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Role of incisura angularis biopsy in gastritis staging and risk assessment of gastric cancer

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HIGHLIGHTS

- Incisura angularis biopsy is significant because it has increased the diagnosis of cases at more advanced stages of intestinal metaplasia and atrophy.
- The prevalence of pre-malignant lesions (gastric atrophy, intestinal metaplasia, and dysplasia) in the gastric mucosa was 33.4%, 34%, and 1.1%, respectively, in the total sample.
- The antrum region exhibited notably higher numbers of pre-malignant alterations.

ABSTRACT – Background – Gastric atrophy (GA) and intestinal metaplasia (IM) are early stages in the development of gastric cancer. Evaluations are based on the Updated Sydney System, which includes a biopsy of the incisura angularis (IA), and the Operative Link on Gastritis Assessment (OLGA) and Operative Link on Gastritis Assessment using Intestinal Metaplasia (OLGIM) gastric cancer risk staging systems. **Objective** – To compare the OLGA and OLGIM classifications with and without IA biopsy. In addition, to determine the prevalence of *Helicobacter pylori* (HP) and pre-neoplastic changes (GA and IM) in different biopsied regions and to identify the exclusive findings of IA. **Methods –** Observational, prospective, descriptive, unicentric study with 350 patients without a diagnosis of gastric cancer, who underwent upper digestive endoscopy with biopsies at *Gastroclínica* Itajaí, from March 2020 to May 2022. The histopathological classification of gastritis followed the Updated Sydney System, and the gastric cancer risk assessment followed the OLGA and OLGIM systems. The methodology applied evaluated the scores of the OLGA and OLGIM systems with and without the assessment of the IA biopsy. Statistical analysis was performed using descriptive measures (frequencies, percentages, mean, standard deviation, 95% confidence interval). Ranks were compared using the Kruskal-Wallis or Wilcoxon tests. To analyze the relationship between the frequencies, the bilateral Fisher's exact test was used. Wilson's score with continuity correction was applied to the confidence interval. **Results –** The median age was 54.7 years, with 52.57% female and 47.43% male patients. The comparison between the used biopsies protocol (corpus + antrum [CA] vs corpus + antrum + incisura angularis [CAI]) and the OLGA and OLGIM stages showed a significant decrease in both staging systems when the biopsy protocol restricted to the corpus and antrum was applied (OLGA CAI vs CA; P=0.008 / OLGIM CAI vs CA; P=0.002). The prevalence of pre-malignant lesions (GA, IM and dysplasia) of the gastric mucosa was (33.4%, 34% and 1.1%, respectively) in the total sample. The antrum region exhibited significantly higher numbers of alteration (P<0.001), except for HP infection, which was present in 24.8% of the patients. **Conclusion –** Incisura angularis biopsy is important because it increased the number of cases diagnosed in more advanced stages of intestinal metaplasia and atrophy. The study had limitations, with the main one being the relatively small sample size, consisting mostly of healthy individuals, although mostly elderly.

Keywords – Gastric cancer, gastric atrophy, intestinal metaplasia, diagnosis, risk factor, *Helicobacter pylori*.

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INTRODUCTION

The development of intestinal-type gastric carcinoma is a multi-step process involving sequential changes of the gastric mucosa, from non-atrophic gastritis to atrophic gastritis, intestinal metaplasia, dysplasia, and finally invasive carcinoma. The process is initiated and promoted by the bacterium *Helicobacter pylori* (HP), which has been classified by the World Health Organization's International Agency for Research on Cancer as a class I carcinogen[1].

Gastric carcinoma is the fifth most common cause of cancer worldwide and has the fourth highest mortality rate, where approximately 1 million people were diagnosed with GC worldwide in 2020, among whom 769.000 died from the disease[2].

Classification of premalignant gastric changes follows specific criteria defined by Dixon et al.[3] in the updated Sydney System, where incisura angularis is considered an area of early onset of atrophic metaplastic transformation in patients with HP gastritis and dyspepsia.

However, the results of recent studies on the value of biopsies of the incisura are contradictory. It has been suggested that routine biopsy of the incisura angularis would provide little additional clinical information[4]. Based on these observations, the MAPS (management of precancerous conditions and lesions in the stomach) guideline of the European Society of Gastrointestinal Endoscopy (ESGE) does not require the inclusion of an incisura biopsy in the minimum workup to assess the severity of gastritis in both its first version[5], and the most recent one published in 2019[6].

In this regard, it is known that the presence of severe gastric atrophy significantly increases the risk – 5.7 times higher - of developing gastric cancer when compared to those patients who were diagnosed as having little or no gastric atrophy[7]. As for intestinal metaplasia, on the other hand, this risk is increased by 10x[8]. Therefore, it is important to predict the risk of malignant transformation when diagnosing these lesions, especially in regions of higher incidence of gastric cancer[9-13].

METHODS

Study population and data collection

This is an observational, prospective, descriptive, unicentric study that was carried out at *Gastroclínica* Itajaí, a referral center in Santa Catarina - Brazil which attends patients from private health system.

