



## Research Article

## Comparison of Clinical Behavior of Cardia and Antral Adenocarcinomas: Revisiting an Old Issue in Brazil

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### Introduction

Despite an overall decline in its incidence in recent decades, gastric adenocarcinoma remains the fourth most common type of cancer and the second or third leading cause of cancer-related deaths worldwide. Conventionally, proximal tumors (Esophagogastric Junction (EGJ)) are distinguished from distal tumors. It seems that, with the decline in *Helicobacter pylori* infections, there has been a decrease in the incidence of distal tumors, while the incidence of proximal tumors has increased [1,2]. A noticeable decrease in mortality may be related to earlier diagnosis and better adjuvant and neoadjuvant treatments [3]. Proximal and distal adenocarcinomas are known to have different behaviors and manifestations, but the literature shows discrepant data on such aspects in this type of cancer, especially regarding proximal tumors [4].

Cardia adenocarcinoma is shown to affect male patients at a disproportionately higher rate [5]. The relationship with hormonal factors is curious, since there seems to be an association between higher concentrations of Dehydroepiandrosterone (DHEA), circulating estradiol and free estradiol and lower risks of cardia adenocarcinoma in men [6-9]. Furthermore, proximal adenocarcinoma is associated with older patients, and unfortunately diagnosed at more advanced pathological stages [3,4,10]. Intestinal metaplasia has been implicated in its genesis in cases related to Barrett's esophagus [11]. The association between *Helicobacter pylori* (*Hp*) and gastric adenocarcinomas is also well-known. Its association with distal tumors is more evident, which is reinforced by studies in eastern populations. On the other hand, when regarding proximal tumors, the literature shows conflicting information. There is both evidence that cardia cancer is associated with the absence of *Hp*, while others, in eastern populations, reveal that there is a direct association between infection and the development of cardia cancer [12-15]. Obesity and alcohol consumption also seem to play a role in the genesis [7,8,16,17].

Regarding the histological origin there are two types: the squamous cell carcinoma and the adenocarcinoma. The first has its causes linked to alcohol consumption, smoking and ingestion of hot beverages as it happens in the south of Brazil. On the other hand, the adenocarcinoma seems to be related to obesity, *H. pylori* infection, reflux disease and also to alcohol [15,16]. Due to its later manifestation and generally less favorable characteristics, EGJ cancer has a worse prognosis, with a lower 5-year, overall and disease-free survival [18,19]. Nevertheless, when the TNM stages are paired, it seems that the overall survival is similar in both cardia and non-cardia tumors [20]. Knowing the relevance of this issue and the contradictions present in the literature, it is necessary to search for a better understanding of the clinical and epidemiological differences between cardia and gastric antral cancer.

### Objectives

To conduct a comparative analysis of the clinical behavior of both cardia and antral adenocarcinomas. The variables analyzed were age, gender, cancer, histological type, TNM staging, operability and survival.

### Methods

Retrospective data was collected from all treated cases in a recording protocol for prospective data collection in the Gastroesophageal Division, Department of Surgery, Santa Casa of São Paulo Medical School. The registry is based on the protocols of the Japanese Gastric Cancer Association [21]. Tumor sites were based on the Japanese Classification of Gastric Carcinomas and are classified into three basic regions: U (upper third), M (middle third) and L (lower third); in cases of esophageal invasion, the letter E is placed, while in the case of duodenal invasion, the letter D. It is always considered the place where the center of the tumor is located. For tumors of the gastroesophageal junction, the letter

U was associated with the word cardia (II or III). The abbreviations II or III refer to the Siewert classification for esophageal gastric junction cancer [22]. For analysis purposes, operated and non-operated patients were separated.

Cardia cancer is defined as all tumors located from 5cm above the EJG to 5cm below. Such methodology is based on the Siewert classification. The epidemiological, histological, clinical, surgical and oncological data of all patients with cardia cancer and gastric antrum (L) cancer patients were analyzed and compared. We excluded Siewert type I tumors, as they must be staged and treated as esophageal cancer. Inclusion criteria: all patients with Esophagogastric Junction (EGJ) cancer (except Siewert type I) and antrum (L) cancer patients from 1997 to 2015. Exclusion criteria: tumors from other regions of the stomach, tumors of the remnant stomach (gastric stump), patients with non-adenocarcinoma stomach cancer, patients with Siewert type I adenocarcinoma and those with unavailable data. Regarding the histological type, we used the Laurén's Classification: diffuse, intestinal, or simply adenocarcinoma, in cases where it was not possible to obtain this data. As much as possible, the definition of mixed was avoided, since many cases were analyzed several years ago, when this terminology was rarely used and all microscope slides were not reviewed. Still, some cases classified as mixed were included, respecting the pathologist's report. The mortality of operated and non-operated patients was analyzed, excluding postoperative deaths (30 days), with no maximum survival period being defined.

