U.PORTO

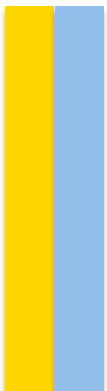
MESTRADO INTEGRADO
MEDICINA

Evaluation of Risk Factors for Metachronous Gastric Lesions Post-Endoscopic Submucosal Dissection

Maria Inês Oliveira Gomes

M

2025



Evaluation of Risk Factors for Metachronous Gastric Lesions Post-Endoscopic Submucosal Dissection

ARTIGO ORIGINAL

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Autora:
Maria Inês Oliveira Gomes
Estudante do 6º ano do Mestrado Integrado em Medicina do Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Endereço de correio eletrónico: miogomes24@gmail.com

Orientador:
Professor Doutor Ricardo Jorge Marcos Pinto
Professor Associado Convidado do Instituto de Ciências Biomédicas Abel Salazar
Assistente Hospitalar Graduado de Gastrenterologia do Hospital de Santo António (Unidade Local de Saúde de Santo António)

Endereço de correio eletrónico: ricardomarcospinto@sapo.pt

Coorientadora:
Dra. Sara Rita e Sousa de Oliveira Barreto Archer
Médica Interna de Formação Específica de Gastrenterologia no Hospital de Santo António (Unidade Local de Saúde de Santo António)

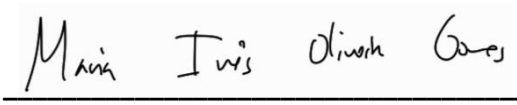
Endereço de correio eletrónico: sararcher_@hotmail.com

Porto, abril 2025

Evaluation of Risk Factors for Metachronous Gastric Lesions Post-Endoscopic Submucosal Dissection

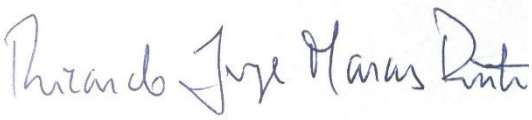
Autora:

Maria Inês Oliveira Gomes



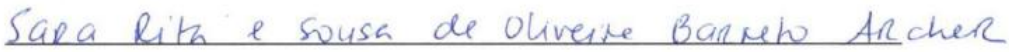
Orientador:

Professor Doutor Ricardo Jorge Marcos Pinto



Coorientadora:

Dra. Sara Rita e Sousa de Oliveira Barreto Archer



Porto, abril 2025

DEDICATION

Dedico este trabalho à minha mãe e ao meu pai, pelo amor incondicional e pelo apoio em cada passo desta caminhada, sem os quais nunca teria sido possível, e à minha irmã, pelo carinho e cumplicidade que tornam tudo mais leve.

Ao Ricardo, pelo incentivo constante, paciência e por acreditar em mim até nos momentos em que duvidei.

Ao Miguel, pelo apoio e paciência ao longo desta caminhada.

Aos meus amigos.

ACKNOWLEDGMENTS

Em primeiro lugar, ao meu orientador, Professor Doutor Ricardo Marcos Pinto, pelo compromisso e disponibilidade constantes. Agradeço não só a orientação científica, mas também a confiança depositada em mim desde o início, permitindo-me desenvolver este trabalho.

À Dra. Sara Archer, minha coorientadora.

À Professora Doutora Carolina Lemos, pelo auxílio valioso na componente estatística.

“O homem é do tamanho do seu sonho.”

Fernando Pessoa

RESUMO

Enquadramento

O cancro gástrico (GC) mantém-se como uma causa relevante de mortalidade oncológica a nível mundial, com uma necessidade crescente de estratégias de vigilância e seguimento eficientes após tratamentos minimamente invasivos como a disseção endoscópica da submucosa (ESD). A ESD é um procedimento que permite a excisão de lesões gástricas malignas precoces, sendo o procedimento eletivo recomendado pela Sociedade Europeia de Endoscopia Gastrointestinal (ESGE) para o tratamento destas. Apesar de que a ESD permite uma resseção curativa preservando a integridade gástrica, o risco de lesões metácronas (MGL) permanece uma preocupação, necessitando de protocolos de seguimento ajustados ao risco individual.

Objetivo

Este estudo tem como objetivo avaliar a ocorrência de MGL após ESD e identificar os fatores de risco associados com o desenvolvimento destas. Analisando variáveis clínicas, endoscópicas e histológicas, pretendemos melhorar e clarificar a estratificação de risco e otimizar as estratégias de seguimento e vigilância destes doentes.

Metodologia

Foi realizada uma análise retrospetiva numa coorte de 138 pacientes que foram submetidos a ESD em lesões gástricas primárias num centro de referência (ULSSA) em Portugal entre 2016 e 2024. Foram colhidos dados acerca das características demográficas, histologia das lesões, achados endoscópicos e seguimento destes doentes. Foi feita uma análise estatística que incluiu o teste exato de *Fisher*, Qui-quadrado, análise de sobrevivência de *Kaplan-Meier* e teste l*og-rank* para determinar preditores importantes de ocorrência de MGL.

Resultados

Desenvolveram-se MGL em 12,3% dos doentes ao longo de uma mediana de 27,55 meses de seguimento, com uma incidência cumulativa de 14,7% aos 5 anos. A presença de metaplasia intestinal (IM) no corpo gástrico ($p = 0,002$) e no antro ($p = 0,016$) revelaram-se fatores de risco relevantes para a ocorrência de MGL. Não foram observadas associações estatisticamente significativas no que diz respeito ao sexo, história familiar de primeiro grau de GC, status de infeção por *Helicobacter pylori (Hp)* ou características de lesões primárias.

Conclusão

A presença de IM no corpo e antro gástrico aumenta significativamente o risco de desenvolvimento de MGL, reforçando a necessidade de um seguimento individualizado dos doentes, tendo em conta o seu risco. As recomendações atuais sobre o seguimento destes doentes podem necessitar de adaptação baseada nos fatores de risco específicos de cada paciente de forma a melhorar a deteção precoce e redução de procedimentos desnecessários. Futuras pesquisas deve também explorar ferramentas com apoio de inteligência artificial (AI) e scores preditivos de risco, como o FAMISH score, para otimização de estratificação de risco e otimização de resultados a longo prazo.

Palavras-chave

Disseção endoscópica da submucosa; Resseção endoscópica, Neoplasia gástrica; Condições pré-neoplásicas; Cancro gástrico precoce; Fatores de risco; Estudos retrospetivos.

ABSTRACT

Background

Gastric cancer (GC) remains a leading cause of oncologic mortality worldwide, with an increasing need for effective surveillance strategies following minimally invasive treatments such as endoscopic submucosal dissection (ESD). ESD is a procedure that allows the excision of early malignant gastric lesions, being the elective method recommended by the European Society of Gastrointestinal Endoscopy (ESGE) for the treatment of these lesions. Although ESD allows for curative resection while preserving gastric integrity, the risk of metachronous gastric lesions (MGL) remains a major concern, necessitating tailored follow-up protocols.

Objective

This study aims to evaluate the occurrence of MGL after ESD and identify the risk factors associated with their development. By analyzing clinical, endoscopic, and histological variables, we seek to enhance risk stratification and optimize surveillance strategies.

Methods

A retrospective analysis was conducted on a cohort of 138 patients who underwent ESD for primary gastric lesions at a high-volume center (ULSSA) in Portugal between 2016 and 2024. Data on demographic characteristics, lesion histology, endoscopic findings, and follow-up outcomes were collected. Statistical analysis included Fisher's exact test, Chi-square test, Kaplan-Meier survival analysis, and log-rank tests to determine significant predictors of MGL.

Results

MGL developed in 12.3% of patients over a median follow-up of 27.55 months, with a cumulative incidence of 14.7% at five years. Intestinal metaplasia (IM) in both the gastric corpus ($p = 0.002$) and antrum ($p = 0.016$) emerged as significant risk factors for MGL occurrence. No statistically significant associations were found for sex, first-degree family history of GC, *Helicobacter pylori* (Hp) infection status or primary lesion characteristics.

Conclusion

The presence of IM in the gastric corpus and antrum significantly increases the risk of MGL, reinforcing the need for individualized surveillance protocols. Current follow-up recommendations may require adaptation based on patient-specific risk factors to improve early detection and reduce unnecessary endoscopic procedures. Future research should explore AI-driven tools and predictive scoring systems, such as the FAMISH score, to refine risk stratification and optimize long-term outcomes.

Keywords

Endoscopic submucosal dissection; Endoscopic resection; Stomach neoplasms; Precancerous conditions; Early gastric cancer; Risk factors; Retrospective studies.

LIST OF ABBREVIATIONS

ADL – Activities of Daily Living

AI – Artificial Intelligence

EBV – Epstein-Barr Virus

EMR – Endoscopic Mucosal Dissection

ESD – Endoscopic Submucosal Dissection

ESGE – European Society of Gastrointestinal Endoscopy

GC – Gastric Cancer

GEJ – Gastroesophageal Junction

HGD – High-grade Dysplasia

Hp – Helicobacter Pylori

IQR – Interquartile Range

IM – Intestinal Metaplasia

LGD – Low-grade Dysplasia

MGL – Metachronous Gastric Lesions

QoL – Quality of Life

SD – Standard Deviation

ULSSA – Unidade Local de Saúde de Santo António

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Gastric Cancer: Epidemiology and Clinical Relevance

Gastric cancer (GC) is one of the most prevalent and deadliest cancers worldwide, representing a significant challenge to healthcare systems. According to GLOBOCAN 2022, it was estimated that there were approximately 1.2 million new cases of gastric neoplasia worldwide in that year, resulting in about 1 million deaths. This makes GC one of the leading causes of cancer-related mortality, ranking as the 5th most common neoplasm (with an incidence of 6.1% in males and 3.5% in females) and also the 5th most common cause of oncologic death globally, with a mortality rate of 7.9% in males and 5.4% in females[1].