The study population was composed of 350 patients with dyspeptic complaints who were seen at the Service and underwent upper digestive endoscopy (UDE) with biopsies, after being oriented and agreeing to participate by signing the informed consent form in the period of March 2020 to May 2022. Histological analysis was performed exclusively in the Infolaudo Pathology Laboratory and always by the same pathologist.

The removal of fragments for biopsies followed the updated Sydney System, with a minimum of five fragments, being at least two biopsies of the antrum, two of the corpus and one of the incisura angularis[3]. In cases where the endoscopic appearance pointed to changes suggestive of more advanced atrophy or intestinal metaplasia, more fragments could be removed at the endoscopist's discretion and stored in the vial corresponding to the biopsied topography.

The samples were stored in three separate vials identified by topography, and later analyzed in the pathology laboratory, where the histopathological report of the biopsies generated a database for statistical analysis.

Inclusion criteria

Dyspeptic patients older than 18 years of age who had upper digestive endoscopy with biopsies showing sufficient material for histopathological analysis, in addition to available or accessible clinical and demographic data.

Exclusion criteria

Patients with diagnosis of gastric cancer, previous gastrectomy, or who have taken proton pump inhibitors in the period of 7 days prior to the endoscopic examination and patients with contraindications to gastric biopsy (for example, uncontrolled coagulation disorder).

Data analysis

The biopsy fragments from each site (corpus, incisura and antrum) were separated into 3 vials (vial 1= antrum, vial 2= corpus, vial 3= incisura angularis) and immediately fixed with 10% formalin. All frag-

ments from each patient were examined by the same pathologist without influence of their clinical history. Histological findings of gastritis, atrophy and intestinal metaplasia (complete and incomplete) were recorded in a table according to the Sydney System score (0= none, 1= discrete, 2= moderate and 3= intense) and of dysplasia according to the type (intestinal) and degree (low and high degree).

Gastric atrophy and intestinal metaplasia were evaluated according to the Operative Link on Gastritis Assessment (OLGA)[14] and Operative Link on Gastritis Assessment using Intestinal Metaplasia (OLGIM)[15] scoring systems and were separated into two results, the first including the incisura angularis in the score (corpus + antrum + incisura = CAI), and the second excluding it (corpus + antrum = CA). When the biopsy of the incisura was considered, it was analyzed together with the two fragments of the antrum for the definition of the percentage of atrophic metaplastic lesions and, consequently, to provide the result of the grade in the OLGA and OLGIM classifications.

Also, in relation to the OLGA and OLGIM staging systems, the patients were classified into grades of risk for malignancy, in this case gastric cancer, being low risk (stages 0, I and II) and high risk (stages III and IV).

The presence of HP was assessed by staining the tissue sample with hematoxylin-eosin and Giemsa and the result was tabulated as positive or negative.

The biopsy reports were imported into Microsoft Excel® and statistical analysis was performed by organizing the data collected from 350 patients. We used information regarding the identification of the patient, such as date of birth, age, gender and the result of the histopathological report of the endoscopic biopsy (gastritis, atrophy, intestinal metaplasia, dysplasia, HP), with and without biopsy of the gastric incisura, also identifying which findings would not have been verified if a biopsy had not been performed in the incisura angularis (findings exclusive to the incisura).

The epidemiological data studied were gender (female and male) and age (age groups 18 to 20 years, 21 to 30 years, 31 to 40 years, 41 to 50 years, 51 to 60 years, 61 to 70 years, 71 to 80 years, and 81 years or older).

For the correlation of HP infection with OLGA/OLGIM staging the patients were classified as positive or negative for infection and grade 0, I, II, III and IV on OLGA/OLGIM protocols.

Statistical analysis

Statistical analysis was performed using descriptive measures (frequencies, percentages, mean, standard deviation, 95% confidence interval). Comparison between ranks was made by the Kruskal-Wallis or Wilcoxon test. To analyze the relationship between frequencies, the two-sided Fisher's exact test was used. The Wilson score with continuity correction was applied to the confidence interval[16]. All results were considered significant at $P<0.05$. The software used for the analyses was ActionStat, Version 3.6.

Ethical considerations

The research protocol was approved by the Research Ethics Committee of the *Universidade do Vale do Itajaí* (UNIVALI), under registration number 73623517.5.0000.0120 and the data were collected after the issue of the Substantiated Opinion, approved by Statement no. 3.917.060.

The patients were approached during medical consultation, at which time they were explained and given the Informed Consent Form – ICF for participation in the study. It was explained that, due to his previous symptomatic health condition, he would already be indicated for an upper digestive endoscopy with biopsies regardless of his participation in this study. It was explained that his contribution to the research includes providing data regarding the anatomopathological examination report and demographic data.

Risks included disclosure of confidential data and unauthorized use of the sample for further research. Confidentiality and privacy were ensured by coding the data.

RESULTS

Data were collected from 351 patients; after applying the inclusion criteria, one patient was excluded from the sample because he was under 18 years of age.

The gender distribution of the sample was as follows: 184 female and 166 male patients. The median age was 54.75 years (18–84 years). The distribution by age group was mostly (177/350–50.57%) older patients (>60 years), as shown in TABLE 1.

TABLE 1. Sample distribution by gender and age group.