As for the surgical procedure, the patients were classified as: a. Inoperable, which constituted a series of conditions: irresectability, carcinomatosis, metastatic disease, poor general condition, or patient refusal. b. Operable (submitted to some type of resection), which included: mucosectomy, esophagogastrectomy, proximal gastrectomy and total gastrectomy for cardia tumors and mucosectomy, subtotal gastrectomy and total gastrectomy for distal tumors; however, the type of resection was not taken into account for analysis. For staging, the 7<sup>th</sup> edition of the Classification of Malignant Tumors was used from the International Union Against Cancer and the American Joint Committee on Cancer (UICC)

[23] (Table 1). In this classification, the parameters T (depth), N (lymph node involvement) and M (metastases) are determined as follows: T1 - tumor penetrates the submucosa; T2 - penetrates the muscularis propria; T3 - penetrates the subserosa; T4a - penetrates the serosa; T4b - invasion of adjacent organs; T0 or Tx - cases in which the depth cannot be verified, either because we did not perform the resection, or because of a complete response to the complementary treatment; N0 - absence of lymph node involvement; N1 - involvement of up to two lymph nodes; N2 - involvement of 3 to 6 lymph nodes; N3a - involvement of 7 to 15 lymph nodes; N3b - involvement of 16 or more lymph nodes; Nx - patients in whom it was not possible to determine lymph node involvement; M0 - absence of distant metastases, and; M1 - presence of distant metastases.

	N0	N1	N2	N3
T1	IA	IB	IIA	IIB
T2	IB	IIA	IIB	IIIA
T3	IIA	IIB	IIIA	IIIB
T4a	IIB	IIIA	IIIB	IIIC
T4b	IIIB	IIIB	IIIC	IIIC
M1	IV			

**Table 1:** Classification of Malignant Tumors from the International Union Against Cancer (Adapted from the TNM Classification of Malignant Tumors 7<sup>th</sup> Edition, UICC, 2007).

The study did not and will not involve any risk to patient integrity and the risk of data exposure was minimal.

For statistical analysis, the Mann-Whitney test was used to verify differences in age and survival time between the groups: cardia and non-cardia, and the Chi-square or Fisher's exact test, to verify possible associations between the studied variables.

## Results

The results are presented in the Tables and in the Figure below.

Characteristics	n (Total = 401)	%
Age	Mean: 61.3	SD: 12.76
Sex		
Male	249	62.09
Female	152	37.91
Histological Type		
Diffuse	218	54.36
Intestinal	172	42.89
Undetermined	11	2.74
Inoperability		
Operable	289	72.07
Inoperable	112	27.93
Staging		
IA	78	19.45
IB	35	8.73
IIA	21	5.24
IIB	30	7.48
IIIA	30	7.48
IIIB	41	10.22
IIIC	56	13.97
IV	110	27.43
Overall survival (months)	Mean: 47.20	DP: 51.83
	Median: 23	
5-year survival		
Less than 5 years	242	60.35
More than or equal to 5 years	159	39.65

**Table 2:** Characteristics of the sample of patients with cancer of the antrum and cardia. Santa Casa of São Paulo Medical School 2021.

Characteristics	Cardia (n = 76)		Antral (n =325)		p
	n	%	n	%	
Age	M: 61.7	SD: 13.1	Mean: 61.3	DP: 12.7	0.569
Sex					0.04
Male	55	72.37	194	59.69	
Female	21	27.63	131	40.31	
Histological Type					0.908
Diffuse	39	56.62	179	55.76	
Intestinal	30	43.48	142	44.24	
Inoperability					< 0.001
Operable	36	47.37	253	77.85	