Consequently, this neoplasm is approximately twice as prevalent in males as in females, with the majority of cases occurring in individuals over the age of sixty. However, recent studies have highlighted a concerning trend of rising incidence among younger adults (under the age of fifty)[2]. The burden of GC is highest in Eastern Asia, with men in countries such as Japan, Mongolia, and the Republic of Korea experiencing the highest incidence rates globally. In contrast, the lowest incidence rates are observed in Africa[3-5].

In 2020, GC showed a notably higher incidence in the northern region of Portugal, ranking as the fourth most prevalent cancer, with 2,615 new cases (14.3 per 100,000 person-years). The districts of Braga (24.7 per 100,000 person-years), Porto (22.1 per 100,000 person-years), and Viana do Castelo (17.7 per 100,000 person-years) reported particularly high rates[4]. This may be attributed to regional dietary patterns, which include a high intake of salt and smoked foods, as well as the elevated prevalence of *Helicobacter pylori* (Hp) infection.

Despite significant advancements in oncological treatments, the survival rate among cancer patients remains low, emphasizing the crucial importance of primary and secondary prevention strategies[6].

Carcinogenesis cascade and risk factors

Approximately 95% of gastric tumors are gastric adenocarcinomas, which can be further subdivided into different primary subtypes: intestinal-type, diffuse-type and mixed histology based on *Lauren's* 1965 classification system. Among these, the intestinal-type accounts for 50% of the cases, the diffuse-type about 30% and the remaining 15-20% as mixed or indeterminate[7]. The intestinal-type GC is more frequently observed in older individuals and men. The cascade of events described in *Correa's* model is observed in the case of intestinal-type gastric carcinogenesis, which involves a sequence of well-defined histological and molecular changes. These changes begin with chronic active gastritis and progress to multifocal atrophic gastritis, intestinal metaplasia (IM), low-grade dysplasia (LGD), high-grade dysplasia (HGD), and ultimately, gastric adenocarcinoma[8].

Conversely, diffuse-type adenocarcinoma is more frequently observed in younger patients and women and does not exhibit this sequence of intermediate events. Although less prevalent, diffuse-type adenocarcinoma is associated with a worse prognosis due to its aggressive behavior and infiltrative growth pattern[9, 10]. The etiology of this type is diverse, with many factors linked to the genesis of this type of adenocarcinoma[11].

This is a complex and multifactorial process involving a sequence of several steps. Genetic susceptibility plays a critical role, as mutations in genes such as *CDH1* and *TP53* have been implicated in hereditary and sporadic forms of GC, particularly in the diffuse-type. (1). Environmental factors, such as dietary habits high in salted and smoked foods or low in fresh fruits and vegetables are also linked to an increased risk of intestinal-type GC[12].

Metabolic and epigenetic alterations also contribute significantly since abnormal DNA methylation patterns and histone modifications have been observed in pre-malignant and malignant gastric tissues, leading to the dysregulation of oncogenes and tumor suppressor genes, as well as genomic instability, that further facilitates the progression to malignancy[13].

Infectious agents, particularly *Hp*, are well-established contributors to gastric carcinogenesis. This bacterium promotes chronic inflammation, the production of virulence factors like *CagA*, and the activation of oncogenic pathways[14]. Similarly, Epstein-Barr Virus (EBV) is associated with a subset of GC cases.

Also chronic inflammation, often driven by *Hp* infection, creates a microenvironment conducive to cancer progression through sustained oxidative stress, cytokine production, and immune evasion[15].

Endoscopic treatment of primary and metachronous lesions

In light of the circumstances mentioned above, the advent of endoscopic submucosal dissection (ESD) represents a pivotal advancement in treating early gastric neoplasia. In conventional ESD, a series of steps is followed. Initially, the lesion is delineated using virtual chromoendoscopy, and coagulation marks are placed along the margin for resection. Subsequently, a colloid/crystalloid solution and dye are injected into the submucosa, followed by meticulous submucosal dissection beneath the mucosa with its subsequent retrieval, culminating in an assessment and treatment of the resection scar[16-18], as we can see in Fig.1. This technique allows for the resection of low- and high-grade non-invasive neoplastic lesions and adenocarcinomas without evidence of deep invasion of the submucosa, thereby preserving the integrity of the stomach and obviating the necessity for radical gastrectomy[19].

ESD was developed in 1955 to overcome the pitfalls of endoscopic mucosal resection (EMR). The guidelines of European Society of Gastrointestinal Endoscopy (ESGE) currently consider ESD to be the first-line endoscopic treatment option for superficial gastric lesions with no/very low risk of lymph node metastasis[20, 21]. When compared to EMR, ESD is associated with significantly higher rates of *en bloc* curative (R0) and complete resection with free margins (curative resection rate of around 92%), lower recurrence and similar post-procedure bleeding; on the other hand, it is associated with a slightly higher risk of perforation and increased procedure duration. EMR should be reserved for other cases (high lesions (0-IIa), < 10 mm, with a low probability of advanced histology, and as long as the endoscopist considers that *en bloc R0* resection can be achieved)[22]. Also, when comparing ESD with gastrectomy, there was a meta-analysis that demonstrated that the survival rates between them were comparable, with a lower complication rate and a shorter length of hospital stay in ESD[23].

For ESD to be feasible, lesions must meet specific criteria: dysplastic lesions of any size; intramucosal differentiated adenocarcinomas without ulceration ≤2cm. Regarding the expanded criteria, these already include intramucosal differentiated adenocarcinomas without

ulceration >2cm; intramucosal differentiated adenocarcinomas with ulcer ≤3cm; intramucosal undifferentiated-type adenocarcinoma, size ≤2cm; and differentiated-type adenocarcinoma with superficial submucosal invasion (sm1,≤500μm) ≤3cm [22].

The fact that the stomach is entirely preserved has the enormous advantage of maintaining patients' quality of life. A study by Libânio *et al.* compared the quality of life (QoL) of patients who underwent gastrectomy versus ESD, concluding that ESD provided better outcomes in physical, social, and emotional functions, while gastrectomy was linked to higher rates of mobility, self-care and Activities of Daily Living (ADL)[24]. In another study, Song *et al.* observed that there was a better overall health status in the ESD group when comparing it to the surgery group (*p-value* < 0.05). Overall, there was a general trend across all functional and symptom scales favoring endoscopic treatment[25].

Thus, the decision between the two therapeutic modalities is challenging, with various aspects having to be considered, such as efficacy, safety and cost. It is essential to weigh the advantages and disadvantages of each procedure, with a thorough discussion with the patient addressing these factors[24].

However, due to the fact that the stomach is entirely preserved, there is also a persistent risk that premalignant mucosa can give rise to metachronous gastric lesions (MGL), with a reported cumulative incidence ranging from 5.2 to 22.7% over a 10-year follow-up period[26, 27]. This then requires close, long-term endoscopic follow-up to ensure early detection of MGL[28].

A previous meta-analysis identified several risk factors for MGL development, including age, sex, family history, presence of synchronous lesions, and persistent *Hp* infection. The male sex is associated with a higher risk of MGL, which is in line with the higher incidence of GC in this group[29, 30]. Age was also a significant risk factor, as well as the presence of synchronous lesions and family history of GC, which supports the existence of a genetic predisposition to GC and MGL. The characteristics of the primary lesions were not significantly associated with the appearance of MGL. However, these morphological characteristics influence the likelihood of curative resection[30]. Also in this Ortigão *et al.* meta-analysis, severe mucosal atrophy and IM in the corpus were identified as risk factors, indicating that this group of patients requires closer monitoring. Additionally, the study confirmed that eradication of *Hp* after resection reduces the incidence of MGL[30]. Successful eradication of *Hp* results in a significant reduction in future incidence rates of gastric neoplasia both in asymptomatic Hp positive individuals (combined incidence rate: 0.62; 95% CI: 0.49-0.79) and after endoscopic resection of EGC (combined incidence rate: 0.46; 95% CI: 0.35-0.60)[31].

Given the risk of developing metachronous lesions after ESD, endoscopic surveillance is essential for the timely identification of MGL and for optimizing long-term clinical outcomes. The ESGE guidelines advocate a control endoscopy within 3-6 months post-ESD, subsequently followed by annual examinations for patients subjected to curative resection[22]. However, recent studies suggest that the risk of MGL remains constant over time, thereby justifying prolonged surveillance, especially in patients with risk factors such as gastric IM[30]. The FAMISH score, a predictive model based on six clinical variables, proposes personalized follow-up, with endoscopies every four years for low-risk patients, every two years for intermediate risk and annually for high-risk patients, including those with gastric corpus IM[28]. Thus, individualizing

surveillance can reduce unnecessary examinations while maintaining an effective approach to the early detection of new lesions.

OBJECTIVES

The primary objective of this study is to evaluate the occurrence of MGL subsequent to ESD and to identify the risk factors associated with their development. The specific aim is to understand how clinical, endoscopic and histological variables influence the risk of MGL, and analyze the relationship between these variables and the MGL genesis.

By identifying key risk factors, assessing the effectiveness of current follow-up recommendations and proposing a model better adjusted to the needs of the study population, the aim is to improve clinical outcomes, reduce the costs associated with follow-up and promote a more personalized approach to patient care, thereby contributing to the optimization of surveillance and management strategies for these patients.

MATERIALS AND METHODS

Study design and patient selection

A retrospective study based on prospectively collected data was conducted on the medical data, endoscopic examination records, endoscopic procedure notes and histological analysis files of 319 cases. These cases comprised all patients who underwent ESD following the implementation of this technique at the *Unidade Local de Saúde de Santo António (ULSSA),* Porto, Portugal, in 2016. Data collection for this study was completed in December 2024.