Gender	N (%)
Female	184 (52.57)
Male	166 (47.43)
Age Group	**N (%)**
18 – 20 years	5 (1.43)
21 – 30 years	19 (5.43)
31 – 40 years	36 (10.23)
41 – 50 years	42 (12)
51 – 60 years	71 (20.28)
61 – 70 years	110 (31.43)
71 – 80 years	57 (16.30)
81 years or older	10 (2.90)

Regarding OLGA/OLGIM stages when performing or not biopsy of the incisura angularis 230 OLGA stage 0 patients were found biopsying corpus + antrum (CA) and when adding the analysis of incisura biopsy (CAI) 223 remained in stage 0 (93.9 to 98.5%), six patients progressed to stage I (1.2 to 5.6%) and one patient progressed to stage II (0.08 to 2.5%). In stage I, 48 patients were found with CA biopsies only, of which 46 remained in stage I (86 to 98.8%), one patient progressed to stage II (0.4 to 10.9%), and one patient progressed to stage III (0.4 to 10.9%) when Incisura biopsy (CAI) analysis was added. Stage II was found in 48 patients when only CA biopsies were analyzed, and when Incisura biopsy analysis was added, 47 patients remained in stage II (89.1 to 99.6%) and one patient progressed to stage III (0.4 to 10.9%). In the 14 stage III patients who had only corpus and antrum biopsies when Incisura biopsy analysis was added, 12 patients remained in stage III (60.1 to 95.9%) and two patients progressed to stage IV (4.1 to 39.9%). And in the 10 patients with stage IV when only corpus and antrum biopsies were performed, no stage change was noted when incisura biopsy analysis was added (TABLE 2).

As for the 225 OLGIM stage 0 patients with corpus and antrum biopsies only (CA), when the analysis of incisura biopsy (CAI) was added, 217 patients remained in stage 0 (93.9 to 98.5%), five patients changed to stage I (0.9 to 5.1%), and three patients changed to stage II (0.5 to 3.8%). Of the 41 stage I patients with CA biopsies, 39 remained stage I (83.8 to 98.6%), one patient progressed to stage II (0.4 to 12.6%), and one patient progressed to stage III (0.4 to 12.6%) when adding the analysis of incisura biopsy (CAI). Of the 57 stage II patients when incisura biopsy analysis was added, 55 patients remained in stage II (88.1 to 99%) and two patients progressed to stage III (1 to 11.9%). In the 18 stage III patients when incisura biopsy analysis was added, 17 patients remained in stage III (74.2 to 99%) and one patient progressed to stage IV (1 to 25.7%). And in the 9 stage IV patients when incisura biopsy analysis was added, there was no change in stage (TABLE 3).

When comparing the CA and CAI biopsy protocols in terms of OLGA and OLGIM stages in the entire study population, we observed a significant decrease in the number of patients in the most advanced stages when using the biopsy protocol limited to the corpus and antrum, both in the OLGA (P=0.008) and OLGIM (P=0.002) systems (TABLE 4).

However, the number of patients diagnosed in the highest risk stages (III and IV) did not change significantly according to the biopsy protocol used, either in the evaluation of atrophy (OLGA) or in the evaluation of intestinal metaplasia (OLGIM) (OLGA CA vs CAI, 24 vs 26, respectively, P=0.783; OLGIM CA vs CAI, 27 vs 29, respectively, P=0.999). No significant difference was also found in the lower risk stages (0, I and II) (OLGA CA vs CAI, 326 vs 324, P=0.794; OLGIM CA vs CAI, 323 vs 321, P=0.858) (TABLE 5).

Regarding the OLGA and OLGIM classifications, we analyzed which would have a better ability to predict more advanced histopathologic changes (atrophy and metaplasia). Thus, when comparing the two systems with the standard biopsy protocol, we also found no significant difference between the moderate to severe stages (II, III and IV) of OLGA vs OLGIM when using the CAI biopsy protocol (OLGA vs OLGIM, 73 vs 89, P=0.630) (TABLE 6).

Of the 350 patients studied, 87 (24.85%) had one or more biopsies (corpus, antrum or incisura) positive for HP infection. When correlating HP infection with OLGA / OLGIM staging, stage 0 showed the

TABLE 2. Percentage OLGA Stage change with addition of incisura biopsy analysis.

OLGA CAI	OLGA CA									
	0		I		II		III		IV	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
	CI (95%)		CI (95%)		CI (95%)		CI (95%)		CI (95%)	
0	223	(97.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	CI (93.9–98.5)									
I	6	(2.6)	46	(95.8)	0	(0.0)	0	(0.0)	0	(0.0)
	CI (1.2–5.6)		CI (86.0–98.8)							
II	1	(0.4)	1	(2.1)	47	(97.9)	0	(0.0)	0	(0.0)
	CI (0.08–2.5)		CI (0.4–10.9)		CI (89.1–99.6)					
III	0	(0.0)	1	(2.1)	1	(2.1)	12	(85.7)	0	(0.0)
			CI (0.4–10.9)		CI (0.4–10.9)		CI (60.1–95.9)			
IV	0	(0.0)	0	(0.0)	0	(0.0)	2	(14.3)	10	(100.0)
							CI (4.1–39.9)			

OLGA: Operative Link on Gastritis Assessment. CI (95) - confidence interval, Wilson score with continuity correction. (CA) corpus + antrum; (CAI) corpus + antrum + incisura.

