

DOUTORAMENTO

MEDICINA

**IMPROVING DIAGNOSIS AND MANAGEMENT OF UPPER
GASTROINTESTINAL NEOPLASIA**

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D

2025



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List of publications

In accordance with the Doctoral studies regulation of Portuguese Universities, this Dissertation comprises the following publications (*Ao Abrigo do Art.º 8º do Decreto-Lei nº 388/70, fazem parte desta Dissertação as seguintes publicações*):

Original research studies

1. Morais R, Moreira J*, Gaspar R, Santos-Antunes J, Marques M, Coelho R, Alves R, Ferreira-Silva J, Dias E, Pereira P, Lopes S, Cardoso H, Sousa-Pinto B, Faria-Ramos I, Gullo I, Carneiro F, Liberal R, Macedo G. *Higher frequency of gastric neoplasia in advanced chronic liver disease patients: Impact of screening endoscopy in an intermediate-high risk country*. **Dig Liver Dis**. 2024 Dec;56(12):2133-2142.

DOI: 10.1016/j.dld.2024.04.035

Epub 2024 May 28.

PMID: 38811247

*Joint first authors

2. Morais R*, Afonso* J, Sousa N, Sousa-Pinto B, Libânio D, Marinho B, Sacramento M, Simplício M, Faria-Ramos I, Azevedo L, Marques M, Silveira H, Gullo I, Carneiro F, Santos-Antunes J, Macedo G. *Cost-utility and clinical impact of endoscopic screening for esophageal and gastric neoplasia in patients with head and neck neoplasms*. **European Journal of Gastroenterology and Hepatology (accepted for publication)**.

*Joint first authors

3. Morais R, Amorim J, Medas R, Sousa-Pinto B, Santos-Antunes J, Legros R, Albouys J, Moll F, Marques M, Vilas-Boas F, Rodrigues-Pinto E, Gullo I, Carneiro F, Soares EG, Amaro P, Mesquita P, Rodrigues J, Andrisani G, Sferrazza S, Archer S, Kuttner-Magalhães R, Manzano F, de Santiago ER, Rimondi A, Murino A, Despott E, Pioche M, Jacques J, Macedo G. *Underwater Endoscopic Mucosal Resection Vs Conventional Endoscopic Mucosal Resection for Superficial Nonampullary Duodenal Epithelial Tumors in the Western Setting*. **Clin Gastroenterol Hepatol**. 2024 May 22:S1542-3565(24)00485-3.

DOI: 10.1016/j.cgh.2024.05.011

Epub ahead of print

PMID: 38782173

4. Morais R*, Libanio D*, Dinis Ribeiro M, Ferreira A, Barreiro P, Bourke MJ, Gupta S, Amaro P, Küttner Magalhães R, Cecinato P, Boal Carvalho P, Pinho R, Rodríguez de Santiago E, Sferrazza S, Lemmers A, Figueiredo M, Pioche M, Gallego F, Albéniz E, Ramos Zabala F, Uchima H, Berr F, Wagner A, Marques M, Pimentel-Nunes P, Gonçalves M, Mascarenhas A, Soares EG, Xavier S, Faria-Ramos I, Sousa-Pinto B, Gullo I, Carneiro F, Macedo G, Santos-Antunes J. *Predicting residual neoplasia after a non-curative gastric ESD: validation and modification of the eCura system in the Western setting: the W-eCura score.* **Gut.** 2023 Dec 7;73(1):105-117.

