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Anatomopathological Agreement Between Pre- and Post- Endoscopic Submucosal Dissection in Early Gastric Cancer – an Observational Retrospective Study

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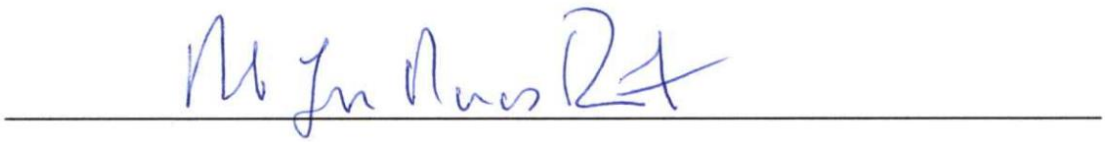

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DEDICATION

Aos meus pais, Marta e Sérgio, que sempre me apoiaram e ensinaram a dar o melhor de mim em cada coisa.

Ao meu namorado, Pedro.

À minha família e amigos.

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Ao meu Pedro, por estar sempre ao meu lado e me apoiar incondicionalmente.

“A força do querer não tem limites conhecidos. Não é previsível o que se consegue quando se quer atingir as coisas. O querer leva-nos até onde ninguém sabe, nem o próprio.”

Nuno Grande

RESUMO

Enquadramento

A disseção endoscópica da submucosa (ESD) é um procedimento endoscópico minimamente invasivo, que permite a exérese de lesões gástricas pré-malignas e malignas precoces, sendo o método recomendado pela Sociedade Europeia de Endoscopia Gastrointestinal (ESGE) para o tratamento do cancro gástrico precoce. A ESD tem excelentes resultados curativos, estando associada a menor morbilidade e mortalidade em comparação com outras alternativas terapêuticas, nomeadamente a cirurgia. Contudo, têm sido publicados estudos que demonstram diferenças entre os resultados anatomopatológicos da biópsia realizada previamente à ESD e a peça removida por ESD.

Objetivo

O objetivo deste estudo é comparar os resultados anatomopatológicos da biópsia com a peça de ESD e determinar a discordância, assim como identificar os fatores que para ela contribuem.

Metodologia

Este estudo incluiu 319 lesões submetidas a ESD entre 1 de janeiro de 2016 e 31 de outubro de 2023.

Foram analisadas várias características da população e das lesões submetidas a ESD (características endoscópicas e anatomopatológicas), assim como características associadas aos procedimentos. Os casos foram agrupados de acordo com a concordância e discordância entre os resultados anatomopatológicos pré- e pós-ESD e foram utilizadas análises univariada e multivariada para avaliar o efeito de cada variável no impacto sobre o risco de discrepância.

Resultados

Este estudo demonstrou que a discrepância pré e pós-ESD é de 42.6%, sendo que houve upgrading em 39.8% dos casos e downgrading em 2.8% dos casos. Verificou-se que 57.5% dos casos classificados como displasia de alto grau na biópsia pré-ESD sofreram upgrading, tendo sido classificados como adenocarcinomas após a ESD. A análise univariada mostrou que a comorbilidade de doença renal crónica, localização no terço superior do estômago, tamanho da lesão >20 mm, tamanho da lesão >30 mm, padrão morfológico de superfície misto elevado, presença de ulceração, análise patológica realizada pelo patologista A e duração da ESD superior a uma hora foram fatores de risco para discrepância. A análise multivariada identificou que o tamanho maior que 20 mm (OR=2.1, 95% CI 1.1-3.9, p=0.021), o padrão morfológico de superfície misto elevado (OR=1.8, 95% CI 1.1-3.2, p=0.031) e a presença de ulceração (OR=3.7, 95% CI 1.8-7.7, p=0.001) são fatores de risco para discrepância.

Conclusão

Este estudo identificou como fatores de risco para discrepância, as lesões de tamanho grande, nomeadamente, superiores a 20 mm, com ulceração, localizadas no terço superior do estômago, em conformidade com o publicado na literatura. O padrão morfológico de superfície de tipo misto elevado também foi identificado como um fator de risco para discrepância, contudo, este foi um achado diferente do previamente descrito na literatura. Como tal e, tendo em conta a discrepância e possibilidade de upgrade histológico nestes doentes, os mesmos poderão ser alocados prioritariamente para realização de ESD.

Palavras-Chave

Biópsia; Discrepância; Cancro gástrico precoce; Disseção endoscópica da submucosa; Anatomopatológico.

ABSTRACT

Background

Endoscopic submucosal dissection (ESD) is a minimally invasive endoscopic procedure that allows for the excision of early pre-malignant and early malignant gastric lesions. It is the recommended method by the European Society of Gastrointestinal Endoscopy (ESGE) for the treatment of early gastric cancer. ESD has excellent healing outcomes, being associated with lower morbidity and mortality compared to other therapeutic alternatives, namely surgery. However, studies have been published demonstrating differences between the histopathological results of the biopsy performed prior to ESD and the specimen removed by ESD.

Objectives

The objective of this study is to compare the histopathological results of biopsy with the specimen from ESD and determine the discrepancy, as well as to identify the factors contributing to this.

Methods

This study included 319 lesions undergoing ESD between January 1, 2016, and October 31, 2023. Various characteristics of the population and lesions undergoing ESD (endoscopic and histopathological characteristics) were analysed, as well as characteristics associated with the procedures. Cases were grouped according to the concordance and discrepancy between pre- and post-ESD histopathological results, and univariable and multivariable analyses were used to assess the effect of each variable on the risk of discrepancy.

Results

This study demonstrated that the pre- and post-ESD discrepancy is 42.6%, considering that there was upgrading in 39.8% of cases and downgrading in 2.8% of cases. It was found that 57.5% of cases classified as high-grade dysplasia in the pre-ESD biopsy underwent upgrading, being classified as adenocarcinomas after ESD. Univariable analysis showed that chronic kidney disease comorbidity, location in the upper third of the stomach, lesion size >20 mm, lesion size >30 mm, mixed elevated morphological surface pattern, presence of ulceration, pathological analysis conducted by pathologist A, and ESD duration exceeding one hour were risk factors for discrepancy. Multivariable analysis identified that size larger than 20 mm (OR=2.1, 95% CI 1.1-3.9, p=0.021), mixed elevated morphological surface pattern (OR=1.8, 95% CI 1.1-3.2, p=0.031), and the presence of ulceration (OR=3.7, 95% CI 1.8-7.7, p=0.001) are risk factors for discrepancy.

Conclusions

This study identified large-sized lesions, specifically those larger than 20 mm, with ulceration, located in the upper third of the stomach, as risk factors for discrepancy, consistent with what has been published in the literature. The morphological pattern of mixed elevated type was also identified as a risk factor for discrepancy, however, this was a different finding from what was previously described in the literature. As such, considering the discrepancy and possibility of histological upgrade in these patients, they may be allocated priority for ESD procedures.

Keywords

Biopsy; Discrepancy; Early gastric cancer; Endoscopic submucosal dissection; Pathology.

LIST OF ABBREVIATIONS

ADC – Adenocarcinoma
AUC – Area under the curve
CI – Confidence intervals
EGC – Early gastric cancer
EMR – Endoscopic mucosal resection
ESD – Endoscopic submucosal dissection
ESGE – European Society of Gastrointestinal Endoscopy
GI – Gastrointestinal
HGD – High-grade dysplasia
Hp – *Helicobacter pylori*
ICBAS – Instituto de Ciências Biomédicas Abel Salazar
IM – Intestinal metaplasia
IQR – Interquartile range
LGD – Low-grade dysplasia
NBI – Narrow-band imaging
OR – Odds Ratio
ROC – Receiver Operating Characteristic
SD – Standard Deviation
ULS – Unidade Local de Saúde
WHO – World Health Organization

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INTRODUCTION

Epidemiological data from 2020 revealed that gastric cancer was the fifth most common cancer overall and the fourth leading cause of death, emphasizing its substantial impact. With an estimated global incidence of around 1 million cases in 2020, and a death rate of 7.7 per 100,000 individuals worldwide, these figures highlight the significant burden of this neoplasm. [1–3]

The primary risk factors associated with gastric cancer include *Helicobacter pylori* (*Hp*) infection, advanced age, smoking, a diet high in meat and salted foods, alcohol consumption, obesity, familial predisposition (accounting for 10% of all gastric cancer cases with familial aggregation), and belonging to a high-risk population group. [2,4–6]

Regarding histologic classification, the World Health Organization (WHO) and Laurén classification systems stand out as the two most utilized systems for gastric cancer. While there are many classification systems for gastric cancer, this paper will focus only on these two. Among these, the Laurén classification of gastric cancer has appeared as the most extensively applied and studied classification for gastric adenocarcinoma. The Laurén classification divides gastric cancer into three distinct categories based on histology: intestinal type, diffuse type, and indeterminate type. The diffuse type includes signet ring cell carcinoma. Most research indicates that the intestinal form is the most prevalent, followed by the diffuse and indeterminate types. There is strong evidence suggesting that the intestinal type is associated with *Helicobacter pylori* infection and intestinal metaplasia. [2,7] The World Health Organization's classification stands out as the most precise, as it not only comprehends gastric adenocarcinoma but also all other less common forms of gastric cancer. The intestinal type, according to the Laurén classification, can be likened to subgroups of gastric adenocarcinoma, including papillary, tubular, and mucinous types. Signet ring cell carcinoma, classified by the WHO, corresponds to the diffuse type according to Laurén classification, which is a poorly cohesive cancer form. Since the other gastric adenocarcinomas classified by the WHO lack significant clinical relevance, they are collectively categorized as uncommon, corresponding to the indeterminate type in the Laurén classification. According to the WHO classification, tubular adenocarcinoma emerges as the most prevalent form of gastric cancer, with papillary and mucinous varieties following closely behind.[2,7] Gastric neoplasms can also be categorized based on their differentiation level, which provides us with the histological grade. This classification includes the differentiated type, which includes well-differentiated and moderately differentiated adenocarcinomas, and the undifferentiated type, which includes poorly differentiated adenocarcinomas and signet ring cell carcinomas.[8]

The Paris classification is employed for endoscopic assessment of the morphology of gastric lesions. [9,10] The most recent Paris classification for superficial neoplastic tumours in the gastrointestinal tract identifies three main morphological patterns. Type 0-I represents polypoid growth, further subdivided into 0-Ip for pedunculated growth, 0-Is for sessile growth and 0-Isp for semi-pedunculated lesions. Type 0-II indicates nonpolypoid growth, subcategorized into 0-IIa for slightly elevated growth, 0-IIb for flat growth, and 0-IIc for slightly depressed growth. Type 0-III denotes excavated growth. These classifications are determined based on morphological patterns observed during endoscopic examination. The Paris classification has increased significance for assessing the depth of invasion. Submucosal invasion is strongly associated with excavated lesions, particularly type 0-IIc lesions. Immediate resection of type 0-IIc lesions is crucial, if it meets criteria for performing endoscopic submucosal dissection (ESD), because they are suggestive of having a more advanced histological type. In cases of type 0-III lesions, ESD may not be sufficient for complete removal, needing surgical resection instead. [9,10]

Regarding the progression to gastric neoplasia, the Gastric Cancer Cascade is the most widely accepted theory to explain this progression. The molecular progression of stomach cancer remains poorly understood. Currently, it is widely believed that most cases of gastric cancer stem from inflammation, primarily triggered by environmental factors such as *Helicobacter pylori* infection. Prolonged inflammation in the stomach leads to alterations in the microenvironment, resulting in mucosal atrophy and metaplasia. Subsequent molecular changes may then progress to neoplasia. [11] The sequence known as the Correa cascade, involving inflammation, atrophy, metaplasia, dysplasia, and ultimately leading to cancer, underlies the development of intestinal-type stomach adenocarcinoma.[6] In that case, intestinal metaplasia (IM) and chronic atrophic gastritis are considered precancerous conditions as they set the stage for the development of dysplasia and adenocarcinoma, thus individually increasing the risk of gastric cancer. [2,6,12]