TABLE 3. OLGIM Stage change percentage with addition of the incisura biopsy analysis.

OLGIM CAI	OLGIM CA									
	0		I		II		III		IV	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
	CI (95%)		CI (95%)		CI (95%)		CI (95%)		CI (95%)	
0	217	(96.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	CI (93.1–98.2)									
I	5	(2.2)	39	(95.1)	0	(0.0)	0	(0.0)	0	(0.0)
	CI (0.9–5.1)		CI (83.8–98.6)							
II	3	(1.3)	1	(2.4)	55	(96.5)	0	(0.0)	0	(0.0)
	CI (0.5–3.8)		CI (0.4–12.6)		CI (88.1–99.0)					
III	0	(0.0)	1	(2.4)	2	(3.5)	17	(94.4)	0	(0.0)
			CI (0.4–12.6)		CI (1.0–11.9)		CI (74.2–99.0)			
IV	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.6)	9	(100.0)
							CI (1.0–25.7)			

OLGIM: Operative Link on Gastritis Assessment using Intestinal Metaplasia. CI (95) - confidence interval, Wilson score with continuity correction. (CA) corpus + antrum; (CAI) corpus + antrum + incisura.

TABLE 4. OLGA and OLGIM stages with and without biopsy of the incisura (n=350).

SYSTEM	Scores	BIOPSY PROTOCOL				WILCOXON
		CAI		CA		
		n	(%)	n	(%)	*P*
OLGA	0	223	(63.7)	230	(65.7)	0.008
	1	54	(15.4)	48	(13.7)	
	2	47	(13.4)	48	(13.7)	
	3	14	(4.0)	14	(4.0)	
	4	12	(3.4)	10	(2.9)	
OLGIM	0	217	(62.0)	225	(64.3)	0.002
	1	44	(12.6)	41	(11.7)	
	2	60	(17.1)	57	(16.3)	
	3	19	(5.4)	18	(5.1)	
	4	10	(2.9)	9	(2.6)	

OLGA: Operative Link on Gastritis Assessment; OLGIM: Operative Link on Gastritis Assessment using Intestinal Metaplasia. (CA) corpus + antrum; (CAI) corpus + antrum + incisura.

TABLE 5. Distribution of patients in OLGA and OLGIM Stages with and without incisura biopsy x group by stage.

Stages	OLGA			OLGIM		
	CA	CAI	P*	CA	CAI	P*
0+I+II	326	324	0.794	323	321	0.858
II+III+IV	72	73	0.941	84	89	0.994
III+IV	24	26	0.783	27	29	0.999

OLGA: Operative Link on Gastritis Assessment; OLGIM: Operative Link on Gastritis Assessment using Intestinal Metaplasia. *Fisher's exact test Two-sided, (CA) corpus + antrum; (CAI) corpus + antrum + incisura.

TABLE 6. Distribution of patients in the OLGA and OLGIM stages using the standard CAI protocol and grouping by stage.

Stages	CAI		P*
	OLGA	OLGIM	
0+I+II	324	321	0.264
II+III+IV	73	89	0.630
III+IV	26	29	0.419

OLGA: Operative Link on Gastritis Assessment; OLGIM: Operative Link on Gastritis Assessment using Intestinal Metaplasia. *Fisher's exact test two-sided, (CA) corpus + antrum; (CAI) corpus + antrum + incisura.

highest number of infected patients. Of the 263 patients without bacterial infection, most were also in OLGA / OLGIM stage 0 (TABLE 7).

When categorizing by age group, it was found that patients in stages III and IV of OLGA/OLGIM were over 50 years old.

The prevalence of histological findings (gastric atrophy, intestinal metaplasia, dysplasia and HP colonization) identified by gastric region (corpus, antrum and incisura) is shown in TABLE 8. When the grades of atrophy (P=0.2659) and intestinal metaplasia (P=0.9529) were stratified by biopsy region, no significant difference was found between biopsy sites.

TABLE 7. Distribution of the presence of *Helicobacter pylori* infection according to OLGA / OLGIM staging.

	STAGE				
	0	I	II	III	IV
Helicobacter pylori negative					
OLGA CA	168	39	43	8	5
OLGA CAI	164	41	43	9	6
OLGIM CA	164	34	46	13	6
OLGIM CAI	159	35	49	13	7
Helicobacter pylori positive					
OLGA CA	59	9	5	6	5
OLGA CAI	59	13	4	5	6
OLGIM CA	58	7	11	5	3
OLGIM CAI	58	9	11	6	3

OLGA: Operative Link on Gastritis Assessment; OLGIM: Operative Link on Gastritis Assessment using Intestinal Metaplasia. (CA) corpus + antrum; (CAI) corpus + antrum + incisura.

TABLE 8. Distribution of histopathologic findings by biopsy region.