DOI: 10.1136/gutjnl-2023-330804

PMID: 37666656

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List of abbreviations

AEs	Adverse events
AI	Artificial Intelligence
ALD	Alcoholic liver disease
ASR	Age-standardized rates
AUC	Area under the curve
BE	Barrett's esophagus
cACLD	Compensated advanced chronic liver disease
C-EMR	Conventional endoscopic mucosal resection
CRC	Colorectal cancer
CS-EMR	Cold-snare endoscopic mucosal resection
EAC	Esophageal adenocarcinoma
EC	Esophageal cancer
EGC	Early gastric cancer
EGD	Esophagogastroduodenoscopy
EMR	Endoscopic mucosal resection
ER	Endoscopic resection
ESCC	Esophageal squamous cell carcinoma
ESD	Endoscopic submucosal dissection
ESGE	European Society of Gastrointestinal Endoscopy
FAP	Familial adenomatous polyposis
GC	Gastric cancer
GEN	Gastro-esophageal neoplasia
GERD	Gastro-esophageal reflux disease
GI	Gastrointestinal
GLOBOCAN	Global Cancer Observatory
GN	Gastric neoplasia
GOEV	Gastroesophageal varices
HGD	High grade dysplasia
HNN	Head and neck neoplasia
Hp	<i>Helicobacter pylori</i>
HPV	Human papillomavirus
IM	Intestinal metaplasia
LGD	Low-grade dysplasia
LMN	Lymph-node metastases
MAPS II	The second European guideline on the Management of Epithelial Precancerous Conditions and Lesions in the Stomach
NBI	Narrow-band imaging
NC	Non-curative
OLGA	Operative Link on Gastritis Assessment
OLGIM	Operative Link on Gastric Intestinal Metaplasia Assessment
OS	Overall survival
RT	Radiotherapy
SNADETs	Superficial nonampullary duodenal epithelial tumors
U-EMR	Underwater endoscopic mucosal resection
USA	United States of America
WHO	World Health Organization

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Acknowledgements

Este projeto Doutoral foi fruto de um longo trajeto que começou ainda antes de saber que seria gastroenterologista, quando tive oportunidade de fazer a minha Tese de Mestrado no Serviço de Gastroenterologia do Centro Hospitalar Universitário São João. Nesse momento, já havia o sonho de um dia poder continuar a desenvolver investigação nesta área.

Desde cedo, ainda como interno de Gastroenterologia, o meu maior fascínio prendeu-se sempre no diagnóstico e tratamento de lesões precoces do trato digestivo. O caminho desde a primeira endoscopia até ao presente momento foi difícil, sinuoso, mas sempre pautado por esforço, dedicação e vontade de saber mais. Mas acima de tudo e sem qualquer tipo de dúvida ou hesitação, “se eu vi mais longe, foi por estar aos ombros de gigantes”. A esses “gigantes” presto o meu agradecimento.

Ao Professor Guilherme Macedo, meu orientador e Diretor de Serviço, pela motivação constante e oportunidades concedidas; por me ter ensinado a importância de organizar “as caixas” da minha vida – tal conselho permitiu-me chegar a bom porto, e a conseguir alcançar todos os objetivos propostos, sem descurar tudo o resto que tanto importa.

À Professora Fátima Carneiro, minha orientadora, por ter aceite embarcar nesta viagem nem sempre fácil; por me ter guiado quando muitas vezes estive perto de estar perdido; por todas as discussões, reflexões e conselhos que trarei e guardarei comigo para sempre.

À Professora Irene Gullo, minha orientadora e amiga, pela disponibilidade constante, pela espírito crítico e brilhantismo que sempre demonstra que me obrigaram a dar não só mais como o melhor de mim.

Ao Professor Bernardo Sousa-Pinto, por ter sido o orientador que não contava ter; por todo o conhecimento e motivação transmitidas; por me ter ajudado a perceber que ainda tenho tanto a aprender no que toca a investigação clínica.

Aos meus “mestres” do ponto de vista clínico: Professor João Santos-Antunes e Dra. Margarida Marques. Por partilharem esta caminhada comigo; por todos os

ensinamentos, momentos de partilha e discussão que nos têm ajudado, todos em conjunto, a melhorar e evoluir.

Aos internos do meu Serviço, internos de Anatomia Patológica, internos do ano comum e alunos de Mestrado que tive oportunidade de orientar, ensinar e que colaboraram ativamente comigo nestes projetos: Dr. Renato Medas, Dr. João Afonso, Dr. Tiago Ribeiro, Dr. Nuno Sousa, Dr. Francisco Mendes, Dr. Miguel Martins, Dr. José Amorim, Dr. João Moreira, Dra. Bárbara Marinho, Dra. Luísa Sacramento e Dra. Mariana Simplício. Um dos meus maiores orgulhos neste caminho é ver a vossa evolução, empenho, dedicação, tendo a certeza de que todos sem exceção têm um futuro brilhante à vossa frente.