There is an ongoing discussion regarding the effectiveness of screening large populations for stomach cancer. [13] Several factors, such as cost, availability, and acceptance, present obstacles to the feasibility of implementing widespread endoscopic screening for stomach cancer. [13,14] East Asian studies utilizing data from the Korean National Cancer Screening Program for gastric cancer have demonstrated the significant impact of screening efforts on reducing gastric cancer mortality rates, reporting an overall reduction of 21% in gastric cancer mortality attributed to screening programs. A reduction of 47% in gastric cancer mortality was identified among individuals aged 40–74 who underwent upper endoscopy screening. [15,16] Therefore, guidelines for stomach cancer screening are established in countries with high disease prevalence, particularly in East Asian countries like Japan. According to the Japanese Guidelines for Gastric Cancer Screening, individuals aged 50-75 should undergo endoscopic screening every two-three year. However, by identifying individuals with a low risk of gastric cancer, it may be possible to extend their screening intervals, thereby optimizing screening programs. [2,17] Nevertheless, in countries with low incidence rates, population-wide endoscopic screening of asymptomatic individuals is not recommended. [18,19] Furthermore, the quality of routine endoscopic examinations can significantly influence the prevalence of gastric cancer, as more thorough inspections can enhance the detection of precancerous lesions. Research indicates that approximately 10% of precancerous lesions in the stomach were overlooked in the three years preceding gastric cancer diagnosis, categorizing them as missed lesions. [2] Therefore, according to European Society of Gastrointestinal Endoscopy (ESGE), individuals should undergo staging and treatment if they present with an endoscopically visible lesion that may indicate low- or high-grade dysplasia or adenocarcinoma. [6]

The implementation of national screening programs in eastern countries has facilitated the early detection of gastric cancers, giving rise to the concept of early gastric cancer (EGC). EGC is characterized as an invasive gastric cancer with tumour infiltration confined to the mucosa or submucosa (T1 cancer), regardless of lymph node metastasis (T1, any N). [15,20,21]

The diagnosis of EGC has had a profound impact on the clinical management of gastric cancer. Studies suggest that patients undergoing endoscopic removal of EGC experience a survival rate exceeding 90% at 5 years. [22] In contrast, the prognosis for advanced gastric cancer, which invades into the muscularis propria or beyond, is significantly poorer and has a survival rate of around 60% or less after five years. [9]

EGC can be managed using a minimally invasive endoscopic procedure known as ESD, offering a less invasive alternative to surgery. [6] According to current guidelines of ESGE, ESD is the preferred treatment for superficial gastric lesions with a low risk of lymph node metastasis.

[23–25] ESD is a recent advancement in endoscopic procedures, enabling the *en bloc* resection of larger lesions. Thus, lesion size may not always be a limiting factor for ESD, suggesting that in certain cases of EGC, ESD can be applied with a curative purpose, regardless of lesion size, therefore avoiding surgery. [21]

Regarding the inclusion criteria for ESD proposed by the guidelines of the ESGE, the absolute criteria include: non-invasive neoplasia (dysplasia) regardless of size; and intramucosal differentiated-type adenocarcinoma, without ulceration, and size ≤20 mm. [23]

The expanded criteria for performing ESD include: intramucosal differentiated-type adenocarcinoma without ulceration and size >20 mm; intramucosal differentiated-type adenocarcinoma with ulceration and size ≤30 mm; intramucosal undifferentiated-type adenocarcinoma with size ≤20 mm; and differentiated-type adenocarcinoma with superficial submucosal invasion (≤500 µm) and size ≤30 mm. [23]

This technique is considered safe and enables the *en bloc* excision of lesions of any size. [26] However, there is a low to moderate risk of recurrence and an incidence of metachronous lesions, even in cases with a low risk of lymphovascular invasion. According to clinical studies, the eradication of *H. pylori* is an efficient strategy for preventing the onset of metachronous lesions. Therefore, the ESGE recommends eradicating *H. pylori* after endoscopic therapy (ESD). [6,27]

According to the guidelines of the ESGE, the criteria for curativeness of resection are as follows. [25]

For a curative/very low-risk resection (risk of lymph node metastasis <0.5%–1%):

- *En bloc* R0 resection.
- Lesion characteristics: dysplastic/pT1a, differentiated, without lymphovascular invasion.
- Size consideration: ≤30 mm if ulcerated, otherwise independent of size.

For a curative/low-risk resection (risk of lymph node metastasis <3%):

- *En bloc* R0 resection.
- Lesion characteristics:
    - pT1a: predominant type is poorly differentiated or undifferentiated, size ≤20 mm, no ulceration.
    - pT1b: invasion ≤500 µm, differentiated, size ≤30 mm, no lymphovascular invasion.

For a local-risk resection (very low risk of lymph node metastasis but increased risk of persistence/recurrence):

- Acceptable procedures: fragmented excision or tumour-positive horizontal margin under specific conditions (no submucosally invasive tumour at the resection margin and lesion characteristics: pT1b, invasion ≤500 µm, well-differentiated, size ≤30 mm, without involvement of the vertical margin).

For a high-risk resection (noncurative):

- Any lesion with positive vertical margin or lymphovascular invasion or deep submucosal invasion (>500 µm from the muscularis mucosae) or presence of ulceration or size >20 mm in poorly differentiated lesions.

Positive lateral or vertical margins, lymphovascular invasion, or undifferentiated histology are indicators of a noncurative ESD. In such cases, surgery may be necessary due to the increased risk of unfavourable outcomes, including lymph node or distant metastasis, and recurrence. [20]

When only positive or unclear lateral margins are visible, and other previously mentioned variables are absent, it suggests a reduced probability of lymph node metastasis. [20]

The risk of noncurative resection is higher in elderly patients, with tumours located in the upper third of the stomach (for ulcerative tumours in the upper and mid-stomach), large tumours (>30 mm), fragmented excision, ulceration, undifferentiated histology (especially >20 mm), and deep submucosal invasion (>500 μm). [20]

Endoscopic Mucosal Resection (EMR) is an alternative endoscopic technique considered suitable for small (≤10–15 mm) elevated (Paris 0-IIa) lesions suspected to have a non-advanced histology. However, compared to EMR, ESD demonstrates significantly higher rates of *en bloc* R0 complete resection, lower recurrence rates, similar post-procedural bleeding, and high rates of curative resections. Nonetheless, ESD is associated with a slightly higher risk of perforation and longer procedural duration. In summary, ESD is recommended as the primary endoscopic treatment for gastric superficial lesions with a very low risk of lymphovascular invasion, including dysplastic lesions of any size and intramucosal carcinomas without evidence of deep submucosal invasion. If lesions are not ulcerated, size is not a limiting factor, but, if they are ulcerated, lesions should be ≤30 mm in size. [2,23,25,28]

While ESD is a minimally invasive procedure associated with lower mortality rates, surgery is another alternative for treating EGC. Compared to ESD, surgery presents inferior results due to longer process and hospitalization durations, as well as a higher number of side effects. Additionally, ESD is associated with a higher quality of life compared to gastrectomy. Considering these factors, ESD is the preferred treatment recommended by the ESGE for EGC with a high prediction success rate and with favourable long-term oncological outcomes. [25] However, in cases where ESD is not possible or the lesion does not meet the criteria for ESD, surgery may be necessary. [2]

It is crucial to make an adequate selection of patients eligible for ESD, since studies have shown a disparity between the histopathological findings of endoscopic biopsy samples taken during endoscopy (pre-ESD sample) and the specimen removed via ESD (post-ESD sample). [24,28] This can be attributed to the fact that biopsies typically collect approximately 1.0 mg of tissue from the mucosal surface in each specimen, making it challenging to obtain samples from the submucosa with this method. [29] These histopathological discrepancies could significantly impact the prognosis of patients undergoing ESD, as they may lead to errors in treatment selection. [30,31] Several studies in Eastern populations have reported a considerable rate of discordance between the histopathological findings of pre- and post-ESD samples, being estimated between 20-34%. [24,31,32] These studies have identified factors contributing to the discrepancy, such as lesion size, surface morphological pattern, presence of ulceration, histological grade, deep submucosal invasion (>500 μm), and lymphovascular invasion. [24,31]

OBJECTIVES

The aim of this study is to compare the histopathological findings of biopsy specimens obtained during upper digestive endoscopy (pre-ESD) with the histopathological features of ESD specimens from Hospital de Santo António – Unidade Local de Saúde de Santo António (ULS de Santo António). And to identify the factors associated with discrepancies, namely the upgrading and downgrading of post-ESD specimens, which may have implications for prioritizing these patients for ESD, on the outcomes of ESD, and the need for additional treatments such as surgery, ultimately impacting patients' quality of life.

METHODS

Context and structure of the Study

This retrospective observational study based on prospectively collected data took place in the Gastroenterology department of ULS de Santo António. This study included all the patients that have undergone gastric ESD in Hospital de Santo António between January 1st, 2016, and October 31st, 2023.

The demographic and clinicopathological data were collected by analysing each clinical process from SClínico®. This included the records of consultations, hospitalization, endoscopy reports, anatomopathological results and other complementary exams that are relevant to answer specific questions about the patient.

The study N/ REF.ª 2023.237 (200-DEFI/189-CE) was approved by: Conselho de Administração do Santo António, Comissão de Ética do Santo António | ICBAS, Gabinete de Projeto de Investigação do CAC, Direção do Centro Académico Clínico ICBAS | Hospital de Santo António – ULS de Santo António and by Presidente do Conselho de Administração.

An informed consent was obtained from all patients prior to the performance of ESD. However, the informed consent was not obtained for their inclusion in this study, as the study did not interfere with the clinical management of the patients, and there was no need for direct patient contact. This is due to it being a retrospective and pseudonymized study.

This study included all cases in which the anatomopathological results of the pre-ESD biopsy and the specimen collected by ESD corresponded to low-grade dysplasia, high-grade dysplasia, or adenocarcinoma.

The exclusion criteria included anatomopathological results from ESD specimens compatible with subepithelial lesions and hyperplastic polyps. The cases in which the anatomopathological result of the pre-ESD biopsy was unknown or undefined were also excluded from the analysis, as well as the cases in which ESD was interrupted.

Since data were collected from patients who underwent more than one ESD with the removal of lesions or patients in whom more than one lesion was removed in the same ESD, we chose to consider for analysis the number of lesions removed, rather than the number of patients involved. For this reason, all analysis were performed on the lesions removed by ESD. Any analysis regarding the type of cases (duplicates or primaries) was disregarded.

The biopsy specimens had anatomopathological analysis conducted externally in most cases, with some cases having this analysis performed at ULS de Santo António. The ESD specimens underwent anatomopathological analysis at ULS de Santo António.

Anatomopathological results pre-ESD and post-ESD were compared and categorized into the following groups: concordant group (if the histological type remained the same in both pre-ESD and post-ESD analysis), upgraded group (if the histological type became more advanced in the post-ESD analysis compared to the pre-ESD analysis), and downgraded group (if the histological type became less advanced in the post-ESD analysis compared to the pre-ESD analysis). We also considered that the upgraded group and the downgraded group are subdivisions of the discordant group.

With the aim of identifying factors contributing to concordance and discrepancy (upgraded and downgraded groups), various variables were analysed.

Regarding population-related characteristics, the following were analysed: gender, age at the time of ESD, presence of comorbidities (hypertension, diabetes mellitus, ischemic heart disease, cerebrovascular disease, lung disease, chronic kidney disease, and liver cirrhosis), personal history

of malignant neoplasms, family history of gastric cancer, and family history of non-gastric GI cancer.

Regarding lesion characteristics, some of these features were assessed endoscopically during the ESD, while others were analysed anatomopathologically through the specimen collected by ESD.

About endoscopic characteristics, the evaluation included: location (transversal plane location and longitudinal plane location), lesion size (analysed as a continuous variable and according to the cut-off of 20 mm and 30 mm), and morphological pattern according to the Paris classification.

With respect to microscopic characteristics, features were assessed in pre-ESD biopsy and in ESD specimens. In biopsy samples, the histological type was evaluated, and in ESD specimens, the following were assessed: presence of ulceration, pre-malignant conditions (presence of atrophy and intestinal metaplasia), *Helicobacter pylori* infection, presence of fibrosis, histological type, histological grade (according to adenocarcinoma differentiation), microscopic vertical neoplastic extension, and the presence of lymphovascular and neural invasion.

The information related to ESD includes its curative outcome, whether there was a change in the endoscopist, the technique employed, the type of knife used, and its duration.

The impact of the specialists involved in both processes of this study was also evaluated, namely the endoscopists who performed the ESD and the pathologists who analysed the ESD specimens. In order to maintain the confidentiality of the professionals, the endoscopists were identified by the numbers 1 and 2, and the pathologists were identified by the letters A and B.