	ANTRUM	INCISURA	CORPUS
Helicobacter pylori			
Negative	274	281	283
Positive	76	69	67
Gastritis			
Absent	21	58	79
Chronic grade 1	227	198	188
Chronic grade 2	85	79	64
Chronic grade 3	7	6	8
Discrete reaction changes	4	7	3
Unspecific reaction changes	3	1	4
Discrete dilatation of fundic glands	0	0	1
Discrete edema	3	1	3
Intestinal metaplasia+			
Absent	239	283	299
Positive complete	89	54	40
Positive incomplete	22	13	11
Atrophy *			
Absent	240	276	296
Present, mild	46	33	16
Present, moderate	55	32	29
Present, intense	9	9	9
Dysplasia			
Absent	348	348	349
Positive low intestinal grade	2	2	1
Positive high intestinal grade	0	0	0

+Fisher's exact test two-sided (P=0.9529); *Fisher's exact test two-sided (P=0.2659).

When comparing the distribution of findings (HP, gastritis, intestinal metaplasia and atrophy) of any degree in the three biopsy sites (corpus, antrum and incisura), the antrum region was the site that showed significantly more changes, except for positivity for HP infection (TABLE 9).

The exclusive findings of the incisura biopsy were seven cases of atrophy, which were only mild to moderate changes. Regarding intestinal metaplasia, seven cases of complete metaplasia and one case of incomplete metaplasia would have been missed. Regarding dysplasia, the diagnosis of low-grade dysplasia would have been missed in two patients.

Furthermore, when comparing the scores of atro-

TABLE 9. Distribution of findings by biopsy region.

Parameters	Antrum (A)		Incisura (I)		Corpus (C)		Fisher's exact test - *P*		
	n	(%)	n	(%)	n	(%)	A x I	A x C	I x C
Helicobacter pylori									
Negative	274	(78.3)	281	(80.3)	283	(80.9)	0.576	0.453	0.924
Positive	76	(21.7)	69	(19.7)	67	(19.1)			
Gastritis									
Absent	21	(6.0)	58	(16.6)	79	(22.6)	0.000	0.000	0.056
Present	329	(94.0)	292	(83.4)	271	(77.4)			
Intestinal metaplasia									
Absent	239	(68.3)	283	(80.9)	299	(85.4)	0.000	0.000	0.129
Present	111	(31.7)	67	(19.1)	51	(14.6)			
Atrophy									
Absent	240	(68.6)	276	(78.9)	296	(84.6)	0.003	0.000	0.063
Present	110	(31.4)	74	(21.1)	54	(15.4)			

(A) antrum; (I) Incisura; (C) Corpus.

phy and intestinal metaplasia in the antrum and incisura, in 10 and 11 cases, respectively, the findings of atrophy and intestinal metaplasia were exclusive of the incisura (excluding corpus evaluation). On the other hand, 52 (15%) cases of atrophy and 56 (16%) cases of intestinal metaplasia were more intense in the antrum than in the incisura. The discrepancies of gastric atrophy and intestinal metaplasia scores between antrum and incisura are shown in FIGURE 1.

DISCUSSION

The classification of premalignant gastric changes follows specific criteria defined by Dixon et al.[3] in the updated Sydney system. In this system, chronic gastritis can be categorized as either atrophic and non-atrophic, based on the histological assessment of five mucosal fragments (two in the antrum and two in the corpus, located in both major and minor curvatures, along with one from the incisura) obtained during an upper gastrointestinal endoscopy.

In the same study, it was defined that the highest degree of atrophy and intestinal metaplasia is consistently observed in the region of the incisura, which is also the most likely site to reveal dysplasia[3]. However, our study demonstrates that the inclusion of the incisura biopsy analysis does not change the classification system, as the histologic changes of chronic gastritis (P<0.001), atrophy (P<0.001) and intestinal metaplasia (P<0.001) were significantly more common in the gas-

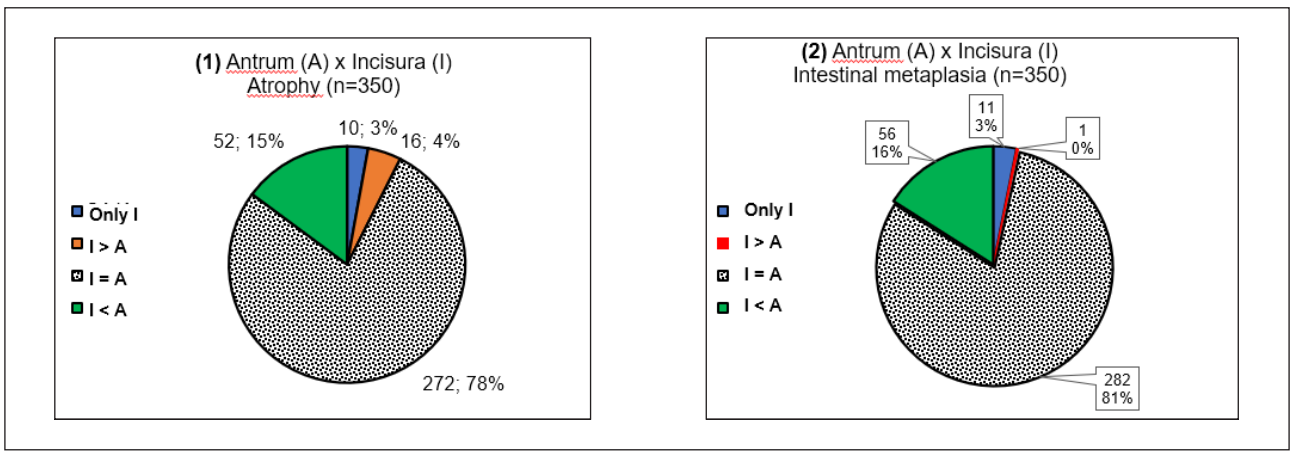

FIGURE 1. Distribution of discrepancy of cases of gastric atrophy (1) and intestinal metaplasia (2) in the antrum compared to incisura (n=350).