The study population is a consecutive cohort of patients performing ESD for a primary gastric lesion with subsequent endoscopic surveillance. ESD was carried out by two specialized endoscopists in accordance with a standardized procedure. The inclusion criteria are: individuals older than eighteen years; patients under endoscopic surveillance after 1) curative ESD for a primary gastric lesion superficial lesion; 2) local-risk resection unfit for surgery; endoscopic follow-up for at least 3 years or until the first MGL (by definition with at least 6 months). Patients were excluded if they had a primary lesion not amenable to ESD; in whom ESD was not feasible; who underwent surgical resection after ESD (noncurative in patients who were fit for surgery) and if the endoscopic follow-up was shorter than 3 years after resection (due to follow-up in another institution or loss of follow-up for any reason).

Ethical statements

The study N/REF.ª 297-24 (234-CAC/268-CE) was approved by the ULSSA Conselho de Administração, Comissão de Ética para a Saúde, Responsável pelo Acesso à Informação and the Gabinete de Projetos de Investigação do Centro Académico Clínico. Prior to the procedure, written informed consent to perform ESD was obtained from all patients. However, due to the retrospective nature of the study and the anonymity of the database, there was no need for informed consent for participation.

Definition of variables

Data collection included clinical and demographic variables for the characterization of the validation cohort such as age, sex, first degree family history of GC, *Hp* infection status, date of the ESD for the primary lesion, presence of synchronous gastric lesions and the presence/absence of gastric atrophy and IM (corpus and antrum). Lesions were classified according to their size (endoscopic assessment at diagnostic, in millimeters), transverse axis location (cardia/gastroesophageal junction (GEJ), upper, middle or lower third of the stomach) and longitudinal axis location (posterior/anterior wall, greater/lesser curvature), pathological diagnosis (LGD, HGD, T1a m1-m2 (intramucosal), T1b sm1 (<0,5mm) or T1b sm2 (>0,5mm) adenocarcinoma) and morphology (according to the *Paris* classification). For convenience, the Paris classification variable was divided into three distinct categories: 1) Is and Ip, 2) IIa or IIb and 3) IIc or III. Information on the last follow-up date as well as the *Hp* infection status at that time were also collected.

A MGL is defined as an epithelial neoplastic lesion detected ≥6 months after resection (or at the second follow-up endoscopy) in a location different from the primary resection site. In the case of lesions that manifest prior to six months following ESD, the lesions are defined as synchronous. Information about MGL was also collected such as the number of lesions, date of

the ESD, *Hp* infection status at that time, and characterized the MGL considering location, size, morphology (*Paris* classification), and pathological diagnosis.

Statistical analysis

The anonymized database comprised demographic and clinical data, along with information on the characteristics of primary lesions as well as MGL for all patients who underwent ESD. The follow-up period was calculated from the day of the initial ESD.

A descriptive statistical analysis was performed, with the categorical variables analyzed using the total number and percentage. Continuous variables were described as mean and standard deviation (SD) if they were normally distributed according to the *Kmolgorov-Smirnov* test, or, if not, as median (interquartile range, IQR).

Fisher's exact test and *Chi*-square test were used to analyze and compare categorical variables. The *Kruskal-Wallis H-test* was used to analyze continuous variables. The cumulative incidence of MGL was estimated using the univariate analysis using *Kaplan-Meier* method, and the comparison between two groups was calculated with *log-rank* test. The threshold for statistical significance was set at *p-value* < 0.05, with a confidence interval of 95%. The statistical analysis was conducted using *IBM® SPSS® Statistics software version 29.0 (IBM Corp., Armonk, New York, USA).*

RESULTS

Study population

A total of 319 cases resulting in 138 patients who were enrolled in this study, including patients with more than one primary lesion, metachronous and synchronous lesions. We excluded a total of 148 cases: 33 (22.3%) had a non-curative dissection with a high-local risk, 115 (77.7%) cases referred to patients with less than 3 years of follow-up or because of loss of follow-up. Some excluded cases referred to the same patient. Among these, there were 18 MGL in 17 patients (one patient had two MGL). Additionally, 7 cases corresponded to synchronous lesions. There were other 4 patients that had two primary lesions, corresponding to 8 cases. Figure 2 shows the flowchart of the patient selection process with inclusion and exclusion criteria.

A baseline sociodemographic data, the clinical predictors, and the characteristics of the primary gastric superficial lesion for the included patients are described in Table I. Regarding the patients' characteristics, the mean age was 72.2 years (SD±9.98), with 58.7% of the patients being male (n=81). First-degree family history of GC was present in 28.3% of patients (n=39). Regarding *Hp* status at the time of diagnosis of the primary lesion, 13.8% (n=19) were *Hp* positive, 27.5% (n=38) had previously undergone eradication, 57,2% (n=79) were negative and in 1,4% (n=2) of patients the *Hp* status was not reported. Regarding endoscopic and mucosal findings in these patients, 31.9% (n=44) presented with IM in the corpus and 43.5% (n=60) in the antrum. The median follow up time of these patients is 4 years (IQR 5-3).

For primary lesion characteristics, 73.2% (n=101) of them presented in the lower third of the stomach, 24.6% (n=34) in the middle third, 1.4% (n=2) in the upper third and only 0.7% (n=1) in cardia/GEJ. Regarding the location in the longitudinal axis, the majority of them were located in the lesser curvature (36.2% (n=50)). The majority of the lesions had a IIa or IIb classification according to the *Paris* classification, corresponding to 72.5% (n=100), 18.1% (n=25) had a Is or Ip classification and 9.4% (n=13) had a IIc or III classification. With regard to post-resection pathological classification, 57.2% (n=79) corresponded to LGD, 13.8% (n=19) to HGD, 24.6% (n=34) of the lesions to intramucosal adenocarcinoma (T1a m1-m2), 2.9% (n=4) to T1b sm1 adenocarcinoma, and 1.4% (n=2) to T1b sm2 adenocarcinoma. The median lesion size was 15mm (IQR 12-23.25).

At the index endoscopy, one synchronous lesion was identified in 5.1% (n=7) of the patients. Additionally, 12.3% (n=17) presented with MGL and, among these, only one patient had more than one MGL (two MGLs), representing an incidence rate of MGL of 3.25 lesions/100 person-years.

Metachronous gastric lesions analysis

These MGL were detected at a mean follow up time of 27.55 months (SD±10.27). The longest interval until MGL was 85 months and 90% of MGL developed within 30 months. A cumulative incidence of MGL of 14.7% at 5 years has been reported. The evolution of the tumors in the MGL patients was examined using the *Kaplan-Meier* method, which entailed the plotting of the cumulative incidence of MGL, represented in Figure 3.

For MGL characteristics, 47.1% (n=8) of them presented in the lower third of the stomach, 35.3% (n=6) in the middle third, 11.8% (n=2) in the upper third and only 5.9% (n=1) in

cardia/GEJ. Most of the lesions had a IIa or IIb classification according to the Paris classification, corresponding to 88.2% (n=15), and 11.8% (n=2) had a IIc or III classification. Regarding post-resection pathological classification, 70.6% (n=12) corresponded to LGD and 5.9% (n=1) to HGD, and 23.5% (n=4) of the lesions to intramucosal adenocarcinoma (T1a); the median lesion size was 15mm (IQR 9-19.5). These characteristics are summarized in Table II.

Comparative analysis of patient groups: with and without metachronous lesions

For the purposes of statistical analysis, the database was divided into two groups: those patients who developed a MGL and those who did not.

Among the MGL patients, 70.6% (n=12) were male, while 29.4% (n=5) were female. The average age was 74 years (IQR 63.5-86). First-degree family history of GC was present in 23.5% (n=4) of the patients. Regarding the status of *Hp* at the time of resection, 52.9% (n=9) of the patients exhibited a negative status, 11.8% (n=2) exhibited a positive status, and 35.3% (n=6) exhibited evidence of eradication. Regarding the presence of IM in gastric corpus, 64.7% (n=11) of the cases were positive, while 35.3% (n=6) were negative. Similarly, 70.6% (n=12) of the cases were positive for IM in the antrum, while 29.4% (n=5) were negative.

About the characteristics of the primary lesion in patients with MGL, regarding its location on the transverse axis, the majority of the cases (70.6% (n=12)) were located in the lower third, and in the anterior wall 35.3% (n=6). The mean size of the lesion was 15mm (IQR 12-23). Regarding *Paris* classification, 11.8% (n=2) patients were classified as Is or Ip, 76.5% (n=13) were classified as IIa or IIb, and 11.8% (n=2) were classified as IIc or III. Regarding the histological diagnosis, more than half of the cases were LGD (64.7% (n=11)).

Among patients without MGL, 57% (n=69) were male, and 43% (n=52) were female. The median age was 72 years (IQR 67-79). First-degree family history was noted in 28.9% (n=35) of these patients. Regarding *Hp* status at the time of resection, 57.9% (n=70) of patients were negative, 14% (n=17) were positive, 26.4% (n=32) showed evidence of eradication, and 1.7% (n=2) had missing data. In terms of IM in the gastric corpus, 27.3% (n=33) were positive, and 72.7% (n=88) were negative. Likewise, 39.7% (n=48) of cases were positive for IM in the antrum, and 60.3% (n=73) were negative.

Regarding the primary lesion's characteristics of the patients without MGL ocurrence, about its location on the transverse axis, the majority was located in the lower third too (73.6% (n=89)), while in the longitudinal axis, most of the lesions were located in the lesser (38% (n=46)) and in greater curvature (30.6% (n=37)). The median lesion size was 15 mm (IQR 12-23.5). Regarding Paris classification, 19% (n=23) were classified as Is or Ip category, 71.9% (n=87) as IIa or IIb and 9.1% (n=11) as IIc or III. On the histological diagnosis, 56.2% (n=68) were classified as LGD and only 14.9% (n=18) as HGD.

All the clinicopathological characteristics of patients according to the development of metachronous neoplasms are shown in Table III.

Risk factors for metachronous gastric lesions ocurrence

Analyzing and comparing the two groups, there were no statistically significant differences regarding sex, first degree family history of GC, *Hp* infection status and overall characteristic of the primary lesion (namely lesion size, transverse and longitudinal axis location, *Paris*

classification and histological diagnosis), regarding Table III. Thus, there is a statistically significant difference regarding the presence of IM in the gastric corpus (p-value = 0.002) and antrum (*p*-value = 0.016), between the patients with and without MGL.