Outcomes definition

The curative outcome of ESD indicates whether the patients achieved a cure or not, according to the cure criteria proposed by the ESGE (as described in the introduction).

The transversal plane location corresponds to the division of the stomach into 3 parts, according to transverse sections, with lesions possibly located in: upper (cardia and fundus), middle (body) and lower third (antrum, incisura, and pylorus).

The longitudinal plane location corresponds to the division of the stomach into 4 parts, according to longitudinal sections, with lesions possibly located in: posterior wall, anterior wall, lesser curvature and greater curvature.

With respect to the size of lesions in ESD, analyses were conducted using two cut-off points, namely 20 mm and 30 mm, because the absolute and expanded criteria for the selection of lesions for ESD propose different cut-offs, depending on the association of its size with other lesion characteristics. Analyses were also performed using lesion size as a continuous variable.

Regarding the morphological pattern of lesions, they were grouped to form the following classification groups: elevated type (0-Ip, 0-Is, 0-Isp, 0-IIa), flat type (0-IIb), depressed type (0-IIc, 0-III), mixed elevated type (0-IIa+0-IIb, 0-IIa+0-IIc, 0-IIa+0-III, 0-Is+0-IIa, 0-Is+0-IIb, 0-Is+0-IIc, 0-Isp+0-IIa, 0-Isp+0-IIb), mixed flat type (0-IIb+0-IIa, 0-IIb+0-IIc, 0-IIb+0-III), mixed depressed type (0-IIc+0-IIa, 0-IIc+0-IIb, 0-IIc+0-III, 0-III+0-IIb, 0-III+0-IIc).

As for the histological type, the lesions were classified into low-grade dysplasia (LGD), high-grade dysplasia (HGD), and adenocarcinoma (ADC). For adenocarcinomas, to obtain the histological grade, differentiation was assessed, and the lesions were grouped into well to moderately differentiated, poorly differentiated, and signet ring cell carcinoma.

Regarding microscopic vertical neoplastic extension, lesions were classified as showing invasion of the lamina propria, invasion of the muscularis mucosae, superficial invasion of the submucosa if invasion ≤500 µm, or deep invasion of the submucosa if invasion >500 µm.

Statistical Analysis

All data was registered and analysed in IBM® SPSS® Statistics, version 27.0 (IMB Corp. Armonk, New York, USA). The registration of this data was anonymized, and the identity and confidentiality of the patient data was guaranteed.

In the descriptive analysis of cases, all anatomopathological results of the ESD specimens were included. However, in the group analysis, only the two main pathologists responsible for most of the analyses were included, as the remaining specialists had few cases analysed.

The descriptive analysis of clinicopathological characteristics was conducted among the concordant, upgraded, and downgraded groups.

Categorical variables were presented in absolute (number of cases) and relative frequencies (%) and were compared using the Pearson Chi-square test or Fisher's Exact test, as considered most appropriate for each case. Continuous variables were described using the mean ± standard deviation (SD), and the median and interquartile range (IQR) (percentile 25 to percentile 75). To assess differences between concordant and discordant groups, one-way ANOVA or Independent-samples proportions test were employed.

Binary logistic regression analysis was conducted, calculating odds ratios (OR) and 95% confidence intervals (CI), aiming to perform univariable and multivariable analyses of predictors of discrepancy. Only variables with statistically significant result in the univariable analysis were included in the multivariable analysis. For binary logistic regression analysis, we used as outcome the concordant and discordant groups (which includes the upgraded and downgraded groups).

We also estimated Cohen's kappa to measure inter-rater agreement. Receiver Operating Characteristic (ROC) curves were plotted to estimate the sensitivity (true positivity rate) against the 1-specificity (false positivity rate). The area under the curve (AUC) was calculated as a measure of diagnostic accuracy, to determine the size from which the risk of discrepancy increases. Results were considered significant if the p-value was <0.05.

RESULTS

Cases included in the study

Data from 344 lesions located in the stomach were collected. 18 cases were excluded from the analysis because the post-ESD histology did not meet the inclusion parameters, namely: 8 cases were subepithelial lesions and 10 cases corresponded to hyperplastic polyps. 5 cases in which the anatomopathological result of the pre-ESD biopsy was unknown or undefined were also excluded from the analysis. Additionally, 2 cases were excluded, in which ESD was interrupted due to a high probability of non-curative procedure and a high probability of complications.

Therefore, the analysis included 319 cases, of which: 269 cases were primary (cases in which an ESD was carried out with the removal of one specimen), and 50 cases were duplicates, involving patients who underwent more than one ESD with lesion removal, or patients in whom more than one lesion was removed in the same ESD.

Clinicopathological features of the patients and lesions under investigation

The characteristics of patients, lesions, ESD procedures, histopathological analysis and outcomes are presented in Table I.

This study comprises data from 7 years and 10 months, involving the analysis of 319 lesions. Of these, 203 cases (63.6%) were male. The mean age of the study cases is 68.7 years ± 9.2, with a median age of 69.0 years (IQR 63.0-75.0). Regarding the distribution of cases by age groups: 163 cases (51.1%) were below 70 years old.

Regarding the presence of comorbidities and personal or family history of neoplasms: 180 cases (56.4%) had hypertension, 86 cases (27.0%) had diabetes mellitus, 27 cases (8.5%) had ischemic heart disease, 13 cases (4.1%) had cerebrovascular disease, 19 cases (6.0%) had lung disease, 14 cases (4.4%) had chronic kidney disease, 10 cases (3.1%) had liver cirrhosis, 50 cases (15.7%) had a personal history of malignant neoplasms, 78 cases (24.5%) had a family history of gastric cancer, and 56 cases (17.6%) had a family history of non-gastric gastrointestinal cancer.

Regarding the location according to the transversal plane, 10 cases (3.1%) were in the upper location, 104 cases (32.6%) in the middle location, and 205 cases (64.3%) in the lower location. Concerning the location according to the longitudinal plane, 65 cases (20.4%) were in the anterior wall, 41 cases (12.9%) in the posterior wall, 125 cases (39.2%) in the lesser curvature, and 88 cases (27.6%) in the greater curvature.

The mean size of the lesions was 22.0 mm ± 13.9, with a median size of 18.0 mm (IQR 12.0-27.0). Considering the cut-off of 20 mm, 182 cases (57.1%) were ≤20 mm. When considering the cut-off of 30 mm, 263 cases (82.4%) were ≤30 mm.

Regarding the morphological pattern, 147 cases (46.1%) were of the elevated type, 10 cases (3.1%) were of the flat type, 12 cases (3.8%) were of the depressed type, and the remaining cases presented a mixed morphological pattern.

Concerning pre-malignant conditions, 85 cases (26.6%) exhibited atrophy, and 153 cases (48.0%) showed intestinal metaplasia.

Regarding the *H. pylori* infection status, 36 cases (11.3%) had *H. pylori* infection, and 55 cases (17.2%) had a history of *H. pylori* eradication.

Regarding the presence of fibrosis and ulceration, 68 cases (21.3%) exhibited fibrosis, and 49 cases (15.4%) were ulcerated lesions.

Regarding the histological type of pre-ESD biopsies, 218 cases (68.3%) corresponded to low-grade dysplasia, 80 cases (25.1%) corresponded to high-grade dysplasia, and 21 cases (6.6%) corresponded to adenocarcinomas.

Regarding the histological type of ESD specimens, 146 cases (45.8%) corresponded to low-grade dysplasia, 74 cases (23.2%) corresponded to high-grade dysplasia, and 99 cases (31.0%) corresponded to adenocarcinomas. In relation to adenocarcinomas, 87 cases (87.9%) were classified as well to moderately differentiated, 8 cases (8.1%) were classified as poorly differentiated, and 4 cases (4.0%) were classified as diffuse type.

Regarding the microscopic vertical neoplastic extension, 52 cases (52.5%) extended to the lamina propria, 18 cases (18.2%) extended to the muscularis mucosae, 8 cases (8.1%) had superficial submucosal invasion (≤500 μm), and 21 cases (21.2%) had deep submucosal invasion (>500 μm).

Regarding lymphovascular and neural invasion, 16 cases (16.2%) showed lymphovascular and neural invasion.

Concerning the endoscopist who performed the ESD, 237 cases (74.3%) were conducted by endoscopist 1, and 82 cases (25.7%) were performed by endoscopist 2. Regarding the pathologist who analysed the ESD specimens, 112 cases (35.1%) were examined by pathologist A, 198 cases (62.1%) were analysed by pathologist B, and 9 cases (2.8%) were examined by other pathologists.

In 4 cases (1.3%), there was a change of operator during the ESD.

The ESD procedures had a mean duration of 77.0 minutes ± 66.6, with a median duration of 56.0 minutes (IQR 35.0-98.0), with 45.8% of the procedures lasting more than an hour.

In 279 cases (87.5%) the standard technique was used, the pocket technique was employed in 5 cases (1.6%), the tunnel technique was utilized in 20 cases (6.3%), and the underwater technique was applied in 15 cases (4.7%).

Regarding the type of knives used in ESD, the dual knife was used in 34.5% of cases and the flush knife in 29.2%, other types of knives in 5.9% and an exchange in the knife used during the procedure in 30.4% of cases.

Comparing the histological type of pre-ESD biopsies with ESD specimens, 183 cases (57.4%) showed concordant results, 127 cases (39.8%) showed upgrading, and 9 cases (2.8%) showed downgrading.

Regarding the therapeutic curative outcome of ESD, it was curative in 289 cases (90.6%) and non-curative in 39 cases (9.4%).

Comparison of histopathological results between the pre-ESD specimen and the ESD specimen

Table II displays the comparison between the histopathological results of the pre-ESD biopsy and the post-ESD dissected specimen. The same information is also presented in the flowchart of Figure 1. For cases classified as low-grade dysplasia in pre-ESD biopsy: 62.8% were classified as low-grade dysplasia in the post-ESD result, showing concordance; 22.5% were classified as high-grade dysplasia and 14.7% were classified as adenocarcinoma in the post-ESD result, showing upgrading. For cases classified as high-grade dysplasia in pre-ESD biopsy: 11.3% were classified as low-grade dysplasia in the post-ESD result, indicating downgrading; 31.3% were classified as high-grade dysplasia in the post-ESD result, showing concordance; and 57.5% were classified as adenocarcinoma in the post-ESD result, indicating upgrading. For cases classified as adenocarcinoma in pre-ESD biopsy: 100.0% were classified as adenocarcinoma in the post-ESD result, showing concordance. These results were statistically significant, with $p<0.001$. The Kappa

value, as a measure of agreement, was kappa=0.3, indicating reasonable agreement between the histopathological result of the pre-ESD biopsy and the specimen removed by ESD.

The cases with concordance were included in the concordant group, while the discordant group comprised cases with upgrading (included in the upgraded group) and cases with downgrading (included in the downgraded group). The discordant group accounts for 93.4% of cases in the upgraded group, with the remaining cases in the downgraded group, meaning that most discordant cases are found in the upgraded group. These results are presented in Table III.

Table IV shows the magnitude of variation in histopathological results pre- and post-ESD between the concordant and discordant groups. It is noted that most cases in the concordant group (74.9%) correspond to low-grade dysplasia. The upgraded group presents 38.6% of cases classified as low-grade dysplasia in the biopsy and high-grade dysplasia in the ESD specimen, 36.2% of cases as high-grade dysplasia in the biopsy and adenocarcinoma in the ESD specimen, and 25.2% as low-grade dysplasia in the biopsy and adenocarcinoma in the ESD specimen. Regarding the downgraded group, all cases correspond to high-grade dysplasia cases that were reclassified as low-grade dysplasia in the ESD specimen.

Comparison of clinicopathological characteristics between the groups with histological concordance and discrepancy

Table V presents the distribution of analysed characteristics (related to patients, lesions, ESD procedures, and their respective histopathological analysis) across the concordant, upgraded, and downgraded groups.

A statistically significant association was found between the presence of chronic kidney disease ($p=0.045$), the lesion size in ESD for the cut-offs of 20 mm and 30 mm ($p<0.001$), and for the analysis of the lesion size as a continuous variable ($p<0.001$), the morphological pattern ($p=0.016$), the presence of ulceration ($p<0.001$), the pathologist who analysed the ESD specimens ($p=0.009$), the duration of ESD for the 60 minute cut-off ($p<0.001$), and for the analysis of ESD duration as a continuous variable ($p=0.002$), as well as the curative outcome of ESD ($p<0.001$) among the concordant, upgraded, and downgraded groups. The remaining analysed variables did not show statistically significant differences among the concordant, upgraded, and downgraded groups.