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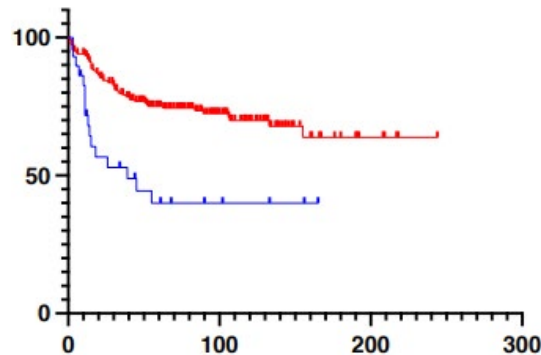
Inoperable	40	52.63	72	22.15	
Staging					0.009*
IA-IB	13	17.11	100	30.77	
IIA - IIB	8	10.53	43	13.23	
IIIA	3	3.95	27	8.31	
IIIB	8	10.53	33	10.15	
IIIC	10	13.16	46	14.15	
IV	34	44.74	76	23.38	
Overall survival					< 0.001
(months)	Mean: 24.30	SD: 36.53	Mean: 52.56	DP: 53.43	
	Median: 10		Median: 33		
5-year survival					< 0.001
Less than 5 years	65	85.53	203	62.46	
More than 5 years	11	14.47	122	37.54	
*Fisher's exact test					

**Table 3:** Comparison of patients with cancer of cardia and antrum. Inoperable cases included. Santa Casa of São Paulo Medical School 2021.

Characteristics	Cardia (n = 36)		Antral (n = 253)		p
	n	%	n	%	
Age	Mean: 61.9	SD: 11.2	Mean: 60.9	SD: 12.8	0.662
Sex					0.149
Male	26	72.22	151	59.68	
Female	10	27.78	102	40.32	
Histological Type					0.167
Diffuse	14	38.89	129	51.19	
Intestinal	22	61.11	123	48.81	
Staging					0.972*
IA-IB	13	36.11	100	39.53	
IIA - IIB	8	22.22	43	17	
IIIA	3	8.33	27	10.67	
IIIB	4	11.11	30	11.86	
IIIC	6	16.67	36	14.23	
IV	2	5.56	17	6.72	

Overall survival (months)	Mean: 43.13	DP: 46.0	Mean: 65.77	DP: 53.57	0.016
	Median: 16.5		Median: 55		
5-year survival Less than 5 years	25	69.44	131	51.78	0.047

**Table 4:** Comparison of patients with cancer of the antrum and cardia. Only operable cases included. Santa Casa of São Paulo Medical School 2021.



**Figure 1:** Actuarial survival curve for patients with gastric adenocarcinoma. Santa Casa of São Paulo Medical School 2021.

The median survival for patients with cardia adenocarcinoma was 39 months and for non-cardia adenocarcinoma it was undefined ( $p < 0.0001$ ).

## Discussion

It is known that cardia adenocarcinomas behave differently from non- cardia tumours, however, the literature does not provide a clear consensus, nor a definitive explanation, for the observed phenomena. In Chinese and European studies [2,18,20,24], a higher prevalence of gastric cancer (cardia and non-cardia) was observed in men (62.09%) than in women (37.91%). Steroid hormone concentrations have been questioned and, although we did not perform this investigation, those findings open a large field of studies, both in terms of etiology and prevention. High concentrations of DHEA and estradiol may be related to a lower risk of proximal gastric cancer in men [9]. In this matter, we intend to promote a study of the concentrations of those hormones in patients with cardia cancer and compare them with a control group without cancer. The higher consumption of alcohol by men, in comparison to women, may be a causal factor, since in Japan, alcohol consumption was related to an increased risk of gastric cancer among men, regardless of the anatomical location [8]. Paradoxically, an American cohort analysis found a lower risk of non-cardia cancer among those who drank up to one drink a day, compared to those who did not [7]. Another meta-analysis found a non-linear association between alcohol consumption and the risk of gastric cancer, demonstrating that excessive consumption was strongly related to increased risk [25]. In Brazil, the greater consumption of alcohol among men is quite evident [26], thus, as our sample is mainly made up of male patients, we can deduce

that alcohol is possibly a preponderant factor, although we did not include this specific analysis in our study. We did not notice a significant difference between cardia and antrum cancer regarding age at diagnosis and those findings are similar to an American study 2, however, in a Chinese sample, it was noted that age at diagnosis was significantly higher for cardia than non-cardia cancer 10.