A verdade é que “You’ll never walk alone”. E dois dos projetos desenvolvidos foram estudos multicêntricos, que seriam impossíveis sem a colaboração, esforço e dinamismo de colegas de outros serviços, nacionais e internacionais. A todos eles, o meu mais profundo agradecimento, mas em particular ao Professor Diogo Libânio, Professor Ricardo Küttner Magalhães, Professor Mathieu Pioche e ao Professor Enrique Rodríguez de Santiago.

Ao Professor Rodrigo Liberal, pela motivação e apoio transmitidos que tornaram possível a concretização do projeto focado no rastreio de cancro gástrico nos doentes com cirrose hepática, ao fim de tantos anos de discussão e trabalho.

À Dra. Helena Silveira do Serviço de Otorrinolaringologia do Hospital de São João, por ter acreditado em mim e ajudado na implementação do programa de rastreio endoscópico em doentes com neoplasia da cabeça e pescoço.

A todos os colegas do meu Serviço: médicos, enfermeiros, assistentes operacionais e assistentes técnicos. Por todo o companheirismo, amizade e motivação constante.

Aos meus amigos mais próximos.

À minha família,

Ao meu irmão Luís, que apesar de mais novo e a milhares de quilómetros de distância nunca se deixou de preocupar comigo, sempre tendo uma palavra amiga num momento de desânimo, uma palavra sábia num momento de dúvida.

À minha mulher Inês. Sem ti seria tudo tão mais difícil. Por todo o amor e por estares realmente “presente” em todos os momentos. Pela tua confiança inabalável, pelo teu apoio e suporte que permitiram concluir este caminho da melhor maneira possível.

E por fim, aos meus pais.

De facto, estes são os “gigantes” para que reservo o meu último e mais sentido agradecimento. Por todo o amor, por todos os (muitos) esforços que fizeram para eu poder alcançar os meus objetivos; por me terem motivado nos momentos de dúvida; por me terem alegrado nos momentos mais tristes; mas acima de tudo por me terem transmitido tudo aquilo que tento aplicar na minha vida pessoal, como médico e investigador: a importância do respeito por todos; a importância de saber cuidar; a importância de lutarmos pelos nossos sonhos mas nunca esquecendo que as adversidades não são o fim – são apenas algo que nos ajuda a tornarmo-nos melhores.

Um muito obrigado.

*The future has many names:
for the weak, it means the unattainable,
for the fearful, it means the unknown,
for the courageous, it means opportunity.*

Victor Hugo, Les Misérables

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1. Abstract

The gastrointestinal (GI) tract is the organ system with the highest cancer burden and cancer mortality. More particularly, upper GI neoplasia encompasses esophageal cancer (EC), gastric cancer (GC) and duodenal cancer. There is a wide variation between these neoplasias regarding epidemiology, natural history, diagnostic and therapeutic management. EC and GC belong to the most commonly diagnosed malignancies worldwide, being associated with a high disease-related mortality. Regarding duodenal neoplasia, while most cases are diagnosed incidentally by esophagogastroduodenoscopy (EGD) performed for other reasons, they are being increasingly detected and pose a significant challenge, since endoscopic resection (ER) in this location is more difficult and associated with a higher risk of adverse events (AEs) compared with other locations.