The upgraded group comprises 54.7% of lesions larger than 20 mm, and 69.6% of cases have sizes exceeding the 30 mm cut-off. In contrast, the concordant group includes 68.7% of lesions smaller than or equal to 20 mm, and 63.5% of lesions of size equal to or less than 30 mm.

The concordant group comprises 66.7%, 90.0%, 58.3%, and 66.7% of elevated, flat, depressed, and mixed depressed lesions, respectively. In contrast, the upgraded group includes 53.5% and 50.0% of mixed elevated and mixed flat morphological patterns, respectively.

In terms of ulceration presence, the upgraded group comprises 69.4% of ulcerated lesions, while 62.6% of non-ulcerated lesions are in the concordant group.

Regarding the analysis of the pathologist who examined the ESD specimen, only the two main pathologists were considered, and the 5 cases whose ESD specimens were analysed by other pathologists were excluded from this analysis since their number was very small. Therefore, the concordant group includes 63.1% of cases analysed by pathologist B, whereas the upgraded group comprises 50.0% of lesions analysed by pathologist A. The Kappa value, a measure of agreement, was found to be 0.038 with a significance level of $p=0.016$, suggesting a lack of agreement in the pathological analysis conducted by the pathologists.

Regarding the duration of ESD, 67.6% of ESD procedures lasting an hour or less corresponded to cases in the concordant group. In contrast, 54.8% of ESD procedures lasting over an hour were cases in the discordant group.

Concerning the curative outcome of ESD, it is noted that most non-curative lesions (83.3%) are in the upgraded group, whereas 61.6% and 3.1% of curative lesions are in the concordant group and the downgraded group, respectively.

Analysis of the factors that affect anatomopathological discrepancy

Table VI shows the univariable and multivariable analysis of factors contributing to the discrepancy.

Regarding the univariable analysis of variables, those that may impact discrepancy is the comorbidity of chronic kidney disease (OR=3.6, 95% CI 1.1-11.6, p=0.036), location in the upper third of the stomach compared to the lower third of the stomach (OR=6.0, 95% CI 1.2-29.0, p=0.026), size >20 mm (OR=3.0, 95% CI 1.9-4.7, p<0.001) and size >30 mm (OR=4.3, 95% CI 2.3-8.2, p<0.001). The mixed elevated morphological pattern (OR=2.4, 95% CI 1.5-3.9, p<0.001), the presence of ulceration (OR=4.2, 95% CI 2.1-8.2, p<0.001), the ESD specimens being analysed by pathologist A (OR=1.8, 95% CI 1.1-2.8, p=0.017), and the duration of ESD exceeding one hour (OR=2.5, 95% CI 1.6-4.0, p<0.001) are also factors associated with discordance.

The remaining variables analysed did not show significant differences between the concordant and discordant groups, in the univariable analysis.

It is important to highlight that the univariable analysis of histological grade only involved the comparison between well to moderately differentiated cases and poorly differentiated cases, with cases with signet ring cells being excluded from the analysis. This exclusion was because all these cases belonged to the discordant group, so they could not be incorporated into the model to evaluate discrepancy.

The variables whose results were statistically significant in the univariable analysis were included in the multivariable regression analysis. Only size greater than 20 mm (OR=2.1, 95% CI 1.1-3.9, p=0.021), the mixed elevated morphological pattern (OR=1.8, 95% CI 1.1-3.2, p=0.031), and the presence of ulceration (OR=3.7, 95% CI 1.8-7.7, p=0.001) were statistically significant.

Analysis of the impact of discrepancy on non-curative ESD outcome

Table VII presents the univariable analysis of the impact of discrepancy on non-curative ESD outcome. Concerning the univariable analysis of variables, the presence of discrepancy (discordant group) impacts the outcome of ESD, particularly, in the procedure being non-curative (OR=8.0, 95% CI 3.0-21.6, p<0.001).

Study of the factors that contributed to the curative outcome of the upgraded group

The variables that were statistically significant in the analysis of differences between the concordant, upgraded, and downgraded groups were used to analyse the curative outcome of the cases included in the upgraded group, with these results presented in Table VIII and IX.

Considering the individuals in the upgraded group, 80.3% were cured with ESD, and 19.7% were not cured with ESD. The variables under study did not have a significant impact on the curative outcome of ESD, except for the variable analysing the pathologist who analysed the ESD specimen.

Impact of lesion size on pathological concordance and discordance

Table X shows the comparison between the lesion size in the concordant and discordant groups.

In both cut-offs, the trend was the same, meaning that it was observed that for lesion sizes below the cut-off point, the highest percentage was of concordant cases (68.7% for size ≤20 mm and 63.5% for size ≤30 mm). For lesion sizes above the cut-off point, the highest percentage was of discordant cases (57.7% for size >20 mm and 71.4% for size >30 mm). The percentage of discordance was higher for cases larger than the cut-off, especially when the cut-off was set at 30 mm. In other words, with a higher cut-off point and lesion size exceeding that cut-off point, the percentage of discrepancy is higher. And these results were statistically significant ($p<0.001$).

Table XI shows that there is a higher proportion of concordant results when the lesions have a size >20 mm than when the size is >30 mm, however, these results are not statistically significant ($p=0.074$).

Table XII shows that in the discordant group, the mean and median lesion sizes are higher than those in the concordant group, and these results are statistically significant ($p<0.001$).

Figure 2 presents a boxplot that graphically displays the distribution of lesion sizes in the concordant and discordant groups. The boxplot shows that in the concordant group, the lesion size values are more similar to each other, with less dispersion of values, and the lesion sizes are smaller. In contrast, in the discordant group, the lesion size values are more diverse, with greater dispersion of values, and the lesion sizes are larger.

Table XIII and figure 3, which displays the distribution of lesion size percentiles in the concordant and discordant groups, shows that, in the discordant group, the lesion size values at each percentile are more different from each other, covering a wide range of values, compared to the concordant group where the values are closer to each other. The lesion size values are more frequently lower in the concordant group and more frequently higher in the discordant group.

Based on these findings, it can be inferred that a lesion size of approximately 20 mm serves as a cut-off point, beyond which larger sizes are associated with a higher discordance rate. This is supported by the observation that the median lesion size exceeds this value in the discordant group and falls below it in the concordant group.

The ROC curve analysis was conducted for all cut-off values ranging from 20 mm to 30 mm. Results for cut-offs of 20 mm and 30 mm are presented in Table XIV, as they were the cut-offs used throughout the analysis. Additionally, results for the cut-off of 21 mm are included because it granted the highest area under the curve, with an AUC=0.635 (95% CI 0.6-0.7, $p<0.001$). It is observed that as the cut-off for lesions selected for ESD increases, the sensitivity of this cut-off to detect discrepancy decreases, while specificity increases.

Figure 4 displays the ROC curve and the corresponding area under the curve for the 21 mm cut-off, which was the cut-off value that showed the highest area under the curve among the values between 20 mm and 30 mm.

DISCUSSION

ESD is an endoscopic technique used in the detection and treatment of pre-neoplastic lesions and EGC, which has been widely used due to its effectiveness, it should be noted that in the cases under this study, a cure was achieved in 90.6% of the cases subjected to ESD. The studies published in the literature have revealed that there are differences between the anatomopathological result of pre-ESD biopsy and the ESD specimen, which is why this study is of great relevance, in order to study the factors that contribute to the discrepancy, allowing for a better selection of lesions proposed for treatment with ESD, improving its curative outcomes and ultimately impacting patients' quality of life.

This study demonstrated that the pre- and post-ESD discrepancy is 42.6%, while a large multicentred study showed 33.9% discrepancy, [31] and other studies reported discrepancy rates in the range of 20-30%. [24,32]

The univariable analysis showed that the only population characteristic contributing to the discrepancy was the comorbidity of chronic kidney disease. Regarding lesion characteristics, factors identified as risk factors for discrepancy were location in the upper third of the stomach, lesion size >20 mm, and lesion size >30 mm, mixed elevated morphological surface pattern, and presence of ulceration. Regarding ESD and pathological analysis characteristics, pathological analysis conducted by pathologist A and ESD duration exceeding one hour were considered risk factors for discrepancy. No statistically significant protective factors for discrepancy were identified. The multivariable analysis identified lesion characteristics as risk factors for discrepancy, namely, size larger than 20 mm, mixed elevated morphological surface pattern, and the presence of ulceration. It was found that patients with lesions larger than 20 mm have twice the risk of discrepancy, as well as lesions presenting a mixed elevated surface pattern, whose risk of discrepancy is twice as high. The presence of ulceration is associated with approximately four times the risk of discrepancy.

Regarding the presence of ulceration, it was also identified as a risk factor for discrepancy in other articles, specifically as a risk factor for upgrading. [24,31–39] Ulceration is often associated with histologically more advanced lesions. During endoscopic procedures, the presence of ulceration can make it challenging to precisely assess the margins and depth of the lesion. This can lead to discrepancies between the pre- and post-ESD findings. Additionally, ulcerated lesions may have heterogeneous characteristics, making it more difficult to obtain representative biopsy samples. [24,31]

Regarding the morphological surface pattern, this study revealed that there was a higher risk of discrepancy associated with the mixed elevated morphological pattern. However, these results differ from those presented in the literature, as other studies have shown an association between the depressed morphological pattern and a higher risk of discrepancy and upgrading. [31–39] However, it seems there was a bias in the analysis of the surface pattern due to the way classifications were grouped for statistical analysis. Because complex lesions have associations with more than one pattern of simple lesions, meaning lesions with different degrees of invasiveness in the same group. For example, a 0-IIa+0-III lesion is more aggressive than a 0-IIa+0-IIb lesion, yet both are included in the same category.

According to the literature, in depressed lesions, the threshold for ESD should be higher because it was observed that this type of lesion more frequently presents upgrading. This occurs because the Paris classification has acquired greater importance in evaluating the depth of invasion. Consequently, submucosal invasion is often linked with excavated lesions. Therefore, it

may not be suitable to propose ESD to all these patients. It is essential to carefully interpret all factors of these lesions to decide if ESD is the most effective treatment method. In our study, we observed that a mixed elevated morphological surface pattern was associated with more discrepancies. However, this may have been due to the way lesions were grouped for statistical analysis, introducing heterogeneity bias. It is noteworthy that other studies have shown that elevated gross morphology was commonly found in cases >30 mm, possibly because of an overrepresentation of patients with discrete elevated gross morphology. Therefore, considering that deviations occurred more frequently in cases with larger lesions, this could be another factor influencing their higher discrepancy rates. These results were dependent on the fact that there was an association with other lesion characteristics associated with higher discrepancy. [24]

The size of lesions, particularly those larger than 20 mm, was a statistically significant risk factor for discrepancy in all analyses employed in this study. There is limited reference in the literature to specific cut-off values beyond which the risk of discrepancy becomes higher, with the cut-off size used in various studies being variable, typically with a threshold of 20 mm. Several published studies have shown that larger lesion sizes, especially those exceeding 20 mm, are associated with a higher risk of discrepancy and upgrading. [31–39] Regarding size, it is known to be an important risk factor because it is associated with disease progression, meaning it serves as a marker of disease advancement – as the lesion progresses, its size increases. [39]

Regarding the impact of lesion size on pre- and post-ESD discrepancy, this study examined the size cut-offs of 20 mm and 30 mm, as both cut-offs can be utilized depending on other lesion characteristics. In the univariable analysis, the 30 mm size cut-off showed a stronger association with discrepancy (OR 4.3, 95% CI 2.3-8.2, $p<0.001$) than the 20 mm size cut-off (OR 3.0, 95% CI 1.9-4.7, $p<0.001$). However, in the multivariable analysis, only the 20 mm size cut-off was considered statistically significant in the risk of discrepancy. Regarding the size of the lesions under study, it was observed that most lesions larger than 20 mm and 30 mm were in the discordant group, and the percentage of discordant lesions in the >30 mm size group is higher than the number of lesions in the discordant group when the size is >20 mm. In other words, this suggests that the larger the size, the greater the contribution to the discrepancy. It should be noted that the analysis of percentiles and the boxplot of lesion size in the concordant and discordant groups reveal that the discordant group consists of larger lesions.