tric antrum. Furthermore, when the degree of atrophy (P=0.2659) and intestinal metaplasia (P=0.9529) was stratified by biopsy region, no significant difference was observed between biopsy sites.

On the other hand, in a recent study by Zhang et al.[17], the degree of atrophy and intestinal metaplasia was evaluated individually in five biopsy sites (incisura and major and minor curvatures of the corpus and antrum) in dyspeptic patients without cancer diagnosis, where grade 1 of atrophy and intestinal metaplasia was most identified in the minor curvature of the antrum, and grades 2 and 3 were most identified in the incisura. Identical results were observed in another study that considered only three biopsy sites (antrum, corpus and incisura), where the most severe changes (score 3) of atrophy (P<0.05) and intestinal metaplasia (P<0.01) were more frequently observed in the mucosa of the incisura than in the antrum and corpus[4]. In contrast, in the study by Varbanova et al.[18], which used a similar methodology to the present study, the absolute number of patients with any degree of preneoplastic status did not vary significantly among the three biopsy sites, as did our results.

Now, when only patients with a previous diagnosis of preneoplastic lesions or adenocarcinoma were evaluated, only the moderate and severe grades of intestinal metaplasia showed a higher proportion in the incisura than in the antrum (P=0.04)[19]. Thus, it is understood that the earlier the gastric preneoplastic process, the more likely it is that these changes of atrophy and intestinal metaplasia will be identified exclusively in the incisura or in a more advanced stage in this site, since it is the primary site of these changes. In more advanced stages of preneoplastic or neoplastic evolution, atrophy and intestinal metaplasia can easily be found in the other biopsy sites. We believe that for this reason we found a significant decrease in the mean of the OLGA (CAI 0.68±1.07 vs CA 0.65±1.04; P=0.008) and OLGIM (CAI 0.75±1.09 vs CA 0.70±1.07; P=0.002) stages when the biopsy protocol limited to the corpus and antrum was applied, with stage 0 presenting the greatest evolutionary change in classification when the evaluation of the incisura biopsy was added to both the OLGA and OLGIM systems.

The findings that would have been missed without incisura biopsy are consistent with the study published by Eriksson et al.[20] in which 5.9% of patients with intestinal metaplasia (versus 2.28% in this study), 1.3% with gastric atrophy (versus 2.0% in this study), and 0.4% with HP infection (versus 0.85% in this study) were found exclusively in the incisura.

The first European guideline (MAPS) suggested that routine biopsy of the incisura provided little additional clinical information in cases of apparent normality on macroscopic examination. At that early time, it was recommended that biopsies should be taken from at least two topographical sites (antrum and corpus, at the major and minor curvatures, respectively) and clearly labeled in two separate vials, and that additional biopsies of suspicious lesions should be taken in separate vials[5].

However, in the most recent update of this guideline in 2019 (MAPS II), strategies for gastric cancer risk stratification were strongly encouraged, with the OLGA and OLGIM staging systems being the main risk assessment tools, and both including the assessment of the incisura, which is scored together with the antrum. Therefore, it is now recommended to perform incisura biopsy only when considering gastric cancer risk staging, following the modified Sydney protocol used in the OLGA and OLGIM staging systems[6]. The same recommendations are applied in the Kyoto Global Consensus on HP gastritis, published in 2015, and in the most recent American Gastroenterological Association guideline, published in 2021[21,22].

In this context, the OLGA system downgraded the staging in 12 patients (3.42%) and the OLGIM system in 13 patients (3.74%) in our study by excluding the incisura biopsy. In contrast, in the study by Isajevs et al.[23], the OLGA and OLGIM systems were downgraded in 18% and 4% of patients, respectively, when evaluated without incisura biopsy. Furthermore, 35% and 30% of patients were downgraded from high-risk (III and IV) to low-risk (0, I and II) OLGA and OLGIM stages, respectively, when evaluated using a protocol without incisura biopsy. In our study, the number of patients diagnosed in high-risk stages had no significant change according to the biopsy protocol applied in both OLGA and OLGIM systems, where only two patients (0.57%) would have their staging changed in both classification systems, reflecting that this is a low-risk population for gastric cancer, despite being in a moderate-risk region.