The cumulative incidence of the MGL between the group with presence of IM in the gastric corpus and antrum and absence was calculated using the *Kaplan-Meier* method and *log-rank* test. The cumulative incidence risk of MGL in the patients with presence of IM in the gastric corpus was higher than in the ones without IM (p-value=0.001), as seen in Fig.4. With the same statistical method, we also concluded that the risk of cumulative incidence of the MGL was higher in the patients with IM in the gastric antrum than in the ones without IM (p-value= 0.006), presented in Fig. 5.

DISCUSSION

Metachronous gastric lesions progression and risk factors

With the increasing use of ESD for treatment of EGC, this procedure has become a preferred approach due to its ability to preserve the entire stomach, offering patients a better QoL compared to gastrectomy. However, the risk of MGL developing in the remaining stomach remains a significant concern due to its potential impact on prognosis. This study focuses on identifying clinicopathologic factors influencing the interval between ESD and the onset of MGL.

In this study, including 138 patients with eligible lesion for ESD, it was reported an incidence of MGL after ESD of 12.3%, during a mean follow-up time of 27.55 (SD±10.27) months, consistent with the data presented in the literature, which reports an incidence of between 3 and 20%[16]. One study indicates an overall incidence of 14% of MGL in a median follow up time of 57 months [32], while a separate study points to an incidence of MGL of 14.5% in a median follow-up time of 26.5 months, which is in line with what is reported in this study[33]. Libânio *et al.* also reported an incidence rate of 5 lesions/100 person-years, and the present study reported an incidence rate of 3.25 lesions/100 person-years, which means that, on average, around 1 in 6 patients will develop a MGL at 5 years of follow-up, a slightly higher incidence than that seen in some other centers[19]. A meta-analysis conducted in 2022 reported a cumulative incidence of MGL at 5 years of approximately 9.5% in comparison, this study reported a cumulative incidence of around 14.7% over the same period[30].

The incidence observed in this study may be influenced by several factors, including the fact that the center is a high-volume center for ESD and is located in northern Portugal, a region with a high prevalence of EGC, as reported in the 2020 National Oncologic Report[4]. These findings highlight the need for adequate endoscopic surveillance following ESD.

Regarding the mean period until MGL occurrence, this study found a mean of 27.55 (SD±10.27) months, consistent with the literature, where similar findings were reported, with Min *et al.* and Rei *et al.* indicating a mean of 30 months [28, 34] and Moon *et al.* reporting a median of 29.5 months[35]. Around half of the MGL cases occurred in the first 2 years of follow-up, which emphasizes the importance of a thorough endoscopic surveillance during this period. However, the longest time until MGL was 85 months, which is over 7 years, suggesting that post-ESD surveillance could eventually be tailored to the patient's risk profile. Patients at low risk might benefit from shorter follow-up periods, whereas those at higher risk could require longer surveillance. This risk-based approach would not only optimize clinical outcomes but also help reduce the burden of care[34].

In this study, we could see that the majority of MGL developed in the same third (lower third) regarding the location on the transverse axis, so there may be a tendency for these new lesions to develop in the same third anatomically and with the same histological characteristics, in line with what has already been observed in other studies[32, 36].

Although in the literature, several risk factors have been identified for the development of MGL, as in this meta-analysis, such as older age (mean difference 1.08 years, 95%CI 0.21-1.96), family history of GC (OR 1.88, 95%CI 1.03–3.41), male sex (OR 1.43, 95%CI 1.22–1.66), a persistent *Hp* infection (OR 2.08, 95%CI 1.60–2.72), presence of synchronous lesions (OR 1.72,

95%CI 1.30–2.28), severe gastric mucosal atrophy (OR 2.77, 95%CI 1.22–6.29) and IM in corpus (OR 3.15, 95%CI 1.67–5.96), in this study, the only risk factor identified was IM in the corpus (*p-value* = 0.002) and gastric antrum (*p-value* = 0.016), with a clearly higher cumulative incidence risk in patients with IM in the corpus and antrum (*p-value* = 0.001, *p-value* = 0.006, respectively)[30]. Our findings are in the line with a several other studies that classify IM as a risk factor[27, 35-39].

It was decided not to include a variable corresponding to the presence of gastric mucosal atrophy in the statistical analysis of this study. It is important to consider that endoscopic biopsies are directed at the lesion and may not accurately reflect the presence of atrophy in the rest of the mucosa. Furthermore, in many cases the information on atrophy came from different hospital centers, making it difficult to establish uniform diagnostic criteria. In addition, the literature indicates that, according to Correa's model, IM arises in a context of atrophy, which implies that the vast majority of patients with IM already have some degree of atrophy[40, 41]. Another relevant factor is inter-observer agreement, which is higher when identifying IM compared to atrophy, with the literature showing a significantly higher kappa coefficient (κ) for IM (κ=0.82 in the antrum vs. κ=0.53 in the antrum)[42]. It was therefore decided to use IM as the preferred phenotype to represent the progression of the gastric mucosa, covering the entire study population.

Additionally, it is important to note that the prevalence of gastric mucosal atrophy and IM may be underestimated in this study, since systematic biopsies for histological assessment of the gastric mucosa are not performed at the time of diagnostic endoscopy. Research suggests that performing biopsies in predetermined areas of the stomach significantly increases the detection rate of mucosal atrophy and IM, impacting risk stratification and possibly influencing the incidence of metachronous lesions[30, 39].

Using the Operative Link on Gastric Intestinal Metaplasia (OLGIM) classification, a retrospective study found that higher OLGIM stages (II to IV) were strongly associated with an increased risk of MGL (HR 2.86, 95% CI 1.29–6.54, *p-value* = 0.01; HR 2.94, 95% CI 1.34–6.95, *p-value* = 0.01; HR 3.64, 95% CI 1.60–8.29, *p-value* = 0.002). This association was even more significant than the link with gastric mucosal atrophy[43]. A prospective study in Japan further reported that individuals with IM had at least a six-fold increased risk of developing GC compared to those without IM[44]. Furthermore, a large chinese cohort study involving 3,306 participants followed for 4–5 years found the odds ratio (OR) for progression from IM to GC to be between 17 and 29[45]. The statistical association was stronger for patients with IM in the corpus, correlating with a higher risk of MGL compared to those with IM in the antrum. This can be explained by the progression of IM, which typically originates in the antrum before advancing to the corpus, suggesting that many patients with corpus IM likely already have antral IM[46].

Some studies refer that the development of gastric mucosal alterations, such as mucosal atrophy and IM, is strongly influenced by the presence of *Hp*. Additional studies identify IM as a risk factor for both synchronous and metachronous recurrences and GC, regardless of prior *Hp* eradication or cancer history[47-49]. In this study, *Hp* was not identified as an independent risk factor for MGL[50].

One possible explanation is that the previous eradication of *Hp* in a significant proportion of patients may have mitigated its impact as an active risk factor, an hypothesis supported by some meta-analyses that report a significant reduction in the risk of gastric neoplasms after *Hp* eradication (combined incidence rate 0.46; 95% CI: 0.35-0.60)[51]. In addition, the chronic inflammation induced by *Hp* can trigger irreversible changes in the gastric mucosa, such as IM, which continue even after *Hp* has been eradicated[39, 52]. This study found a strong association between IM and the risk of MGL, corroborating this hypothesis. Similarly, studies such as that by Yang *et al.* suggest that the role of *Hp* may be secondary in patients with advanced mucosal changes, such as IM[39]. Another possibility is the heterogeneity of *Hp* detection methods, since some studies use more sensitive techniques, such as histology and PCR, increasing diagnostic accuracy[27]. Thus, although *Hp* did not emerge as a risk factor in this study, the literature reinforces its relevance as a target in the primary and secondary prevention of MGL[9, 51].

The proportion of patients with a negative *Hp* status in this study (57.2%) gives rise to questions regarding the accuracy of diagnosis and the potential underestimation of infection. Research suggests that spontaneous eradication of *Hp* can occur, particularly in the elderly or in patients with advanced gastric mucosal atrophy, where chronic inflammation and reduced stomach acidity create an unfavorable environment for the bacteria[44]. Thus, the high rate of *Hp*-negative patients in our sample may reflect the presence of these factors and, consequently, underestimate the true number of infected patients, introducing a bias into the results.

Furthermore, the post hoc power analysis in this study for detecting an association between *Hp* infection status and the development of MGL yielded a power of 5.77%. This extremely low power indicates that the study was not adequately powered to detect a significant association between *Hp* infection status and the outcome. This result is likely due to the small difference in proportions in patients with and without MGL (11.8% vs. 14.0%) and the relatively small sample size for this variable.

As it is very important to identify risk factors associated with the development of MGL, it is crucial to explore all the factors that can increase this risk in order to guide clinical decision-making and improve patient outcomes. Various studies have explored the characteristics of lesions and patient-related factors that influence prognosis, besides IM, shedding light on predictors of aggressive behavior and poor outcomes.

The identification of IM as a significant risk factor for MGL underscores the need for rigorous surveillance, as IM represents a pivotal step in the gastric carcinogenesis pathway. Structured, risk-adjusted endoscopic follow-up, tailored to the severity and extent of IM, is essential for the early detection of metachronous lesions and underscores the importance of personalized surveillance strategies.

Surveillance

Endoscopic surveillance after ESD is essential for patients who undergo curative resection of gastric lesions, as the incidence of MGL is higher in these patients, given the preservation of the stomach, compared to those who undergo surgical treatment[53]. Consequently, long-term survival in these patients is likely influenced by the development of MGL[54]. To personalize

follow-up, aspects such as risk factors (namely IM), characteristics of the primary lesion, and the time to MGL occurrence should be taken into account.