Furthermore, as the median lesion size in the concordant group is below 20 mm and in the discordant group is above 20 mm, it seems to indicate that around 20 mm is the cut-off point to detect the threshold from which it is more likely to detect discrepant lesions. In the analysis of the ROC curve, whose AUC value is between 0.6 and 0.7, thus considered satisfactory, it is observed that the 30 mm cut-off has low sensitivity for detecting discrepancy, meaning many discrepant lesions will not be detected by this cut-off. In the analysis of all absolute values of cut-offs between 20 mm and 30 mm, the size of 21 mm had the highest AUC value, showing good sensitivity and specificity for detecting discrepancy. This may indicate that it is the best predictor of pre- and post-ESD discrepancy, thus potentially serving as a good size cut-off value for lesions in this analysed population. However, further studies are needed to determine the optimal cut-off value for analysing lesions and reducing discrepancy, especially in the presence of other risk factors for discrepancy.

Regarding the differences between the pathologists who analysed the ESD specimens, it is observed that analysis conducted by pathologist A is a risk factor for discrepancy. However, this could introduce bias, as pathologist A examined a smaller number of cases and analysed a similar

number of cases from both the concordant and discordant groups, while pathologist B examined a larger number of cases, with most of these cases being from the concordant group. In other words, this difference between the two pathologists may be due to the different sample sizes analysed by each specialist, with the number of lesions examined by each specialist serving as a confounding factor.

In this study, the majority of pre-ESD biopsies were collected and analysed in various centres external to ULS de Santo António, and by different pathologists. The ESD specimens were evaluated by pathologists from Hospital de Santo António, considering for this analysis the specimens evaluated by the 2 pathologists who performed the highest number of analyses. In contrast, multicentred studies that assessed pre- and post-ESD discrepancy depend on histopathological analysis of all specimens by 2 experienced pathologists, with cases referred from external sources having their pre-ESD biopsy specimens re-evaluated by the 2 pathologists involved in the study. In other words, the fact that both pre- and post-ESD analyses were performed by fewer specialists leads to greater homogeneity of comparison parameters. Therefore, it can be extrapolated that the pre- and post-ESD discrepancy in this study could be lower if pre-ESD biopsies were always analysed by the same pathologists, using rigorous analysis criteria, as it would reduce interobserver variability. However, it should be noted that this study is more realistic, since it had pre-ESD analysis performed at various locations. This is because, in clinical practice, there are many logistical constraints in performing pre-ESD histopathological analyses all in the same location and by the same pathologists. [31]

This study also identified longer ESD duration as a risk factor for discrepancy, which is consistent with previous publications where longer ESD durations were considered risk factors for upgrading. [38] This may be justified by the fact that more complicated lesions, which posed more doubts and difficulties during ESD, are cases with more discrepancy.

The location in the upper third of the stomach was considered a risk factor for discrepancy in the univariable analysis of this study, although it did not have a statistically significant result in the multivariable analysis. Published studies up to the present moment have results that support the findings of this study. The region of the cardia and fundus, corresponding to the upper third of the stomach, are technically challenging gastric regions to approach, with more limited endoscopic fields. [24,31,38,39] The increased difficulty in approaching lesions in this topographic region may justify the higher percentage of discrepant cases in this location. Additionally, due to the difficulty of their evaluation, lesions located in this topography may be associated with delayed or missed diagnoses. [39] This region is also associated with underestimation of lesion size, with these lesions classified as smaller than their actual size. [24] Consequently, this factor may include these lesions in the criteria for performing ESD, although this may occur because they are falsely indicated as being smaller than their actual size. Furthermore, this region of the stomach has denser mucosal folds, and the gastric wall is thinner, so lesions of the same size, but located in the upper region, will exhibit greater invasion of the vertical layers (in contrast to lesions located in the lower region, where the layers are thicker). [38,39] It's also worth noting that the treatment of lesions located in the upper third of the stomach is more difficult and it is associated with a higher number of complications. [39]

Most published studies focus on upgrading contributing to discrepancy. However, studies analysing factors contributing to downgrading identified lesion size smaller than 10 mm and age younger than 60 years as factors that may enhance the occurrence of downgrading. [31] Additionally, in the literature, the hypothesis was raised that downgrading may occur because

lesion parts were removed by pre-ESD biopsy and were not present at the time of ESD, or due to the possibility of overestimation of histological type in the biopsy. [33] However, the logistic regression analysis in this study did not individually analyse the upgrading and downgrading groups, instead analysing the discordant group. Moreover, it should be noted that the sample size in the downgrading subgroup (6.6%) is very small compared to the upgrading subgroup (93.4%) in the discordant group, so it would be important to have greater homogeneity between the samples of these groups to perform this analysis.

This study included the analysis of both pre-neoplastic and neoplastic lesions, with the pathological results of the ESD specimens identifying dysplasia and adenocarcinoma in 69.0% and 31.0% of cases, respectively. The number of adenocarcinomas analysed was reduced compared to other studies. Variables such as histological grade, depth of neoplastic extension, and lymphovascular and neural invasion only apply to adenocarcinomas. Therefore, the small number of adenocarcinomas analysed in this study may be one of the reasons why these variables were not statistically significant as risk factors for discrepancy. It may then be important to expand the sample amount with the aim of increasing the number of adenocarcinoma cases and thus better studying these variables. Furthermore, regarding histological grade, signet ring cells were removed from the logistic regression analysis because all of them fitted into the discordant group, making it impossible to analyse their impact on discrepancy. This may have introduced selection bias.

Also, other studies that analysed the impact of histological grade on discrepancy evaluated this variable in the pre- and post-ESD samples. They found that over 97% of cases of differentiated adenocarcinoma (pre-ESD) showed concordance with the post-ESD result, whereas lesions classified as undifferentiated adenocarcinoma (pre-ESD) had approximately 83% concordance with post-ESD histology. It was also observed that cases in the undifferentiated group had deeper vertical neoplastic extension and were associated with a higher number of cases of lymphovascular invasion. [24,33] Additionally, it's noted that the presence of lesions with more than one histological grade simultaneously was indicative of higher discrepancy. [33] It should be emphasized that our study only assessed histological grade in post-ESD lesions because this variable was not always included in the histopathological reports of pre-ESD biopsies, which could be an aspect for improvement in future studies.

The pre-malignant conditions analysed (atrophy and intestinal metaplasia) were not considered statistically significant risk factors for discrepancy. However, it's important to note that, since they are pre-malignant conditions, they are involved in the Correa cascade and may eventually progress to gastric cancer. This means that they may not influence discrepancy between pre and post-ESD, but they increase the risk of gastric cancer.

Gastric lesion biopsy is the preferred method for early identification of dysplastic and adenocarcinoma lesions. For a biopsy to be considered of good quality, it needs to be precise and targeted towards visible lesions on endoscopy because blind or non-directed biopsies can contribute to discrepancy. The use of narrow-band imaging (NBI) during endoscopy before biopsy is a technical support that enhances biopsy quality by better targeting the biopsy to the lesion, allowing for more precise biopsies. [39] Furthermore, sampling error can contribute to discrepancy since the lesion may have hidden focal neoplastic cells that are not biopsied, rendering the biopsy non-representative of the entire lesion. [31,32,39] Additionally, it should be noted that the histopathological analysis of biopsies involves examining various fragments of a lesion (which may not be representative of the whole lesion and its more advanced histological grade), as opposed

to the *en bloc* analysis of ESD specimens, the latter allowing an accurate histological examination because the lesion is analysed as a whole in the dissected specimen. Therefore, the fact that biopsies provide small and non-representative samples of the entire lesion may contribute to discrepancy. [33,38,39] Biopsy induces some degree of tissue inflammation, which acts as an artefact and may impair histopathological analysis. [31,32] It is important to note that if a lesion exhibits characteristics suggestive of being a candidate for endoscopic resection, care should be taken to perform few biopsies. This is because biopsies cause some degree of inflammation and fibrosis at the site from which they are taken, altering the lesion's characteristics, and complicating its approach by endoscopic resection techniques. [31,32]

As it has been observed that pre-neoplastic lesions (dysplasia) in the pre-ESD biopsy can exhibit upgrading and be identified as adenocarcinoma in the ESD specimen, it is important to correctly address them to prevent progression to lesions with worse prognosis. Therefore, the MAPS II guidelines propose ESD for visible dysplastic lesions on endoscopy to prevent progression to adenocarcinoma. They also recommend close surveillance with experienced endoscopist, high-quality devices, white light evaluation and NBI for dysplastic samples detected in the pre-ESD biopsy but not visible endoscopically. [6,31]

Studying the factors that affect discrepancy is of great importance because it is one of the aspects contributing to the non-curative outcome of ESD. In this study, it was shown that the discordant group had an 8 fold higher risk of non-curative outcome of ESD ($p<0.001$). It should be noted that the discordant group is predominantly (over 90%) composed of individuals from the upgraded subgroup. Therefore, these results may be biased because if the discordant group were equally composed of individuals from both the upgrading and downgrading subgroups, the curative outcomes could be different.

Despite large-sized lesions, located in the upper third of the stomach, with ulceration may have led to an increase in discrepancy, it does not necessarily mean they have resulted in a worse prognosis, particularly with non-curative outcomes of ESD. In other words, it cannot be concluded that each factor contributing to discrepancy, by itself, leads to a non-curative outcome, although discrepancy is a risk factor for non-curative outcomes of ESD.

Strengths and limitations

This study's strengths included the inclusion of a reasonable number of cases (over 300 lesions) and being conducted in a tertiary centre with experience in performing ESD, with this procedure being carried out by only 2 specialized endoscopists in this field.

As negative aspects include the fact that it is a single-centre study, and despite having a significant number of patients, it is limited compared to multicentred studies, suggesting that increasing the sample size would be beneficial, and proposing the possibility of a subsequent national multicentred study.

As mentioned earlier, the fact that pre-ESD biopsies are performed at various locations without well-established criteria for their analysis is also a limitation.

Furthermore, the way lesions were grouped into categories for statistical analysis may have introduced a heterogeneity bias. For example, in the case of the variable of surface morphological pattern, more than one pattern was included in each group. This difference may be even more evident in mixed groups, where lesions with very different characteristics were included.

Another limitation of this study is the disparity among the number of cases in each group, with the discordant group predominantly consisting of upgrading cases, which may distort the

analysis. The same applies to the number of lesions analysed by each pathologist, among other factors.

Future directions

It is important to identify the risk factors that may be at the root of the discrepancy between pre- and post-ESD results, with the aim of improving lesion assessment prior to ESD. Pre-ESD analysis can be enhanced by paying attention to the characteristics identified by this study as factors of discrepancy, particularly upgrading, being more vigilant with lesions exhibiting these characteristics, and relying on evaluation by an experienced endoscopist, with quality equipment, under white light and NBI. Furthermore, it is important to perform biopsies directed at the site of potential higher histological grade, aiming to obtain a biopsy with greater representativeness of the sample.

It should be noted that gastroenterology is currently a rapidly growing medical specialty, allowing for increasingly complex diagnostic and therapeutic endoscopic procedures. Therefore, it is important to correctly select patients undergoing these procedures, especially because Portugal has an intermediate prevalence of gastric cancer.

Furthermore, the proper selection of patients proposed for ESD can impact the curative outcome of the procedure. As such, considering the discrepancy and possibility of histological upgrade in these patients, they may be allocated priority for ESD procedures. Therefore, more studies, particularly large-scale multicentred studies, are essential to better identify the factors of discrepancy and understand the true impact of each one.

CONCLUSIONS

The analysis of lesions is a continuum, involving various factors such as size, morphological surface classification, location in the stomach, presence of ulceration, histological type, degree of differentiation, lymphovascular and neural invasion, among others. In other words, for its analysis, not just one factor is considered, but rather the combination of several factors, and endoscopic characteristics should be evaluated in conjunction with histological biopsy findings to assess the lesions more accurately.

According to this study, large-sized lesions, specifically those larger than 20 mm, located in the upper third of the stomach, with ulceration were considered by this study and by others previously published in the literature as factors associated with greater discrepancy. This study also identified the morphological pattern of mixed elevated type as a risk factor for discrepancy, despite being slightly different from that proposed in the literature.