In the publication by Varbanova et al.[18], the absolute number of patients diagnosed as high risk by the OLGA and OLGIM systems did not change significantly depending on the biopsy protocol applied (OLGA: CAI vs CA, 15 vs 13; OLGIM: CAI vs CA, 7 vs 4). In the same study, the standard OLGA protocol generated significantly more moderate to advanced stages than the OLGIM protocol, with 34 patients in the OLGA protocol and 17 patients in the OLGIM protocol. In contrast, our study showed no difference between the number of patients in high-risk stages in both protocols (OLGA: 26/350–7.42%; OLGIM: 29/350–8.28%) when compared to the number of patients in low-risk stages. On the other hand, when comparing our data with high-risk areas for gastric cancer, we found similar results as in the Iranian study by Mansour-Ghanaei et al.[24], which evaluated 345 patients, where 4.3% and 4% of patients had high-risk OLGA and OLGIM stages, respectively.

Quach et al.[25] evaluated the association between endoscopic findings suggestive of gastric atrophy and extensive intestinal metaplasia with histopathologic analysis of OLGA and OLGIM stages III and IV in 280 patients with functional dyspepsia. They found that OLGA and OLGIM stages III and IV were more likely to be classified in patients with moderate to severe endoscopic gastric atrophy, thus concluding that endoscopic assessment of the severity of gastric atrophy can help monitor and prevent gastric cancer. However, there is much controversy between these two staging methods, and this difference is mainly due to the greater diagnostic efficacy of OLGA in the early stages of atrophic gastritis, which cannot be detected by OLGIM[24]. This translates in clinical practice to the inclusion of incisura biopsy in patients with endoscopic findings of mild atrophy or with normal endoscopy, and this behavior is supported by the results found by de Vries et al.[26], where when considering the sites of affected non-targeted gastric biopsies, the highest overall prevalence of premalignant diagnoses was present in non-targeted incisura biopsies 86/221 (39%).

In our study, premalignant lesions (atrophy and intestinal metaplasia) of the gastric mucosa had a lower prevalence (117/350, 33.42% and 119/350, 34%, respectively) compared to the Chinese study (156/368, 42.39% and 161/368, 43.75%)[17]; and a similar prevalence compared to the German study (atrophy + intestinal metaplasia; 79/213, 37%)[18]. However, in a recent systematic review of the prevalence of advanced gastric premalignant lesions in countries with a low/moderate incidence of gastric cancer (such as Brazil), the incidence of atrophic gastritis was estimated to be 7.3% (95%CI: 5.6–9.05) and of intestinal metaplasia 7.7% (95%CI: 3.2–12.1)[27]. Therefore, our data are higher than the estimate for low/medium risk countries and compared to high-risk areas for gastric cancer, such as China, our data are lower. We should consider the large size of the national territory, in addition to the critical role of environmental factors in gastric carcinogenesis, where, in this sense, our results coincide with the data published by INCA in 2020, in which the spatial distribution of GC in Brazil showed higher rates in the north and south regions[28,29].

Regarding chronic gastritis, 322/350 (92%) of the patients had some degree of gastritis (between atrophic and non-atrophic) in one of the biopsy sites, and this result was higher than in the German study (62.4%) and similar to the Chinese study (100%)[17,18].

HP infection was present in 87/350 (24.85%) patients, with no significant difference (P=0.6733) between biopsy sites (TABLE 9). In comparison with the study conducted in Lithuania by Isajevs et al.[4], no difference was also found in the prevalence of HP infection between different biopsy sites (antrum 56.36%, incisura 55.53%, corpus 57.79%), but the overall prevalence of HP infection was higher (56.56%). We suspect that the reason for our lower rate of HP infection is related to the fact that the study was conducted in a private clinic that serves patients with higher socioeconomic status and better sanitation, and that we did not exclude patients who had already eradicated the bacteria at another time[30]. When the relationship between HP infection and OLGA and OLGIM stages was evaluated, no significant associations between low and high-risk stages with HP infection status were observed, as in the study conducted in Iran (HP vs OLGA P=0.300; HP vs OLGIM P=0.500)[24]. However, in the same study, when positive HP infection was correlated with age group and high-risk stages (III and IV) of OLGA and OLGIM protocols, no patient was younger than 40 years, which is in line with our results where all high-risk patients were older than 50 years, confirming

what has been described in previous studies, where older age is an independent risk factor for patients with chronic atrophic gastritis and gastric cancer, justifying early surveillance of GC for individuals aged 40 years and older, as already introduced in China, Japan and South Korea[24,31].

Our research has limitations because the majority of patients in the study population lacked pre-neoplastic changes and were therefore considered a low--risk population. This study focused on subjects of a private clinic in Southern Brazil (a region with a relatively higher incidence of gastric cancer), where there is a higher socioeconomic status and a lower prevalence of HP (crucial for gastric carcinogenesis)[32].

One of the major difficulties in conducting this study was the period of the COVID-19 pandemic, during which we did not perform endoscopic examinations in dyspeptic patients without alarm signs for almost a year (we only performed examinations for consumptive syndrome and endoscopic urgencies and emergencies), thus limiting our sample.