The ESGE guidelines recommended a follow-up endoscopy at 3-6 months post-procedure, and then annually thereafter, for curative or local-risk ESD without recurrence. It is recommended an endoscopic surveillance with high-definition white-light and chromoendoscopy (virtual or dye-based), for curative resection of superficial gastric lesions (*en bloc* R0 resection, no more advanced than intramucosal cancer, well to moderately differentiated, with no lymphovascular invasion). Biopsies should be performed only on suspicious areas[22, 55].

Yang *et al.,* in a retrospective cohort study, emphasizes the importance of a long-term surveillance, for more than 5 years, in male patients with corpus IM, due to their elevated risk of progression to GC. The authors highlight that while IM is a recognized precursor lesion in gastric carcinogenesis, its risk stratification should account for demographic and clinical factors, particularly sex[39]. Abe *et al*. suggested that the duration of surveillance could be extended beyond 5 years, as well as Rei at al., as MGL continue to develop at a constant incidence rate even after 5 years from the initial ESD[28, 54]. Some studies report that, although there is a high risk of developing other gastric lesions after ESD, this risk is likely not continuous beyond 10 years post-ESD[21]. Another study showed a low MGL incidence, favouring a less tight follow-up, with a follow-up endoscopy at 1 year to confirm the absence of synchronous or early MGL and then every 5 years, since they observed a steady increase in the cumulative incidence along the years (7% at 3 years, 10% at 5 years and 15% at 10 years). However, they emphasize that follow-up should be according to individual risk, reinforcing the need to study these risk factors[30]. Most importantly, the stratification of the risk of developing MGL has yet to be investigated, which would enable the application of tailored surveillance strategies for different risk groups.

Given the difficulty of stratifying these patients in order to better personalize and optimize their follow-up, Rei at al. developed a score to estimate the risk of developing MGL after gastric ESD, the FAMISH score, which assesses the risk using 6 clinical predictors: positive family history of GC, older age, male gender, corpus IM, synchronous gastric lesions and persistent *Hp* infection, with points varying from 0 to 3 and a score of 0-9. The score makes it possible to identify patients at low risk (0-1 points), intermediate risk (2 points) and high risk (3-9 points), adjusting the frequency of endoscopic surveillance on an individual basis. The model proposes following the initial recommendations of the ESGE, with surveillance endoscopy at 3-6 months and 12 months after ESD, and then in the 4th year for low-risk patients, every 2 years for intermediate-risk patients, and annually for high-risk patients, with this last category including those with corpus IM[28].

In the present study, factors such as the presence of IM in the gastric corpus also showed a strong association with the occurrence of MGL, corroborating the validity of the predictors included in the FAMISH score. On the other hand, although persistent *Hp* was considered an important predictor in the FAMISH score, our results did not indicate this association, possibly due to the high rate of *Hp* eradication in our cohort or the independent progression of irreversible changes in the gastric mucosa after the initial infection, as mentioned above.

Interestingly, although the FAMISH score prioritized corpus IM as a central predictor, in this study, antrum IM emerged as a relevant factor for the occurrence of MGL too. This difference may reflect regional variations in the distribution of precursor lesions or methodological differences in endoscopic and histological assessment, suggesting that both patterns of metaplasia may have clinical importance depending on the context of the population being assessed.

Thus, applying the FAMISH score to larger populations and in a multicenter setting could help to further validate its clinical usefulness and adjust it to different regional prevalences of risk factors, encouraging a more environmentally friendly and cost-effective approach.

However, currently, annual endoscopic examinations are deemed acceptable. The tendency for the future is that the development of these models and tailored surveillance systems will be prioritized, incorporating the assessment of various risk factors for gastric carcinogenesis.

Strengths and limitations

This is a study carried out in a high-volume center for ESD, which provides meaningful evidence on a challenging topic where concrete data is limited. It is also an important study for improving patient selection and follow-up, which should be personalized regarding the clinical characteristics of each patient. Thus, the high incidence of MGL alerts us to the need for continued endoscopic surveillance. A notable strength of this study is that, even though it was retrospective, it effectively analyzed the relationship between two factors and the development of MGL, achieving a comprehensive dataset almost without any missing values. In addition, this study offers a clear and detailed analysis of possible relevant factors contributing to the development of MGL. Moreover, only patients with a minimum of 3 years' follow-up were included, ensuring that our sample included sufficient follow-up time, as many studies have shown that the 3-year cut-off provides the greatest sensitivity and negative predictive value. Huang *et al.* identified the third year following resection as a pivotal time for the emergence of MGL, further emphasizing the importance of ensuring a follow-up period of at least three years to detect and manage these lesions effectively[56]. Furthermore, this study opens the door to proposing a risk-based personalized surveillance approach after ESD, tailoring follow-up strategies to individual patient profiles. Such an approach has the potential to reduce the burden of care and optimize resource allocation, improving both patient outcomes and healthcare efficiency.

However, this study has some limitations. First, it is a retrospective study, with it being conducted as a retrospective review and analysis of an electronic medical database. However, ESD for EGC has been performed since 2016 at ULSSA, and the clinical workup and process have been well established. The homogeneity of the study data and ESD performance are likely to be reliable, but the lack of a prospective control can introduce some biases. Second, it is a single center study, which made the sample size not sufficiently large. The number of enrolled participants was less than 200 (n=138) in the final analysis. Our cohort sample is smaller than that evidenced in many other studies in the literature, which may make this study underpowered to detect the influence of the risk of other factors named in the literature, such as age, gender, the presence of synchronous lesions, mucosal atrophy, first-degree family history of GC, *Hp* positive status, and to evaluate the influence of the characteristics of the

primary lesions on the development of MGL. Thus, the results of this study would need to be confirmed with a large-scale multicenter study, with a larger sample of patients.

Futures perspectives

Some studies hypothesize that the high risk of developing MGL after ESD is the result of synchronous lesions not detected at the time of ESD, but which have grown sufficiently to be detected during follow-up[21]. In the future, with advancements in endoscopic technology, numerous hidden cancers and previously undetected synchronous cancers could be identified early during follow-up, potentially reducing the significance of metachronous cancer after ESD.

Artificial intelligence (AI) is poised to play a transformative role in the detection and management of gastric lesions, as well as in long-term patient follow-up. Recent advancements, as discussed in Vasconcelos *et al.* [16] and other studies, highlight the potential of AI-powered systems to enhance the accuracy of detecting precancerous and cancerous gastric lesions during endoscopic procedures, for example, predicting the depth of invasion. Zhu *et al.*[57] and Tang *et al.*[58] reported an impressive accuracy of approximately 88–89% in predicting tumor invasion depth. Meanwhile, Yoon *et al.*[59] provided insights into the diagnostic capabilities of AI systems, demonstrating a sensitivity of 79.2% and a specificity of 77.8% for this purpose. Despite initial promising results, AI systems have yet to demonstrate greater accuracy than human experts in predicting the depth of invasion.

Additionally, AI can assist in risk stratification by analyzing patient data, including histological findings, and recommending tailored follow-up schedules based on individual risk profiles. This not only improves clinical outcomes but also optimizes resource allocation. The integration of AI in routine endoscopy and surveillance programs could significantly reduce the burden on clinicians while ensuring timely and effective monitoring of patients at risk for MGL.

Future perspectives in this field should also involve the conduction of prospective studies to evaluate specific interventions, such as different follow-up strategies. These studies would provide valuable insights into how such measures could potentially influence the occurrence of MGL. By establishing a clear understanding of the impact of these interventions, future research could guide clinical practice and improve long-term outcomes for patients at risk of developing GC.

The elevated prevalence of GC in Portugal, particularly in the northern region, underscores the necessity for individualized strategies in the management of this disease. Although we currently follow the ESGE recommendations, these guidelines are predominantly based on data derived from populations with a lower incidence of GC than that observed in Portugal. The creation of specific national guidelines could integrate regional particularities, adapting surveillance and treatment protocols to local needs. In addition, national guidelines could promote more effective preventive strategies, optimize healthcare resources and improve patients' QoL, especially by incorporating tools such as the FAMISH score and other adaptations for high-risk populations. This collaborative effort between reference centers would contribute to strengthening the clinical response and reducing the socio-economic impact of GC in Portugal.

CONCLUSION

ESD has become the preferred endoscopic resection method for superficial gastric lesions, outperforming EMR and being favored over surgery due to its benefits in reducing morbidity and enhancing quality of life. The adoption of ESD has been successful, with outcomes for efficacy and safety in the stomach. However, it is necessary to optimize the identification of patients who carry a higher risk of development of MGL, in the short and long term, so that we can provide information to patients and avoid under- and over-surveillance.

The effectiveness of follow-up after resection remains a topic of discussion, as there is limited evidence supporting intensive, long-term protocols. Future studies should assess surveillance strategies tailored to an individual's risk of developing MGL.