TABLES

Table I – *Clinicopathologic characteristics of patients and lesions undergoing ESD.*

Variable	Total
Number of cases, n (%)	319 (100.0%)
Caracteristics of patients	
Gender, n (%)	
Male	203 (63.6%)
Female	116 (36.4%)
Age (years)	
Mean (±SD)	68.7 (±9.2)
Median (P25-P75)	69.0 (63.0-75.0)
Age, n (%)	
<70 years	163 (51.1%)
≥70 years	156 (48.9%)
Hypertension, n (%)	
Absent	139 (43.6%)
Present	180 (56.4%)
Diabetes mellitus, n (%)	
Absent	233 (73.0%)
Present	86 (27.0%)
Ischemic heart disease, n (%)	
Absent	292 (91.5%)
Present	27 (8.5%)
Cerebrovascular disease, n (%)	
Absent	306 (95.9%)
Present	13 (4.1%)
Lung disease, n (%)	
Absent	300 (94.0%)
Present	19 (6.0%)
Chronic kidney disease, n (%)	
Absent	305 (95.6%)
Present	14 (4.4%)
Liver cirrhosis, n (%)	
Absent	309 (96.9%)
Present	10 (3.1%)
Personal history of malignant neoplasms, n (%)	
Absent	269 (84.3%)
Present	50 (15.7%)
Family history of gastric cancer, n (%)	
Absent	241 (75.5%)
Present	78 (24.5%)
Family history of non-gastric GI cancer, n (%)	
Absent	263 (82.4%)
Present	56 (17.6%)
Caracteristics of lesions	
Location – Transversal Plane, n (%)	
Upper	10 (3.1%)
Middle	104 (32.6%)
Lower	205 (64.3%)
Location – Longitudinal Plane, n (%)	
Anterior wall	65 (20.4%)
Posterior wall	41 (12.9%)
Lesser curvature	125 (39.2%)

Greater curvature	88 (27.6%)
Size (mm)	
Mean (±SD)	22.0 (±13.9)
Median (P25-P75)	18.0 (12.0-27.0)
Size, n (%)	
≤20 mm	182 (57.1%)
>20 mm	137 (42.9%)
≤30 mm	263 (82.4%)
>30 mm	56 (17.6%)
Morphological pattern, n (%)	
Elevated	147 (46.1%)
Flat	10 (3.1%)
Depressed	12 (3.8%)
Mixed elevated	142 (44.5%)
Mixed flat	2 (0.6%)
Mixed depressed	6 (1.9%)
Pre-malignant conditions	
Atrophic gastritis, n (%)	
Absent	234 (73.4%)
Present	85 (26.6%)
Intestinal metaplasia, n (%)	
Absent	166 (52.0%)
Present	153 (48.0%)
***Hp* infection, n (%)**	
Absent	134 (42.0%)
Present	36 (11.3%)
Eradicated	55 (17.2%)
Unknown	94 (29.5%)
Fibrosis, n (%)	
Absent	251 (78.7%)
Present	68 (21.3%)
Ulceration, n (%)	
Absent	270 (84.6%)
Present	49 (15.4%)
Pre-ESD histological type, n (%)	
Low-grade dysplasia	218 (68.3%)
High-grade dysplasia	80 (25.1%)
Adenocarcinoma	21 (6.6%)
Post-ESD histological type, n (%)	
Low-grade dysplasia	146 (45.8%)
High-grade dysplasia	74 (23.2%)
Adenocarcinoma	99 (31.0%)
Differentiation - Histological grade, n (%)	
Well to moderate differentiated	87 (87.9%)
Poorly differentiated	8 (8.1%)
Signet ring cell	4 (4.0%)
Neoplastic extension in depth, n (%)	
Lamina propria	52 (52.5%)
Muscularis mucosae	18 (18.2%)
Superficial submucosal invasion	8 (8.1%)
Deep submucosal invasion	21 (21.2%)
Lymphovascular and neural invasion, n (%)	
Absent	83 (83.8%)
Present	16 (16.2%)

Caracteristics of ESD and anatomopathological analysis	
Endoscopist, n (%)	
Endoscopist 1	237 (74.3%)
Endoscopist 2	82 (25.7%)
Pathologist, n (%)	
Pathologist A	112 (35.1%)
Pathologist B	198 (62.1%)
Others	9 (2.8%)
Operators change, n (%)	
Absent	315 (98.7%)
Present	4 (1.3%)
ESD time (min)	
Mean (±SD)	77.0 (±66.6)
Median (P25-P75)	56.0 (35.0-98.0)
ESD time, n (%)	
≤60 min	173 (54.2%)
>60 min	146 (45.8%)
ESD technique, n (%)	
Standard	279 (87.5%)
Pocket	5 (1.6%)
Tunnel	20 (6.3%)
Underwater	15 (4.7%)
Knifes, n (%)	
Dual Knife	110 (34.5%)
Flush Knife	93 (29.2%)
Gold Knife	17 (5.3%)
MFK	2 (0.6%)
Insulated Tip + Dual	76 (23.8%)
Flush + Insulated Tip	5 (1.6%)
Needle + Insulated Tip	14 (4.4%)
Gold + Micro + Dual	2 (0.6%)
Outcomes	
Discrepancy, n (%)	
Concordant	183 (57.4%)
Upgrade	127 (39.8%)
Downgrade	9 (2.8%)
Curative outcome of ESD, n (%)	
Healed	289 (90.6%)
Not healed	39 (9.4%)

Table II – *Comparison of the anatomopathological result pre- and post-ESD.*

Pre-ESD	Post-ESD				
	Low-grade dysplasia	High-grade dysplasia	Adenocarcinoma	*P-value*	Kappa
Low-grade dysplasia, n (%)	137 (62.8%)	49 (22.5%)	32 (14.7%)		
High-grade dysplasia, n (%)	9 (11.3%)	25 (31.3%)	46 (57.5%)	**<0.001**	0.3
Adenocarcinoma, n (%)	0 (0.0%)	0 (0.0%)	21 (100.0%)		

Table III – *Characterization of the concordant and discordant groups.*

Discrepancy	Concordant group, n (%)	Discordant group		
		Upgraded group, n (%)	Downgraded group, n (%)	*P-value*
No	183 (100.0%)	0 (0.0%)	0 (0.0%)	**<0.001**
Yes	0 (0.0%)	127 (93.4%)	9 (6.6%)	

Table IV – *Characterization of the magnitude of variation in anatomopathological results pre- and post-ESD between the concordant and discordant groups.*

Variation		Concordant group, n (%)	Discordant group		
Pre-ESD	Post-ESD		Upgraded group, n (%)	Downgraded group, n (%)	*P-value*
LGD	LGD	137 (74.9%)			
HGH	HGD	25 (13.7%)			
ADC	ADC	21 (11.5%)			
LGD	HGD		49 (38.6%)		**<0.001**
HGD	ADC		46 (36.2%)		
LGD	ADC		32 (25.2%)		
HGD	LGD			9 (100.0%)	
ADC	HGD			0 (0.0%)	
ADC	LGD			0 (0.0%)	

Table V – *Clinical and pathological characteristics of patients and lesions undergoing ESD associated with histological discrepancy.*

Variable	Concordant group	Discordant group		
		Upgraded group	Downgraded group	*P-value*
Caracteristics of patients				
Gender, n (%)				0.475
Male	118 (58.1%)	81 (39.9%)	4 (2.0%)	
Female	65 (56.0%)	46 (39.7%)	5 (4.3%)	
Age (years)				0.379
Mean (±SD)	68.1 (±9.6)	69.4 (±8.8)	70.9 (±8.6)	
Median (P25-P75)	70.0 (63.0-76.0)	69.0 (64.0-75.0)	69.0 (62.5-77.5)	
Age, n (%)				0.846
<70 years	91 (55.8%)	67 (41.1.%)	5 (3.1%)	
≥70 years	92 (59.0%)	60 (38.5%)	4 (2.6%)	
Hypertension, n (%)				0.953
Absent	81 (58.3%)	54 (38.8%)	4 (2.9%)	
Present	102 (56.7%)	73 (40.6%)	5 (2.8%)	
Diabetes mellitus, n (%)				0.879
Absent	135 (57.9%)	92 (39.5%)	6 (2.6%)	
Present	48 (55.8%)	35 (40.7%)	3 (3.5%)	
Ischemic heart disease, n (%)				0.310
Absent	170 (58.2%)	113 (38.7%)	9 (3.1%)	
Present	13 (48.1%)	14 (51.9%)	0 (0.0%)	
Cerebrovascular disease, n (%)				0.609
Absent	174 (56.9%)	123 (40.2%)	9 (2.9%)	
Present	9 (69.2%)	4 (30.8%)	0 (0.0%)	
Lung disease, n (%)				0.416
Absent	174 (58.0%)	117 (39.0%)	9 (3.0%)	
Present	9 (47.4%)	10 (52.6%)	0 (0.0%)	
Chronic kidney disease, n (%)				**0.045**
Absent	179 (58.7%)	117 (38.4%)	9 (3.0%)	
Present	4 (28.6%)	10 (71.4%)	0 (0.0%)	
Liver cirrhosis, n (%)				0.085
Absent	174 (56.3%)	126 (40.8%)	9 (2.9%)	
Present	9 (90.0%)	1 (10.0%)	0 (0.0%)	
Personal history of malignant neoplasms, n (%)				0.786
Absent	156 (58.0%)	106 (39.4%)	7 (2.6%)	
Present	27 (54.0%)	21 (42.0%)	2 (4.0%)	
Family history of gastric cancer, n (%)				0.633
Absent	137 (56.8%)	96 (39.8%)	8 (3.3%)	
Present	46 (59.0%)	31 (39.7%)	1 (1.3%)	
Family history of non-gastric GI cancer, n (%)				0.449
Absent	152 (57.8%)	105 (39.9%)	6 (2.3%)	
Present	31 (55.4%)	22 (39.3%)	3 (5.4%)	
Caracteristics of lesions				
Location – Transversal Plane, n (%)				0.081
Upper	2 (20.0%)	8 (80.0%)	0 (0.0%)	
Middle	58 (55.8%)	44 (42.3%)	2 (1.9%)	
Lower	123 (60.0%)	75 (36.6%)	7 (3.4%)	
Location – Longitudinal Plane, n (%)				0.447
Anterior wall	41 (63.1%)	23 (35.4%)	1 (1.5%)	

Posterior wall	25 (61.0%)	14 (34.1%)	2 (4.9%)	
Lesser curvature	63 (50.4%)	59 (47.2%)	3 (2.4%)	
Greater curvature	54 (61.4%)	31 (35.2%)	3 (3.4%)	
Size (mm)				**<0.001**
Mean (±SD)	18.0 (±9.7)	28.0 (±17.0)	17.2 (±7.5)	
Median (P25-P75)	15.0 (12.0-22.0)	24.0 (15.0-36.0)	15.0 (10.5-22.0)	
Size, n (%)				**<0.001**
≤20 mm	125 (68.7%)	52 (28.6%)	5 (2.7%)	
>20 mm	58 (42.3%)	75 (54.7%)	4 (2.9%)	
≤30 mm	167 (63.5%)	88 (33.5%)	8 (3.0%)	
>30 mm	16 (28.6%)	39 (69.6%)	1 (1.8%)	
Morphological pattern, n (%)				**0.016**
Elevated	98 (66.7%)	43 (29.3%)	6 (4.1%)	
Flat	9 (90.0%)	1 (10.0%)	0 (0.0%)	
Depressed	7 (58.3%)	5 (41.7%)	0 (0.0%)	
Mixed elevated	64 (45.1%)	76 (53.5%)	2 (1.4%)	
Mixed flat	1 (50.0%)	1 (50.0%)	0 (0.0%)	
Mixed depressed	4 (66.7%)	1 (16.7%)	1 (16.7%)	
Pre-malignant conditions				
Atrophic gastritis, n (%)				0.407
Absent	139 (59.4%)	88 (37.6%)	7 (3.0%)	
Present	44 (51.8%)	39 (45.9%)	2 (2.4%)	
Intestinal metaplasia, n (%)				0.953
Absent	94 (56.6%)	67 (40.4%)	5 (3.0%)	
Present	89 (58.2%)	60 (39.2%)	4 (2.6%)	
***Hp* infection, n (%)**				0.314
Absent	75 (56.0%)	55 (41.0%)	4 (3.0%)	
Present	24 (66.7%)	10 (27.8%)	2 (5.6%)	
Eradicated	36 (65.5%)	19 (34.5%)	0 (0.0%)	
Unknown	48 (51.1%)	43 (45.7%)	3 (3.2%)	
Fibrosis, n (%)				0.144
Absent	147 (58.6%)	95 (37.8%)	9 (3.6%)	
Present	36 (52.9%)	32 (47.1%)	0 (0.0%)	
Ulceration, n (%)				**<0.001**
Absent	169 (62.6%)	93 (34.4%)	8 (3.0%)	
Present	14 (28.6%)	34 (69.4%)	1 (2.0%)	
Differentiation - Histological grade, n (%)				0.065
Well to moderate differentiated	17 (19.5%)	70 (80.5%)	0 (0.0%)	
Poorly differentiated	4 (50.0%)	4 (50.0%)	0 (0.0%)	
Signet ring cell	0 (0.0%)	4 (100.0%)	0 (0.0%)	
Neoplastic extension in depth, n (%)				0.964
Lamina propria	11 (21.2%)	41 (78.8%)	0 (0.0%)	
Muscularis mucosae	3 (16.7%)	15 (83.3%)	0 (0.0%)	
Superficial submucosal invasion	2 (25.0%)	6 (75.0%)	0 (0.0%)	
Deep submucosal invasion	5 (23.8%)	16 (76.2%)	0 (0.0%)	
Lymphovascular and neural invasion, n (%)				0.741
Absent	17 (20.5%)	66 (79.5%)	0 (0.0%)	
Present	4 (25.0%)	12 (75.0%)	0 (0.0%)	
Caracteristics of ESD and anatomopathological analysis				
Endoscopist, n (%)				0.870
Endoscopist 1	134 (56.5%)	96 (40.5%)	7 (3.0%)	
Endoscopist 2	49 (59.8%)	31 (37.8%)	2 (2.4%)	
Pathologist, n (%)				**0.009**
Pathologist A	55 (49.1%)	56 (50.0%)	1 (0.9%)	