A direct implication for clinical practice is the need to include non-targeted biopsies of incisura in patients with apparently normal endoscopy in order to optimize histopathologic evaluation of early-stage premalignant gastric conditions[33]. We acknowledge the importance of cost reduction strategies. Nonetheless, we can attain this objective by utilizing the validated biopsy protocol of the Updated Sydney System, which incorporates incisura biopsy as a standard assessment. Therefore, our study does not support the conclusion that reducing the number of biopsies is safe. It is important to emphasize that adequate preparation of the upper digestive tract and a careful inspection of the gastric mucosa are crucial for the early detection of premalignant changes.

In the future, we believe in the development of high-definition endoscopy and artificial intelligence, which will eliminate the need for non-targeted biopsies to identify individuals at high risk of developing gastric cancer. Today, convolutional neural network models proposed by Yang et al.[34] are closely related to the OLGA/OLGIM histologic staging systems in risk assessment of gastric precancerous lesions and are therefore promising tools to identify populations at high risk of developing gastric cancer without using biopsies.

CONCLUSION

In the process of gastric neoplasm screening, biopsying the incisura is important. When we compared the biopsy protocols of corpus and antrum (CA) versus including incisura (CAI) with the OLGA and OLGIM stages, we found a significant decrease in the number of cases in more advanced stages when the biopsy protocol limited to the corpus and antrum was used. However, the results exclusively found in the incisura did not show significance. The antrum emerged as the biopsy site with the highest number of premalignant changes (atrophy, intestinal metaplasia and dysplasia).

The study had limitations, the most noteworthy of which was the relatively small sample of patients with pre-neoplastic changes and infected with HP, despite being mostly elderly.

Therefore, the main clinical implication of our results is to perform non-targeted biopsies of the incisura in patients with apparently normal endoscopy. This approach is important as incisura biopsy contributed significantly to optimizing the staging of early--stage premalignant gastric conditions.

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Authors' contribution

Ferrari F and Mello CAL: conceptualization, data curation, formal analysis, investigation, methodology, project management, resources, software, supervision, validation, writing (original draft), and writing (proofreading and editing). Ogata DC: conceptualization, investigation, methodology, validation.

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Ferrari F, Ogata DC, Mello CAL. Papel da biópsia da incisura angular no estadiamento da gastrite e na avaliação de risco do câncer gástrico. Arq gastroenterol. 2023;60(4):478-89.

RESUMO – Contexto – A atrofia gástrica (AG) e a metaplasia intestinal (MI) são estágios iniciais do desenvolvimento do câncer gástrico. As avaliações são baseadas no Sistema de Sydney Atualizado, que inclui uma biópsia da incisura angular (IA), e nos sistemas de estadiamento de risco de câncer gástrico *Operative Link on Gastritis Assessment* (OLGA) e *Operative Link on Gastritis Assessment using Intestinal Metaplasia* (OLGIM). **Objetivo –** Comparar as classificações OLGA e OLGIM com e sem biópsia da IA. Além disso, determinar a prevalência de *Helicobacter pylori* (HP) e alterações pré-neoplásicas (AG e MI) em diferentes regiões biopsiadas e identificar os achados exclusivos da IA. **Métodos –** Estudo observacional, prospectivo, descritivo, unicêntrico, com 350 pacientes sem diagnóstico de câncer gástrico, submetidos à endoscopia digestiva alta com biópsias na Gastroclínica Itajaí, no período de março de 2020 a maio de 2022. A classificação histopatológica da gastrite seguiu o Sistema de Sydney Atualizado, e a avaliação do risco de câncer gástrico seguiu os sistemas OLGA e OLGIM. A metodologia aplicada avaliou os escores dos sistemas OLGA e OLGIM com e sem a avaliação da biópsia da IA. A análise estatística foi realizada por meio de medidas descritivas (frequências, porcentagens, média, desvio padrão, intervalo de confiança de 95%). As classificações foram comparadas usando os testes de Kruskal-Wallis ou Wilcoxon. Para analisar a relação entre as frequências, foi usado o teste exato de Fisher bilateral. O escore de Wilson com correção de continuidade foi aplicado ao intervalo de confiança. **Resultados –** A idade média foi de 54.7 anos, com 52.57% de pacientes do sexo feminino e 47.43% do sexo masculino. A comparação entre o protocolo de biópsias utilizado (corpo + antro [CA] vs corpo + antro + incisura angular [CAI]) e os estágios OLGA e OLGIM mostrou uma diminuição significativa em ambos os sistemas de estadiamento quando o protocolo de biópsia restrito ao corpo e ao antro foi aplicado (OLGA CAI vs CA; P=0.008 / OLGIM CAI vs CA; P=0.002). A prevalência de lesões pré-malignas (GA, MI e displasia) da mucosa gástrica foi de (33.4%, 34% e 1.1%, respectivamente) na amostra total. A região do antro exibiu um número significativamente maior de alterações (P<0.001), com exceção da infecção por HP, que estava presente em 24.8% dos pacientes. **Conclusão –** A biópsia de IA é importante porque aumentou o número de casos diagnosticados em estágios mais avançados de MI e AG. O estudo teve limitações, sendo a principal delas o tamanho relativamente pequeno da amostra, composta principalmente por indivíduos saudáveis, embora em sua maioria idosos.

Palavras-chave – Câncer gástrico, atrofia gástrica, metaplasia intestinal, diagnóstico, fator de risco, *Helicobacter pylori*.

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