FIGURES

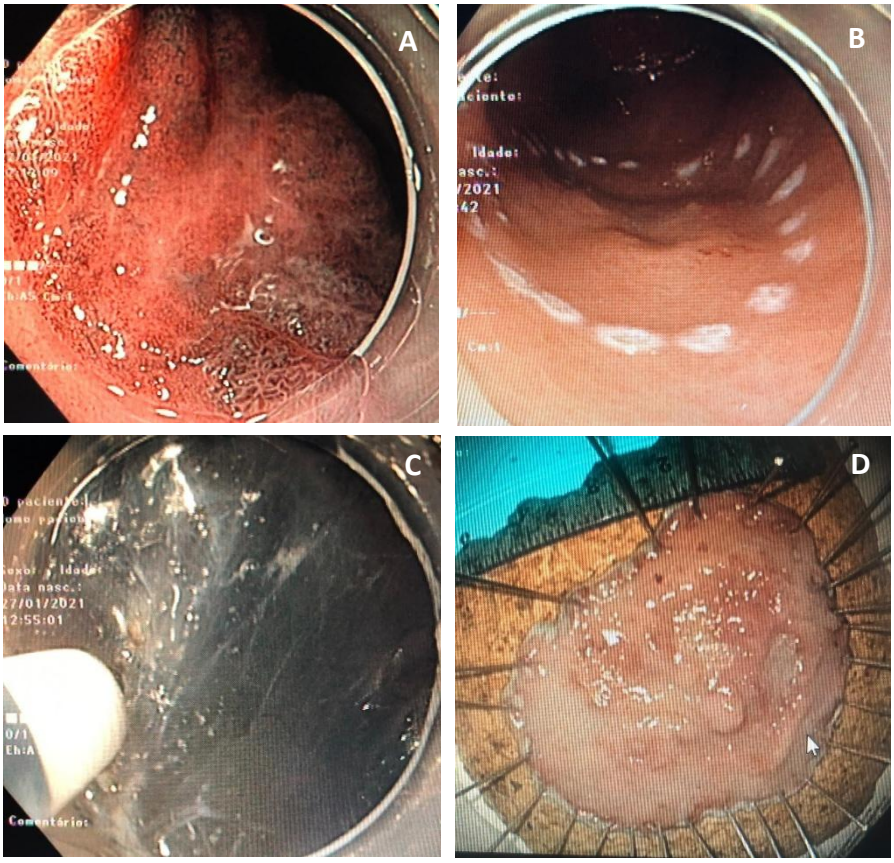


Figure 1. Visual representation of Endoscopic Submucosal Dissection (ESD). A) Visualization of the lesion on the gastric mucosa under chromoscopy (narrow band imaging) (B) Marking the limits of the lesion with coagulation marks. (C) Dissection of the lesion (D) Mucosal piece after complete resection. Images provided by the supervisor.

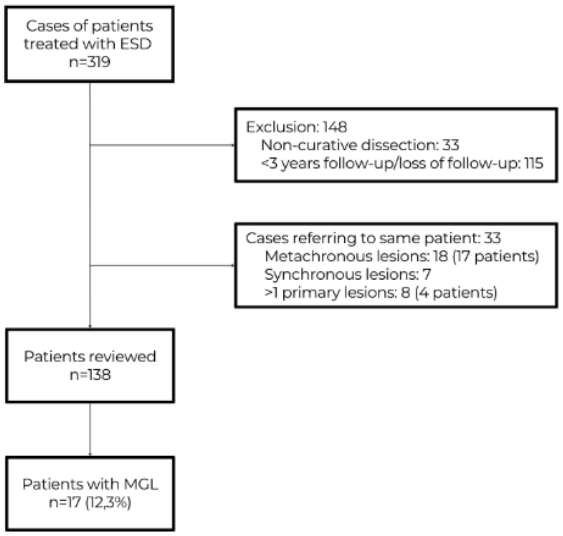


Figure 2 Overview of patient selection process. Inclusion and exclusion criteria for enrolled patients are shown. ESD, endoscopic submucosal dissection; MGL, metachronous gastric lesion

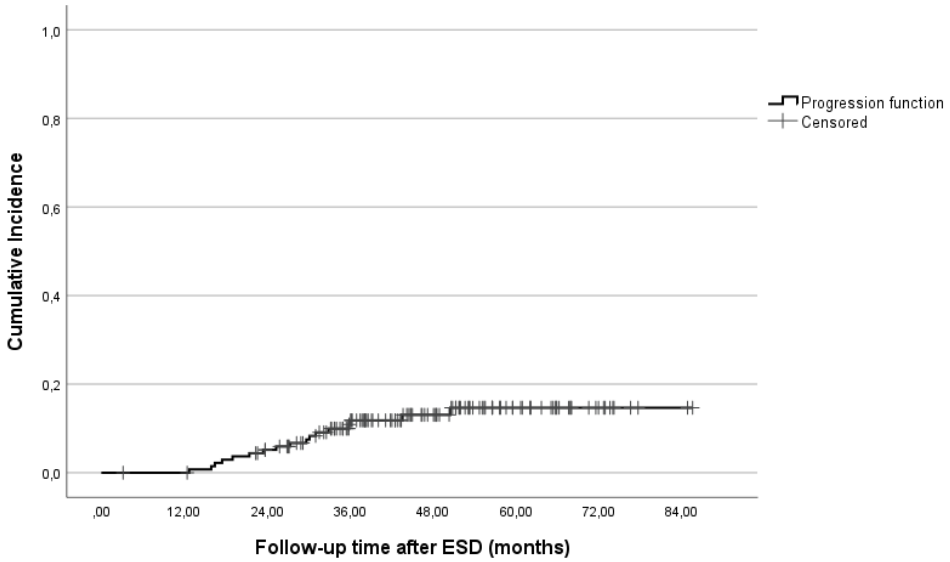


Figure 3. Cumulative incidence of MGL after ESD. *Kaplan-Meier* method shows the trend of development of MGL over time, after the procedure. ESD, endoscopic submucosal dissection; MGL, metachronous gastric lesion

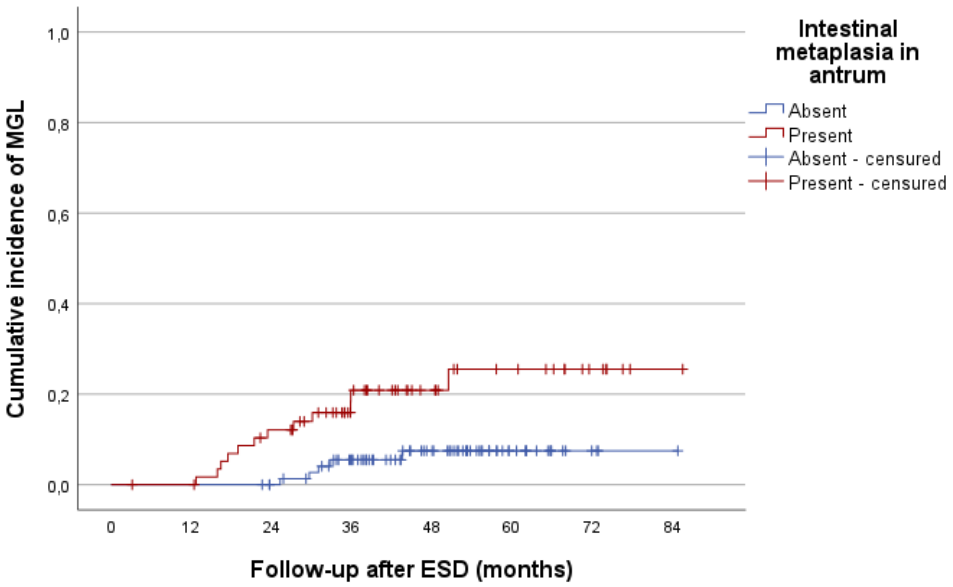


Figure 4. Cumulative incidence of the metachronous recurrence (Intestinal metaplasia in the gastric antrum at primary lesion endoscopic diagnosis or resection date).

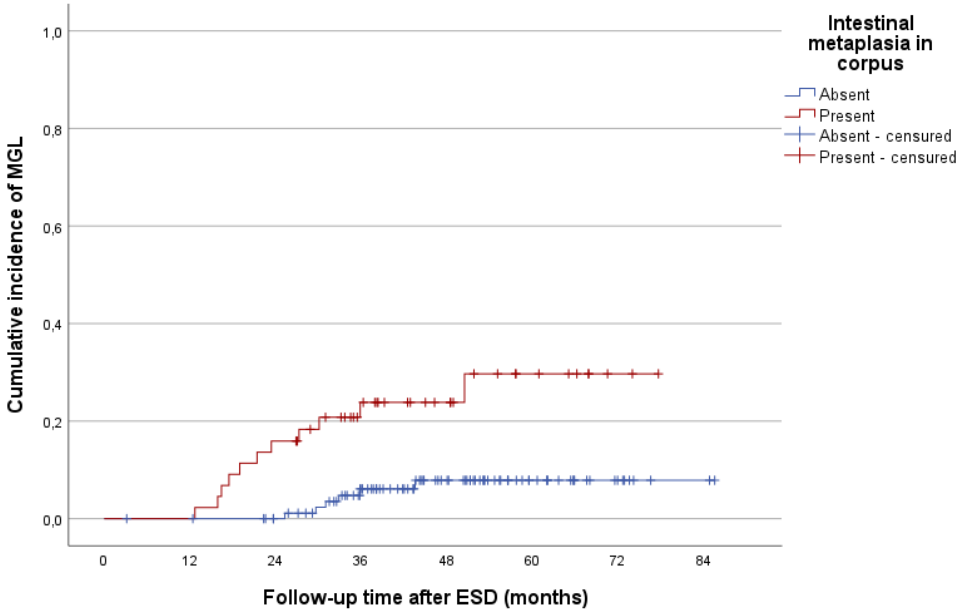


Figure 5. Cumulative incidence of the metachronous recurrence (Intestinal metaplasia in the corpus at primary lesion endoscopic diagnosis or resection date)

TABLES

Table I. Baseline patient characteristics, lesion characteristics and endoscopic and histological findings of the study population

Baseline characteristics	n (%) n=138
Patient	
Age, years, mean (SD)	72.2 (±9.98)
Sex	
Male	58.7 (81)
Female	41.3 (57)
First degree family history of GC	
Positive	28.3 (39)
Negative	71.7 (99)
Status H. Pylori at time of diagnosis primary lesion*	
Positive	13.8 (19)
Negative	57.2 (79)
Erradicated	27.5 (38)
Follow-up time, years, median (IQR)	4 (3-5)
Lesion	
Primary lesion size, milimeters, median (IQR)	15 (12-23.25)
Primary gastric lesion location	
Transverse axis	
Lower third	73.2 (101)
Middle third	24.6 (34)
Upper third	1.4 (2)
Cardia/GEJ	0.7 (1)
Longitudinal axis	
Lesser curvature	36.2 (50)
Greater curvature	29.0 (40)
Anterior wall	21.7 (30)
Posterior wall	13.0 (18)
Primary lesion morphology (*Paris* classification)	
Is or Ip	18.1 (25)
IIa or IIb	72.5 (100)
IIc or III	9.4 (13)
Endoscopic and histological findings	
Corpus IM	31.9 (44)
Antrum IM	43.5 (60)
Gastric synchronous lesion	5.1 (7)
Gastric metachronous lesion	12.3 (17)
Pathological diagnosis (post-resection)	
LGD	57.2 (79)
HGD	13.8 (19)
T1a**	24.6 (34)
T1b (<0.5mm)**	2.9 (4)
T1b (>0.5mm)**	1.4 (2)