Pathologist B	125 (63.1%)	66 (33.3%)	7 (3.5%)	
Operators change, n (%)				1.000
Absent	181 (57.5%)	125 (39.7%)	9 (2.9%)	
Present	2 (50.0%)	2 (50.0%)	0 (0.0%)	
ESD time (min)				**0.002**
Mean (±SD)	67.0 (±57.7)	93.1 (±76.2)	52.4 (±47.6)	
Median (P25-P75)	48.0 (30.0-90.0)	70.0 (44.0-120.0)	40.0 (24.0-67.0)	
ESD time, n (%)				**<0.001**
≤60 min	117 (67.6%)	49 (28.3%)	7 (4.0%)	
>60 min	66 (45.2%)	78 (53.4%)	2 (1.4%)	
Outcomes				
Curative outcome of ESD, n (%)				**<0.001**
Healed	178 (61.6%)	102 (35.3%)	9 (3.1%)	
Not healed	5 (16.7%)	25 (83.3%)	0 (0.0%)	

Table VI – *Logistic regression analysis of risk factors for histological discrepancy.*

Variable	Crude OR		*P*-value	Adjusted OR		*P*-value
	OR	95% CI		OR	95% CI	
Caracteristics of patients						
Gender - Female (vs Male)	1.1	0.7-1.7	0.716			
Age ≥70 years	0.9	0.6-1.4	0.570			
Comorbidities						
Hypertension	1.1	0.7-1.7	0.774			
Diabetes mellitus	1.1	0.7-1.8	0.733			
Ischemic heart disease	1.5	0.7-3.3	0.314			
Cerebrovascular disease	0.6	0.2-1.9	0.382			
Lung disease	1.5	0.6-3.9	0.367			
Chronic kidney disease	3.6	1.1-11.6	**0.036**	2.0	0.6-7.4	0.278
Liver cirrhosis	0.1	0.0-1.1	0.067			
Personal and family history of neoplasms						
Personal history of malignant neoplasms	1.2	0.6-2.2	0.600			
Family history of gastric cancer	0.9	0.5-1.5	0.741			
Family history of non-gastric GI cancer	1.1	0.6-2.0	0.738			
Caracteristics of lesions						
Location – Transversal Plane						
Upper	6.0	1.2-29.0	**0.026**	4.3	0.7-24.6	0.103
Middle	1.2	0.7-1.9	0.476			
Lower	1.0		0.074			
Location – Longitudinal Plane						
Anterior wall	1.0		0.249			
Posterior wall	1.1	0.5-2.4	0.828			
Lesser curvature	1.7	0.9-3.1	0.097			
Greater curvature	1.1	0.6-2.1	0.829			
Size						
Size >20 mm	3.0	1.9-4.7	**<0.001**	2.1	1.1-3.9	**0.021**
Size >30 mm	4.3	2.3-8.2	**<0.001**	1.9	0.8-4.5	0.119
Morphological pattern						
Elevated	1.0		**0.004**			
Flat	0.2	0.0-1.8	0.159			
Depressed	1.4	0.4-4.7	0.559			
Mixed elevated	2.4	1.5-3.9	**<0.001**	1.8	1.1-3.2	**0.031**
Mixed flat	2.0	0.1-32.7	0.627			
Mixed depressed	1.0	0.2-5.7	1.000			
Pre-malignant conditions						
Atrophic gastritis	1.4	0.8-2.2	0.223			
Intestinal metaplasia	0.9	0.6-1.5	0.781			
***Hp* infection**						
Absent	1.0		0.227			
Present	0.6	0.3-1.4	0.250			
Eradicated	0.7	0.4-1.3	0.230			
Unknown	1.2	0.7-2.1	0.465			
Fibrosis	1.3	0.7-2.2	0.406			

Ulceration	4.2	2.1-8.2	**<0.001**	3.7	1.8-7.7	**0.001**
Differentiation - Histological grade						
Well to moderate differentiated	1.0					
Poorly differentiated	0.2	0.1-1.1	0.062			
Neoplastic extension in depth						
Lamina propria	1.0		0.946			
Muscularis mucosae	1.3	0.3-5.5	0.682			
Superficial submucosal invasion	0.8	0.1-4.6	0.806			
Deep submucosal invasion	0.9	0.3-2.9	0.804			
Lymphovascular and neural invasion	0.8	0.2-2.7	0.686			
Caracteristics of ESD and anatomopathological analysis						
Endoscopist						
Endoscopist 2	0.9	0.5-1.5	0.612			
Pathologist						
Pathologist A	1.8	1.1-2.8	**0.017**	1.6	0.9-2.7	0.120
Operators change	1.4	0.2-9.7	0.765			
ESD time						
Time >60 min	2.5	1.6-4.0	**<0.001**	1.2	0.7-2.2	0.466

Table VII – *Logistic regression analysis of the impact of discrepancy on the non-curative outcome of ESD.*

Variable	Crude OR		*P*-value
	OR	95% CI	
Discrepancy			
Discordant group	8.0	3.0-21.6	**<0.001**

Table VIII – *Curative outcome of ESD in the upgraded group.*

Variable	Healed	Not healed	*P*-value
Cases of upgraded group, n (%)	102 (80.3%)	25 (19.7%)	
Caracteristics of patients			
Chronic kidney disease, n (%)			0.685
Absent	93 (79.5%)	24 (20.5%)	
Present	9 (90.0%)	1 (10.0%)	
Caracteristics of lesions			
Size (mm)			0.962
Mean (±SD)	28.0 (±16.7)	28.2 (±18.5)	
Median (P25-P75)	24.0 (15.8-35.3)	23.0 (14.5-38.0)	
Size, n (%)			
≤20 mm	44 (84.6%)	8 (15.4%)	0.310
>20 mm	58 (77.3%)	17 (22.7%)	
≤30 mm	71 (80.7%)	17 (19.3%)	0.876
>30 mm	31 (79.5%)	8 (20.5%)	
Morphological pattern, n (%)			0.590
Elevated	38 (88.4%)	5 (11.6%)	
Flat	1 (100.0%)	0 (0.0%)	
Depressed	4 (80.0%)	1 (20.0%)	
Mixed elevated	57 (75.0%)	19 (25.0%)	
Mixed flat	1 (100.0%)	0 (0.0%)	
Mixed depressed	1 (100.0%)	0 (0.0%)	
Ulceration, n (%)			0.245
Absent	77 (82.8%)	16 (17.2%)	
Present	25 (73.5%)	9 (26.5%)	
Caracteristics of ESD and anatomopathological analysis			
Pathologist, n (%)			**0.014**
Pathologist A	50 (89.3%)	6 (10.7%)	
Pathologist B	47 (71.2%)	19 (28.8%)	
ESD time (min)			0.061
Mean (±SD)	86.9 (±73.3)	118.0 (±83.7)	
Median (P25-P75)	70.0 (40.0-107.8)	88.0 (61.0-152.5)	
ESD time, n (%)			
≤60 min	43 (87.8%)	6 (12.2%)	0.095
>60 min	59 (75.6%)	19 (24.4%)	

Table IX – *Logistic regression analysis of the curative outcome of ESD in the upgraded group.*

Variable	Crude OR		*P*-value
	OR	95% CI	
Caracteristics of patients			
Comorbidities			
Chronic kidney disease	0.4	0.1-3.6	0.435
Caracteristics of lesions			
Size			
Size >20 mm	1.6	0.6-4.1	0.313
Size >30 mm	1.1	0.4-2.8	0.876
Morphological pattern			
Elevated	1.0		0.713
Flat	0.0	0.0	1.000
Depressed	1.9	0.2-20.6	0.597
Mixed elevated	2.5	0.9-7.4	0.088
Mixed flat	0.0	0.0	1.000
Mixed depressed	0.0	0.0	1.000
Ulceration	1.7	0.7-4.4	0.248
Caracteristics of ESD and anatomopathological analysis			
Pathologist			
Pathologist A	0.3	0.1-0.8	**0.017**
ESD time			
Time >60 min	2.3	0.9-6.3	0.101

Table X – *Injury size associated with anatomopathological discrepancy.*

Size, n (%)	Concordant group	Discordant group	*P-value*
≤20 mm	125 (68.7%)	57 (31.3%)	**<0.001**
>20 mm	58 (42.3%)	79 (57.7%)	
≤30 mm	167 (63.5%)	96 (36.5%)	
>30 mm	16 (28.6%)	40 (71.4%)	

Table XI – *Impact of lesion size on the proportion of concordant cases.*

Size	Proportion	*P-value*
>20 mm	0.4	0.074
>30 mm	0.3	

Table XII – *Impact of lesion size on anatomopathological discrepancy.*

	Concordant group	Discordant group	*P-value*
Mean (mm)	18.0	27.3	**<0.001**
Median (mm)	15.0	22.0	

Table XIII – *Analysis of sizes by percentile in the concordant and discordant groups.*

	Percentiles - Size																		
	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95
Concordant group (mm)	8	9	10	11	12	12	12	14	14	15	16	17	20	21	22	25	27	30	35
Discordant group (mm)	9.9	11.0	12.0	15.0	15.0	17.0	18.0	20.0	22.0	22.0	25.0	25.2	30.0	30.0	34.5	39.2	45.0	51.5	68.3

Table XIV – *ROC Curve analysis to predict the impact of lesion size on the discrepancy of pre- and post-ESD anatomopathological results.*

	Size			Size			Size		
	20 mm	95% CI	*P-value*	21 mm	95% CI	*P-value*	30 mm	95% CI	*P-value*
Sensitivity	0.581			0.559			0.294		
Specificity	0.683			0.710			0.913		
Area under the curve	0.632	0.6-0.7	**<0.001**	0.635	0.6-0.7	**<0.001**	0.603	0.5-0.7	**0.002**

FIGURES

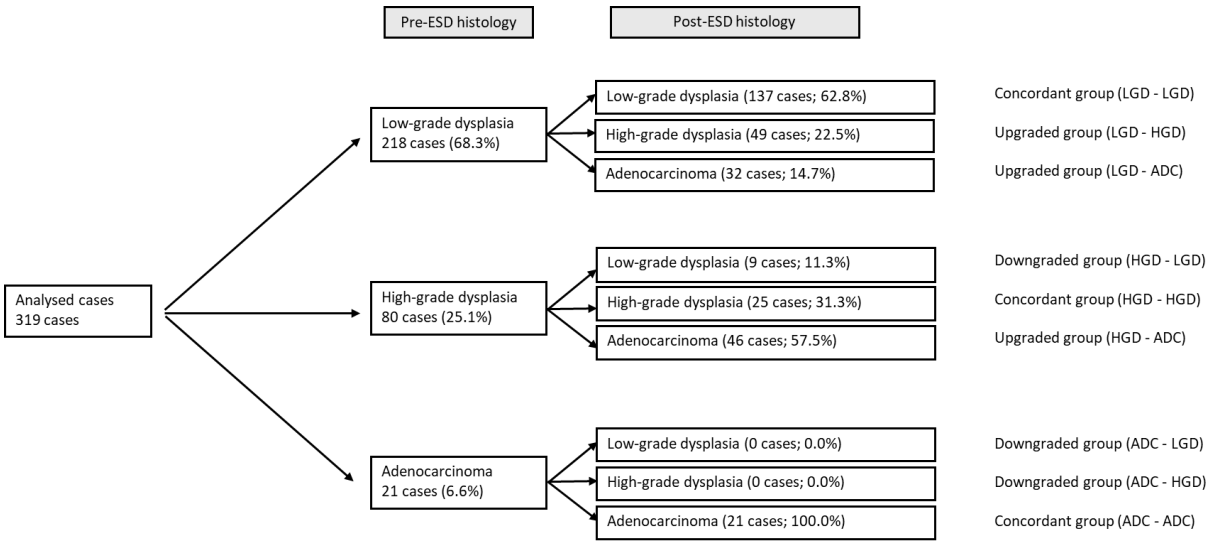

Figure 1 – *Flowchart illustrating histological discrepancy and concordance between pre- and post-ESD.*

