymph nodes (N)	N0	24 (100)	19 (79)	5 (21)	0.001 ^a
	N+	14 (100)	11 (78.5)	3 (21.5)	
Total		38 (100)	30 (79)	8 (21)	

a: chi-squared test

Discussion

This study describes the clinical, pathological, and neoadjuvant staging I in 63 patients with gastric adenocarcinoma. This is one of the first epidemiologic studies evaluating TN staging in the era of neoadjuvant treatment and its comparison to clinical and pathological staging's in a Latin American population. Our results showed reduction of tumor (T) and regional lymph nodes (N) staging on patients classified as T3/T4 and positive lymph nodes (N+) submitted to neoadjuvant treatment. However, there was no difference regarding the tumor and lymph nodes when comparing clinical and pathological staging.

The MAGIC trial written by Cunningham, et al. (2006)⁶ was one of the first studies that identified improved long-term survival rates using preoperative chemotherapy for resectable gastric or gastroesophageal cancer,

due to decreased tumor size and stage⁶. Although this study did not evaluate survival rates, reduction on tumor and lymph nodes scale for cases treated with neoadjuvant chemotherapy were observed, which could influence overall survival.

In the systematic review of Miao et al. (2018)¹¹ they included 12 randomized clinical studies with neoadjuvant chemotherapy in 1,538 patients with gastric adenocarcinoma, it was observed increased global overall survival and progression free survival¹¹. Ychou et al. (2011)¹² in France, compared treatments with and without neoadjuvant chemotherapy for gastric adenocarcinoma and concluded that patients who underwent neoadjuvant treatment had better overall 5-year survival rate than the ones that underwent only surgery¹². A study by Coccolini et al. (2018)¹³ about the treatments of gastric cancer, included neoadjuvant chemotherapy to convert unresectable

tumors into resectable ones, which resulted on an increased overall survival¹³.

Very similarly with the present study, Xu et al. (2014)¹⁴, observed lesser number of cases with positive lymph nodes for patients who underwent neoadjuvant chemotherapy¹⁴. In 2016, a systematic review with 1,240 patients described positive results regarding the effectiveness of neoadjuvant therapy in comparison of other treatments¹⁵. In this study, 34 tumors T3/T4 migrated to T1/T2, becoming resectables tumors after neoadjuvant chemotherapy, confirming the findings of Coccolini et al. 2018¹³.

Gastric cancer has been reported as more common in men above 60 years and twice more frequent on Caucasians^{3,16}. This profile was found on the present study, except for the age, with an average of 58 years old, lower than the literature.

A systematic review done in Italy, 2017, by Patreli et al.¹⁷ with 61,468 patients, observed that patients with histological diffuse type had worse prognosis.¹¹ In a study done in Romania, where the tumors histological type was analyzed in 154 patients, the intestinal type was more frequent (49.1%). In the present study, the diffuse type was more frequent on patients with advanced cTNM (T3/T4) while early cTNM (T1/T2) in the intestinal type^{17,18}

One of the limitations of this study is the small number of patients at an early Stage I, which prevents stratification of groups for more detailed analysis.

Conclusion

In this study we evidence the epidemiological aspects and main T (tumor) and N (regional

lymph-nodes) profiles of gastric adenocarcinoma from clinical, pathological, and neoadjuvant settings, which are the main indicators of prognosis for gastric cancer. It was possible to identify regression of both diffuse and intestinal types of tumor (T) and positive lymph nodes (N) on the group treated with neoadjuvant chemotherapy. Regarding patients with stage, I who underwent only surgery, without neoadjuvant therapy, there was no significant differences between clinical and pathological Stage I, which supports consistence between the three Stages settings on cases of gastric adenocarcinoma.

Competing Interest:

The authors declare that they have no competing interest

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Ethics approval

The Ethics Committee of A. C. Camargo Cancer Center have approved this study.

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