On the other hand, when analyzing our data, there was a statistically significant difference in the distribution of cardia cancer stages, compared to distal ones. Most cardia tumors (44.74%) were stage IV, while most antral tumors (30.77%) were stage I. These findings are similar to those in the literature that report that cardia adenocarcinomas are diagnosed in more advanced stages, when compared to those in non-cardia 10. Such data may help to explain the shortest 5-year survival we have found. When we analyzed only operable cases, the stage distribution was similar. Apparently, in stages II and III, the survival and prognosis of the two types of adenocarcinomas (cardia and antrum) are similar 2,10, therefore, it can be concluded that the worse prognosis of patients with cardia cancer, when compared with antrum cancer, is due in part to the advanced stage at the time of diagnosis and the elevated out-of surgery cases. Interestingly, the resectability at each stage is similar in operated cases, however, we noticed much less resectability in cardia tumors when we looked at advanced cases.

When analyzing the actuarial survival, patients with antrum neoplasms had a significantly longer survival. When pairing the stages, comparing cardia and antrum cancer, we noticed a

significant difference between them, being statistically relevant in stages I, II and IIIA, both in operable and inoperable, and even in inoperable patients in stage IV, also presented a worse prognosis in cardiac cancer. Those findings are similar to an American study that states that, even in early stages, cardia adenocarcinoma is more aggressive 2, has a shorter survival and worse outcome than non-cardia. However, other studies state that when the stages are paired, there is no difference in survival 3. The significant difference in operability caught our attention. The vast majority of antrum cancers (77.85%) were operable, while only 47.37% of cardia cancers were operable. This is a very intriguing finding, since cardia adenocarcinomas are expected to cause early symptoms, which in fact did not occur. The fact that there is a large proportion of men may be an explanation, as men tend to seek medical care much later, not valuing the symptoms and, obviously, the diagnosis being late, the stage tends to be more advanced, with a greater possibility of unresectability.

Another factor that corroborates this hypothesis is that, when we analyze only operable tumors (Table 4), there is no significant difference between the stage of cardia and antral tumors ( $p = 0.972$ ). That is, among operable tumors, regardless of the location, the staging was statistically similar. Thus, it is possible to deduce that staging is an independent prognostic factor involved in the operability criteria. The high percentage of explorative surgeries in EGJ tumors is due: first to the fact that our data refers to many years, beginning in 1997. In addition, Brazil does not have an efficient screening program and the incidence of very advanced cancers is extremely high all over the country. In this particular matter, Santa Casa Medical School, reflects exactly the Brazilian scenario, because receives patients from all over the country. Also, in the last 20 years the incidence of non-operable gastric cancers remains in 30%.

Regarding the histology, there was a predominance of the Lauren diffuse histological type, both in the cardia group and in the antrum group, when the entire sample is considered. This is a curious finding, as in adenocarcinomas of the esophagogastric junction, there is usually a higher prevalence of intestinal-type neoplasms, possibly due to the occurrence of neoplasms originating from Barrett's oesophagus 11,24. When considering only operable cases (Table 4), the cardia adenocarcinomas had a predominance of the intestinal type (61%), but without statistical significance, perhaps because the number of cases in this group is still small. This finding is similar to the literature where is noted that the intestinal type had less aggressive clinicopathological characteristics than the diffuse type 24. In fact, among operable cases, we noted the presence of more cases of the intestinal type. On the other hand, among the inoperable cases, there was a predominance of the diffuse histological type; the findings above confirm the likely greater aggressiveness and, therefore, worse prognosis of diffuse type neoplasms.

Besides all research involving those tumors there are still controversies. Since the introductions of the CROSS trial [27], it seems that the prognosis of EGJ cancers has improved significantly, and a study recently published by the same group confirmed the benefit of this treatment [28]. Also, the introduction of chemotherapy for distal tumors revealed a noticeable improvement in the survival, especially after the introduction of the FLOT [29] (Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel) scheme which showed superiority when compared to the ECF (Epirubicin, Cisplatin, Fluorouracil) scheme (50 x 35%). Unfortunately, in the public service in Brazil and also in our service the FLOT is still not available. We use the FOLFOX (folinic acid, Fluorouracil and Oxaliplatin) or the XELOX (Capecitabine and Oxaliplatin) treatment and intend to present our results in an incoming study.

## Conclusion

When compared to gastric antrum cancer, the cardia adenocarcinoma was more prevalent in males, had higher rates of inoperability and was diagnosed in more advanced stages with lower survival. If only the operable cases are analyzed, the stages were similar, but with a lower survival rate in proximal tumors.

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