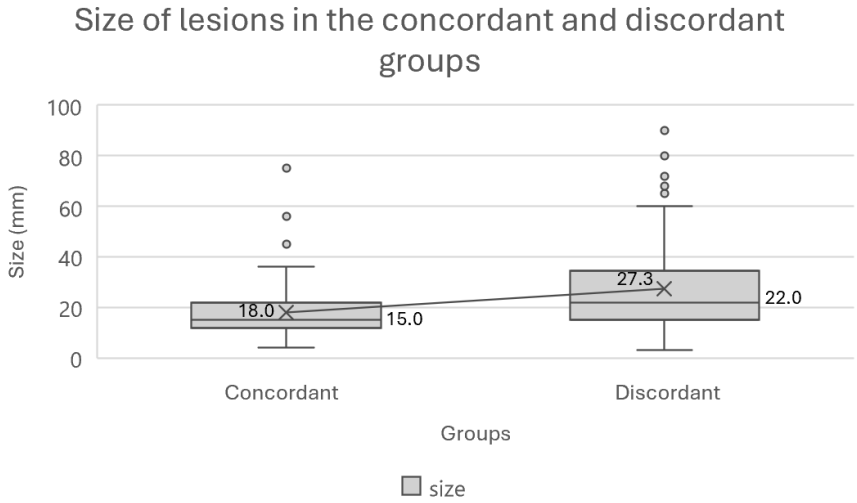

Figure 2 – *Boxplot displaying the dispersion of lesion sizes in the concordant and discordant groups.*

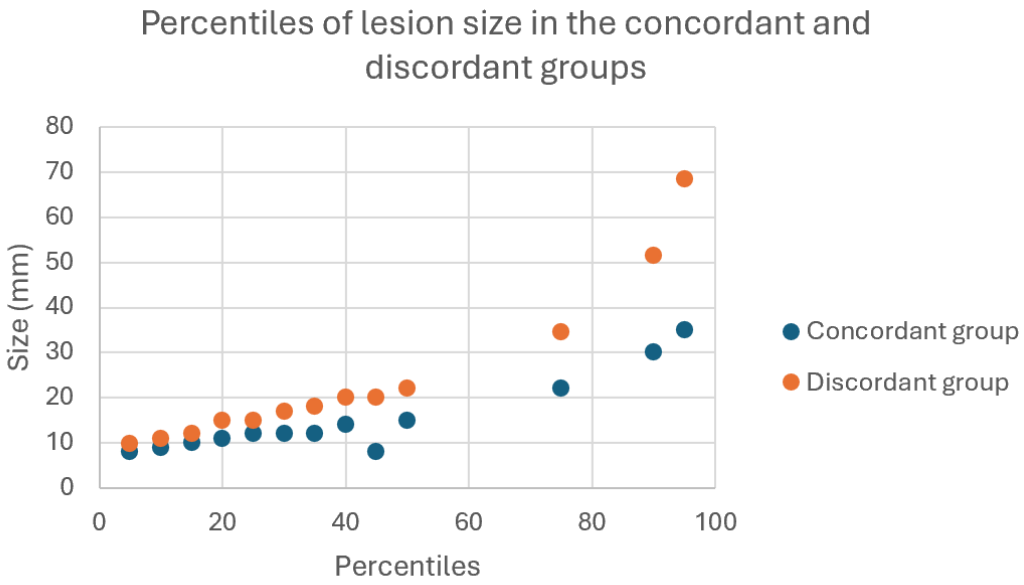

Figure 3 – *Distribution of percentiles of lesion size in the concordant and discordant groups.*

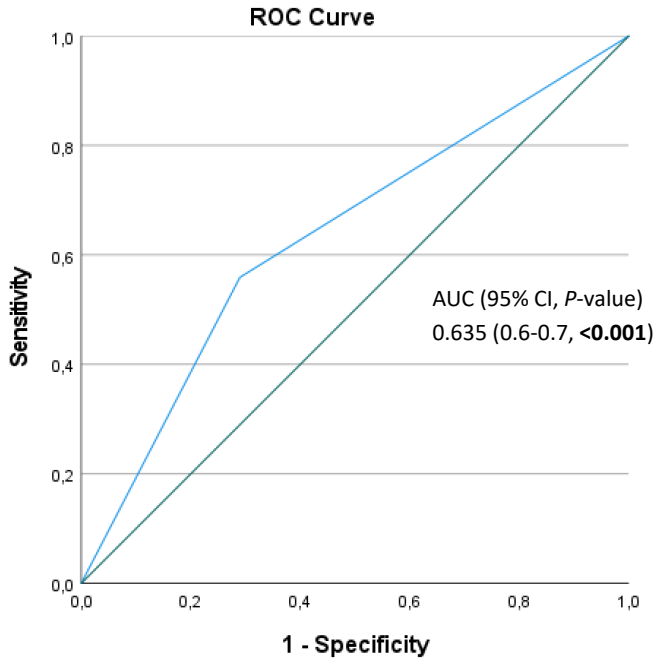

Figure 4 – *ROC curve analysis of the cut-off of 21 mm lesion size on the discrepancy of pre- and post-ESD histopathological results.*

APPENDIX

REPÚBLICA PORTUGUESA SAÚDE | SNS SERVIÇO NACIONAL DE SAÚDE | santo antónio CENTRO HOSPITALAR UNIVERSITÁRIO DE SANTO ANTÓNIO

Exma. Sra. Cláudia Sofia Alves
Estudante do ICBAS

ASSUNTO: Trabalho Académico - MIM - **"Anatomopathological Agreement Between Pre- and Post-Endoscopic Submucosal Dissection in Early Gastric Cancer - an Observational Retrospective Study"** - N/ REF.ª 2023.237(200-DEFI/189-CE)

O Conselho de Administração do Santo António, na reunião de 10 de janeiro de 2024, emitiu a seguinte Deliberação: "Autorizado" para a realização do estudo acima mencionado, a realizar no Serviço de Gastrenterologia desta Instituição e tendo como Investigador Principal Cláudia Sofia Alves, estudante do ICBAS.
O estudo foi previamente analisado pela Comissão de Ética do Santo António |ICBAS, pelo Gabinete de Projeto de Investigação do CAC, pela Direção do Centro Académico Clínico ICBAS|CHUdSA e pelo Presidente do Conselho de Administração, tendo obtido parecer favorável.

Cumprimentos,

Assinado por: **Cláudia Alexandra Oliveira Santos**
Num. de Identificação: 11089889
Data: 2024.01.11 10:12:15+00'00'

CHAVE MÓVEL

CENTRO HOSPITALAR UNIVERSITÁRIO DE SANTO ANTÓNIO, E.P.E.
Largo Prof. Abel Salazar | 4099-001 Porto | Portugal | www.chusantoantonio.pt

ET

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COMISSÃO DE ÉTICA CHUdSA / ICBAS

APRECIAÇÃO E VOTAÇÃO DO PARECER

Deliberação	Data: 1 3 [illegible] 2023	Órgão: Reunião Plenária

Título: **"Anatomopathological Agreement Between Pre- and Post-Endoscopic Submucosal Dissection in Early Gastric Cancer – an Observational Retrospective Study"**		Ref.ª: **2023.237(200-DEFI/189-CE)**
Protocolo/Versão: **TA-MIM**	Promotor: **o(a) próprio(a)**	Investigador / Local: **Cláudia Sofia Alves** **Serviço de Gastrenterologia - CHUdSA**

A Comissão de Ética CHUdSA / ICBAS, ao abrigo do disposto no Decreto-Lei n.º 80/2018, de 15 de outubro, em reunião realizada nesta data, apreciou a fundamentação do relator sobre o pedido de parecer para a realização do **TA-MIM** acima referenciado:

Ouvido o Relator, o processo foi votado pelos Membros da Comissão de Ética CHUdSA / ICBAS presentes:

Presidente: Prof. Doutor João Nuno Melo Beirão
Vice-Presidente: Dr.ª Paulina Aguiar

Dr. Aníbal Albuquerque, Prof.ª Doutora Carla Teixeira, Doutora Cármen de Carvalho, Dr.ª Fernanda Manuela Costa, Prof. Doutor José António Pinho, Prof.ª Doutora Margarida Araújo, Prof.ª Doutora Maria Strecht, Prof.ª Doutora Susana Magalhães, Mestre Virgínio Costa Ribeiro.

Resultado da votação:

PARECER FAVORÁVEL

A deliberação foi aprovada por unanimidade.

Pelo que se submete à consideração superior.

Data 1 3 [illegible] 2023

O Presidente da Comissão de Ética CHUdSA / ICBAS

Prof. Doutor João Nuno Melo Beirão

Imp.10/2023

- Não haverá realização de estudos genéticos.
- Será efetuado um registo pseudoanonimizado dos dados recolhidos.
- São garantidas a proteção da identidade do participante e a confidencialidade dos dados recolhidos
- Foi anexada carta a solicitar dispensa de consentimento informado dirigida CE

Aspetos Financeiros:
Não aplicável.

Requisitos Preenchidos:
☑ Pedidos de autorização: Conselho de Administração do CHUP e Comissão de Ética
☑ Termo de responsabilidade do Estudante/Investigador (Cláudia Alves)
☑ Termo de responsabilidade do Orientador (Doutor Ricardo Pinto)
☑ Termo de responsabilidade do coorientador (Dra. Sara Archer)
☑ Autorização do diretor da clínica de Medicina (Dr. Severo Torres)
☑ Autorização do diretor do serviço Gastrenterologia (Doutora Isabel Pedroto)
☑ Discriminação das variáveis no processo
☑ Carta a solicitar dispensa de consentimento informado dirigida à CE
☑ Pedido de Reutilização de Registos Clínicos com listagem dos processos clínicos a consultar dirigido ao Responsável pelo Acesso à Informação (RAI)
☑ Formulário de Proteção de dados

APRECIAÇÃO e PARECER FINAL do GABINETE DE PROJETOS DE INVESTIGAÇÃO DO CAC:
A proposta de investigação *"Anatomopathological Agreement Between Pre- and Post- Endoscopic Submucosal Dissection in Early Gastric Cancer – an Observational Retrospective Study"* foi avaliada pelo Gabinete de Projetos de Investigação do CAC, não tendo suscitado dúvidas nem questões a clarificar pelo estudante/investigador. No entanto a análise suscita a seguinte observação:

Na proposta a estudante/investigadora refere que pretende colher dos processos clínicos os seguintes dados demográficos, entre outros: Nome, nº do processo, data de nascimento; idade (…).

Estes dados permitem a identificação clara do doente. Ainda que seja referido que haverá pseudoanonimização dos dados, é nosso entender que bastará colher o nº do processo para elaborar a chave de descodificação, não sendo necessário o nome. De igual forma não se vê necessidade de colher a data de nascimento e a idade do participante. A recolha simples da variável idade será suficiente e dificulta a identificação do participante a pessoas externas ao estudo.

Estritamente no que se refere à componente científica do trabalho académico de investigação, **PARECER FAVORÁVEL,** no pressuposto que serão efetuadas as alterações referidas nas observações.

No contexto científico, o Gabinete de Projetos de Investigação do CAC dá por concluída a análise do processo, sendo enviado ao Estudante/Investigador, Orientador e Ensino Médico Pré-Graduado o Parecer elaborado para conhecimento.

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