* valid n=136

**TMN classification for GC

MGL, metachronous gastric lesion; GC, gastric cancer; IM, intestinal metaplasia; IQR, interquartile range; GEJ, gastroesophageal junction; LGD, low grade dysplasia; HGD, high grade dysplasia; T1a, intramucosal adenocarcinoma; T1b, submucosal adenocarcinoma

Table II. Characteristics of MGL

Metachronous lesions characteristics	n (%) n=17
Lesion	
Metachronous lesion size, milimeters, median (IQR)	15 (9-19.5)
Metachronous gastric lesion location	
Transverse axis	
Lower third	47.1 (8)
Middle third	35.3 (6)
Upper third	11.8 (2)
Cardia/GEJ	5.9 (1)
Longitudinal axis	
Lesser curvature	36.2 (50)
Greater curvature	29.0 (40)
Anterior wall	21.7 (30)
Posterior wall	13.0 (18)
Metachronous lesion morphology (Paris classification)	
Is or Ip	-
IIa or IIb	88.2 (15)
IIc or III	11.8 (2)
Pathological diagnosis (post-resection)	
LGD	70.6 (12)
HGD	5.9 (1)
T1a*	23.5 (4)
T1b (<0.5mm)*	-
T1b (>0.5mm)*	-

*TMN classification for GC

MGL, metachronous gastric lesion; IQR, interquartile range; GEJ, gastroesophageal junction; LGD, low grade dysplasia; HGD, high grade dysplasia; T1a, intramucosal adenocarcinoma; T1b, submucosal adenocarcinoma

Table III. Clinicopathologic characteristics of patients with and without MGL

Parameters	Patients with MGL (n=17)	Patients without MGL (n=121)	*P* value
Patient			
Sex			
Male	70.6 (12)	57 (69)	0.288
Female	29.4 (5)	43 (52)	
Age, years, median (IQR)	74 (63.5-86)	72 (67-79)	0.328
Positive first degree family history of GC	23.5 (4)	28.9 (35)	0.644
Status H. Pylori at time of diagnosis primary lesion*			
Negative	52.9 (9)	57.9 (70)	0.844
Positive	11.8 (2)	14 (17)	
Erradicated	35.3 (6)	26.4 (32)	
Corpus IM	64.7 (11)	27.3 (33)	0.002
Antrum IM	70.6 (12)	39.7 (48)	0.016
Lesion			
Primary lesion size, milimeters, median (IQR)	15 (12-23)	15 (12-23.5)	0.938
Primary gastric lesion location			
Transverse axis			
Lower third	70.6 (12)	73.6 (89)	0.059
Middle third	23.5 (4)	24,8 (30)	
Upper third	-	1.7 (2)	
Cardia/GEJ	5.9 (1)	-	
Longitudinal axis			
Lesser curvature	23.5 (4)	38 (46)	0.172
Greater curvature	17.6 (3)	30.6 (37)	
Anterior wall	35.3 (6)	19.8 (24)	
Posterior wall	23.5 (4)	11.6 (14)	
Primary lesion morphology (*Paris* classification)			
Is or Ip	11.8 (2)	19 (23)	0.843
IIa or IIb	76.5 (13)	71.9 (87)	
IIc or III	11.8 (2)	9.1 (11)	
Pathological diagnosis (post-resection)			
LGD	64.7 (11)	56.2 (68)	0.322
HGD	5.9 (1)	14.9 (18)	
T1a**	17.6 (3)	25.6 (31)	
T1b (<0.5mm)**	5.9 (1)	2.5 (3)	
T1b (>0.5mm)**	5.9 (1)	0.8 (1)	

*valid n = 136

**TMN classification for GC

MGL, metachronous gastric lesion; GC, gastric cancer; IM, intestinal metaplasia; IQR, interquartile range; GEJ, gastroesophageal junction; LGD, low grade dysplasia; HGD, high grade dysplasia; T1a, intramucosal adenocarcinoma; T1b, submucosal adenocarcinoma

APPENDIX

APRECIAÇÃO DO GABINETE DE PROJETOS DE INVESTIGAÇÃO do CAC ICBAS-Santo António:

A proposta de investigação "EVALUATION OF RISK FACTORS FOR METACHRONOUS GASTRIC LESIONS POST-ENDOSCOPIC SUBMUCOSAL DISSECTION" foi avaliada pelo Gabinete de Projetos de Investigação do CAC, não havendo questões a clarificar.
Nesse contexto e especificamente no que se refere à componente científica do projeto de investigação, PARECER FAVORÁVEL, na condição de enviar o documento em falta.

Do ponto de vista científico, o Gabinete de Projetos de Investigação do CAC dá por concluída a análise do processo, sendo enviado Estudante/Investigador, Orientador e Ensino Médico Pré-Graduado o Parecer elaborado para conhecimento.

O estudo dispensa avaliação pela Encarregada da Proteção de Dados, de acordo com o despacho do Conselho de Administração do CHUPorto de 06/04/22, relativo à proposta de mitigação de avaliação dos projetos de investigação no âmbito da Proteção de Dados.

O processo segue para a Comissão de Ética e Responsável pelo Acesso à Informação para avaliação.

Deve ser aguardada a comunicação da autorização institucional para a realização do estudo.

Unidade Local de Saúde Santo António, 23 de janeiro de 2025

Pedro Rocha, Gabinete de Projetos de Investigação
Centro Académico Clínico ICBAS-Santo António

Isabel Fonseca, Responsável pelo Gabinete de Projetos de Investigação,
Centro Académico Clínico ICBAS-Santo António

Assinado por : **Isabel Maria da Silva Fonseca**
Num. de Identificação: BI09549171
Data: 2025.01.23 10:05:22 Hora padrão de GMT

ASSUNTO: Trabalho Académico de Mestrado- **"Evaluation of Risk Factors for Metachronous Gastric Lesions Post-Endoscopic Submucosal Dissection"** - N/ REF.ª 2024.297(234-CAC/268-CE)

O Conselho de Administração da ULS de Santo António na reunião do dia 27 de março, emitiu a seguinte deliberação "autorizado" para a realização do estudo acima mencionado, a realizar no Serviço de Gastroenterologia desta Instituição e tendo como Investigador Principal a Dra. Maria Gomes da Universidade do Porto e o Investigador Responsável o Dr. Ricardo Pinto.
O estudo foi previamente analisado pela Comissão de Ética da ULS de Santo António|ICBAS, pelo Gabinete de Projetos de Investigação do CAC, pela Direção do Centro Académico Clínico ICBAS-CHP e pelo Presidente do Conselho de Administração, tendo obtido parecer favorável.

Cumprimentos,

Assinado por: **Lígia Maria da Cruz Tavares**
Num. de Identificação: 12418755
Data: 2025.04.15 12:36:59+01'00'

CHAVE MÓVEL

REFERENCES

1. Bray, F., et al., *Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.* CACancerJClin.2024;1–35., 2024.
2. Arnold, M., et al., *Is gastric cancer becoming a rare disease? A global assessment of predicted incidence trends to 2035.* Gut, 2020. **69**(5).
3. Petryszyn, P., N. Chapelle, and T. Matysiak-Budnik, *Gastric Cancer: Where Are We Heading?* Digestive Diseases, 2020. **38**(4): p. 280-285.
4. Bento, M.J., et al., *Registo Oncológico Nacional de todos os tumores na população residente em Portugal, em 2020.* 2023.
5. Morgan, E., et al., *The current and future incidence and mortality of gastric cancer in 185 countries, 2020–40: A population-based modelling study.* eClinicalMedicine, 2022. **47**: p. 101404.
6. Iwu, C.D. and C.J. Iwu-Jaja, *Gastric Cancer Epidemiology: Current Trend and Future Direction*. Hygiene, 2023. **3**(3): p. 256-268.
7. Laurén, P., *The Two Histological Main Types of Gastric Carcinoma: Diffuse and so-called Intestinal-type Carcinoma- An Attempt at a Histo-Clinical Classification*. Acta Pathologica Microbiologica Scandinavica, 1965. **64**(1): p. 31-49.
8. *Comprehensive molecular characterization of gastric adenocarcinoma*. Nature, 2014. **513**(7517): p. 202-209.
9. Poorolajal, J., et al., *Risk factors for stomach cancer: a systematic review and meta-analysis.* Epidemiology and Health, 2020. **42**: p. e2020004.
10. Toh, J.W.T., R.B. Wilson, *Pathways of Gastric Carcinogenesis, Helicobacter pylori Virulence and Interactions with Antioxidant Systems, Vitamin C and Phytochemicals.* International Journal of Molecular Sciences 2020. **21**.
11. Iyer, P., et al., *Diffuse gastric cancer: histologic, molecular, and genetic basis of disease.* Translational gastroenterology and hepatology, 2020. **5**(52).
12. Wu, Q.J., et al., *Cruciferous vegetable consumption and gastric cancer risk: A meta-analysis of epidemiological studies.* Cancer Science, 2013. **104**(8): p. 1067-1073.
13. Heng, H.H., et al., *Imaging genome abnormalities in cancer research.* Cell & Chromosome, 2004. **3**(1): p. 1.
14. Imai, S., et al., *Helicobacter pylori CagA elicits BRCAness to induce genome instability that may underlie bacterial gastric carcinogenesis.* Cell Host & Microbe 2021. **29**.
15. Das, D., N. Karthik, and Taneja R., *Crosstalk Between Inflammatory Signaling and Methylation in Cancer.* Frontiers in Cell and Developmental Biology, 2021. **9**.
16. Vasconcelos, A.C., Dinis-Ribeiro M., and Libânio D., *Endoscopic Resection of Early Gastric Cancer and Pre-Malignant Gastric Lesions.* Cancers, 2023.
17. Kondo, T.G.H., et al., *A new endoscopic mucosal resection procedure using an insulation-tipped electrosurgical knife for rectal flat lesions: report of two cases.* 1999. **50**(4).
18. Libânio, D., et al., *Endoscopic submucosal dissection techniques and technology: European Society of Gastrointestinal Endoscopy (ESGE) Technical Review.* Endoscopy, 2023. **55**(04): p. 361-389.
19. *Articles of Significant Interest Selected from This Issue by the Editors.* Infection and Immunity, 2015. **83**(9): p. 3341-3341.
20. Seo, J.H., et al., *Undifferentiated histology after endoscopic resection may predict synchronous and metachronous occurrence of early gastric cancer.* 2010. **81**.
21. Kobayashi, M., et al., *Self-limiting risk of metachronous gastric cancers after endoscopic resection.* 2010.

22. Pimentel-Nunes, P., et al., *Endoscopic submucosal dissection for superficial gastrointestinal lesions: European Society of Gastrointestinal Endoscopy (ESGE) Guideline– Update 2022*. Endoscopy, 2022. **54**.
23. Shin, D.W., Hwang H.Y., and Jeon S. W., *Comparison of Endoscopic Submucosal Dissection and Surgery for Differentiated Type Early Gastric Cancer within the Expanded Criteria*. Clinical Endoscopy, 2017. **50**(2): p. 170-178.
24. Libânio, D., et al., *Prospective comparative study of endoscopic submucosal dissection and gastrectomy for early neoplastic lesions including patients' perspectives*. Thieme Endoscopy, 2019.
25. Song, W.-c., X.-l. Qiao, and X.-z. Gao, *A comparison of endoscopic submucosal dissection (ESD) and radical surgery for early gastric cancer: a retrospective study*. World J Surg Onc 2015. **13**(309).
26. Shimada, S., et al., *Endoscopic causes and characteristics of missed gastric cancers after endoscopic submucosal dissection*. Gastrointestinal Endoscopy 2023. **98**(5): p. 735.
27. Libânio, D., et al., *Long-Term Outcomes of Gastric Endoscopic Submucosal Dissection: Focus on Metachronous and Non-Curative Resection Management*. GE - Portuguese Journal of Gastroenterology, 2017. **24**(1): p. 31-39.
28. Rei, A., et al., *Metachronous lesions after gastric endoscopic submucosal dissection: the FAMISH predicting score to reduce the burden of care.* Endoscopy, 2023. **51**.
29. SUGIURA, J., et al., *Multiple Early Gastric Carcinoma in Cases Treated Endoscopically.* Digestive Endoscopy 2007. **4**.
30. Ortigão, R., et al., *Risk factors for gastric metachronous lesions after endoscopic or surgical resection - a systematic review and meta-analysis*. 2022. **54**.
31. Yi-Chia Lee 1, T.-H.C., Chu-Kuang Chou, Yu-Kang Tu, Wei-Chih Liao, Ming-Shiang Wu, David Y Graham, *Association Between Helicobacter pylori Eradication and Gastric Cancer Incidence: A Systematic Review and Meta-analysis*. Gastroenterology, 2016. **150**(5): p. 1113-1124.
32. J Nasu, T.D., H Endo, T Nishina, S Hirasaki, I Hyodo, *Characteristics of metachronous multiple early gastric cancers after endoscopic mucosal resection*. Endoscopy, 2005.
33. Seo, J.H., et al., *Undifferentiated Histology after Endoscopic Resection May Predict Synchronous and Metachronous Occurrence of Early Gastric Cancer*. Digestion, 2010. **81**(1).
34. Min, B.-H., et al., *Surveillance strategy based on the incidence and patterns of recurrence after curative endoscopic submucosal dissection for early gastric cancer*. Endoscopy, 2015. **47**(9).
35. Hee Seok Moon, G.Y.Y., Ju Seok Kim, Hyuk Soo Eun, Sun Hyung Kang, Jae Kyu Sung, Hyun Yong Jeong, Kyu-Sang Song, *Risk factors for metachronous gastric carcinoma development after endoscopic resection of gastric dysplasia: Retrospective, single-center study.* Word Journal of Gastroenterology 2017.
36. Joo Hyun Lim, S.G.K., Jeongmin Choi, Jong Pil Im, Joo Sung Kim, Hyun Chae Jung, *Risk factors for synchronous or metachronous tumor development after endoscopic resection of gastric neoplasms*. Gastric Cancer, 2015.
37. Yoon, S.B., et al., *Incidence of gastric cancer after endoscopic resection of gastric adenoma*. Gastrointestinal Endoscopy, 2016.
38. Suzuki, T., et al., *Risk Factors for Developing Metachronous Superficial Gastric Epithelial Neoplasms after Endoscopic Submucosal Dissection*. Journal of Clinical Medicine, 2024. **13**(6): p. 1587.

39. Yang, H.-J., et al., *Novel risk stratification for metachronous recurrence after curative endoscopic submucosal dissection for early gastric cancer.* Gastrointest Endosc, 2016. **87**(2): p. 419-428.
40. Kim, N. and Y.H. Park, *Atrophic Gastritis and Intestinal Metaplasia.* Helicobacter pylori 2016: p. 187–206.
41. Tong, Q.-Y., et al., *Gastric intestinal metaplasia: progress and remaining challenges.* Journal of Gastroenterology 2024. **59**: p. 285–301.
42. Isajevs, S., et al., *Gastritis staging: interobserver agreement by applying OLGA and OLGIM systems.* Virchows Arch, 2014. **464**: p. 403–407.
43. Yun Suk Na, S.G.K., Soo-Jeong Cho, *Risk assessment of metachronous gastric cancer development using OLGA and OLGIM systems after endoscopic submucosal dissection for early gastric cancer: a long-term follow-up study.* 2022.
44. N Uemura 1, S.O., S Yamamoto, N Matsumura, S Yamaguchi, M Yamakido, K Taniyama, N Sasaki, R J Schlemper, *Helicobacter pylori infection and the development of gastric cancer.* N Engl J Med, 2001. **345**(11).
45. You, W.C., et al., *Evolution of precancerous lesions in a rural Chinese population at high risk of gastric cancer.* 1999. **83**(5).
46. Correa, P., *Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention.* Cancer Res, 1992. **52**(24).
47. Satoki Shichijo, Y.H., Ryota Niikura, Yoku Hayakawa, Atsuo Yamada, Tetsuo Ushiku , Masashi Fukayama, Kazuhiko Koike, *Histologic intestinal metaplasia and endoscopic atrophy are predictors of gastric cancer development after Helicobacter pylori eradication.* Gastrointest Endosc, 2016.
48. Sungmo Jung, C.H.P., Eun Hye Kim, Su Ji Shin, Hyunsoo Chung, Hyuk Lee, Jun Chul Park, Sung Kwan Shin, Yong Chan Lee, Sang Kil Lee, *Helicobacter pylori eradication is insufficient to prevent metachronous gastric lesions after ESD.*
49. Kyu Yeon Hahn, J.C.P., Eun Hye Kim, Suji Shin, Chan Hyuk Park, Hyunsoo Chung, Sung Kwan Shin, Sang Kil Lee, Yong Chan Lee, *Incidence and impact of scheduled endoscopic surveillance on recurrence after curative endoscopic resection for early gastric cancer.* Gastrointest Endosc, 2016.
50. Chung CS, W.H., Chung JW, Jeong SH, Kwon KA, Kim YJ, Kim KO, Park DK. , *Risk Factors for Metachronous Recurrence after Endoscopic Submucosal Dissection of Early Gastric Cancer.* J Korean Med Sci, 2017.
51. Khan, M.Y., et al., *Effectiveness of Helicobacter pylori eradication in preventing metachronous gastric cancer and preneoplastic lesions. A systematic review and meta-analysis.* Eur J Gastroenterol Hepatol, 2020. **32**(6): p. 686-694.
52. Uemura, N., et al., *Helicobacter pylori Infection and the Development of Gastric Cancer.* New England Journal of Medicine, 2001. **345**(11): p. 784-789.
53. Choi, K.-S., et al., *EMR versus gastrectomy for intramucosal gastric cancer: comparison of long-term outcomes.* Gastrointest Endosc, 2011.
54. Abe, S., et al., *Long-term surveillance and treatment outcomes of metachronous gastric cancer occurring after curative endoscopic submucosal dissection.* Endoscopy, 2015. **47**(12): p. 1113-8.
55. Pimentel-Nunes, P., et al., *Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline.* Endoscopy, 2015. **47**.
56. Huang, K., D. Jin, and G. Zhang, *Individualized Endoscopic Surveillance for Metachronous Gastric Cancer After Endoscopic Submucosal Dissection: A Retrospective Observational Study.* Turk J Gastroenterol, 2023. **34**(7): p. 728-735.
57. Zhu, Y., et al., *Application of convolutional neural network in the diagnosis of the invasion depth of gastric cancer based on conventional endoscopy.* Gastrointest Endosc, 2019. **89**(4): p. 806-815.

58. Tang, D., et al., *A Novel Model Based on Deep Convolutional Neural Network Improves Diagnostic Accuracy of Intramucosal Gastric Cancer (With Video).* Frontiers in Oncology, 2021. **11**.
59. Yoon, H.J., et al., *A Lesion-Based Convolutional Neural Network Improves Endoscopic Detection and Depth Prediction of Early Gastric Cancer.* Journal of Clinical Medicine, 2019. **8**(9): p. 1310.

INSTITUTO DE **CIÊNCIAS BIOMÉDICAS ABEL SALAZAR**