Differences in the modifiable risk factors, genetic background and in the distribution of tumor subtypes across populations have been found to partially explain the worldwide and even regional differentials in the burden from GI cancers; more particularly, wide variations between Western and Asian populations are evident, especially for EC and GC. This may significantly impact on the applicability of the results and data from Asian centers to Western populations and vice-versa. Some Asian countries (such as Japan and Korea) have structured, nationwide endoscopic screening programs for EC and GC, whose cost-effectiveness has been demonstrated, given the high incidence of these cancers. Nevertheless, many questions remain to be answered in the context of Western countries, namely: (i) the efficacy and cost-effectiveness of screening for upper GI neoplasia [particularly in high-risk populations such as patients with compensated advanced chronic liver disease (cACLD) and patients with head and neck neoplasia (HNN)], (ii) the applicability and safety of advanced ER techniques and (iii) the long-term management after ER of upper GI neoplasia, especially in the undesirable event of a non-curative resection, which could have a significant impact in the decision-making process.

Therefore, the main aim of this thesis was to present case studies on how to improve the screening, therapeutic approach and long-term management of upper GI neoplasia in the Western setting.

The first study was a retrospective study that aimed to evaluate the frequency of gastric neoplasia in cACLD patients who underwent EGD for screening for gastroesophageal varices compared to healthy individuals who underwent EGD for GC screening (at the same time as colonoscopy performed for colorectal cancer screening). We found an increased frequency of gastric neoplasia in patients with cACLD in comparison to healthy individuals. Our results support that, at least in Portugal and other European countries with intermediate-high incidence of GC, continuing to perform EGD in patients with cACLD should be considered, instead of a non-invasive approach for evaluation of gastroesophageal varices.

The second study was a prospective single-center study that aimed to evaluate the clinical impact and cost-effectiveness of an endoscopic screening program for esophageal (EN) and gastric neoplasia (GN) in patients with HNN. We identified EN or GN in a fifth of HNN patients, most presenting at an early stage and being amenable to ER. In the health economic analysis, the program implementation was shown to be cost-effective in Portugal. These results may be applicable to other medium-high-income Western countries.

The third study was a retrospective multinational Western study (10 European centers) that aimed to compare the efficacy and outcomes of underwater endoscopic mucosal resection (U-EMR) versus conventional endoscopic mucosal resection for the management of superficial nonampullary duodenal epithelial tumors. U-EMR recently emerged as potential alternative in the therapeutic management of these lesions, but previous studies focused on Asian populations and small lesions. We found that U-EMR was associated with a lower rate of AEs and residual lesion, regardless of lesion size. Our results confirm the possible role of U-EMR as an effective and safe technique in the management of superficial nonampullary duodenal epithelial tumors.

The fourth study was a retrospective multinational study (19 European and Australian centers) that aimed to validate the eCura scoring system [previously created and validated in Japan to aid in decision-making after a non-curative gastric

endoscopic submucosal dissection by stratifying patients into low, intermediate and high risk for lymph node metastasis]. We confirmed that the eCura may be applied in Western countries. In addition, a modified version of the eCura was created (W-eCura). The W-eCura showed a higher accuracy than the original eCura system. This new score may be particularly helpful in high-risk surgical patients, avoiding unnecessary surgeries, while maintaining a very high sensitivity.

This thesis provides data that may contribute to improving the diagnosis, therapeutic approach and long-term management of upper GI neoplasia; in fact, with tailored patient selection, judicious use of ER techniques and score-guided decision-making after ER, it may be possible to achieve similar results in the Western setting to those observed in Asian countries, such as Japan.

2. Resumo

O trato gastrointestinal é o órgão com maior incidência e mortalidade por cancro. Mais particularmente, a neoplasia do tubo digestivo superior abrange o cancro do esófago (CE), o cancro gástrico (CG) e o cancro duodenal. Existe uma grande variação entre estas neoplasias no que respeita à epidemiologia, história natural, abordagem diagnóstica e terapêutica. O CE e o CG são das neoplasias mais comumente diagnosticadas em todo o mundo, estando associadas a uma elevada mortalidade relacionada com a doença. Em relação às neoplasias duodenais, embora a maioria dos casos seja diagnosticada incidentalmente por esofagogastroduodenoscopia (EGD) realizada por outros motivos, estão a ser cada vez mais detetadas e representam um desafio significativo, uma vez que a ressecção endoscópica (RE) nesta localização é mais difícil e está associada a um maior risco de eventos adversos em comparação com outras localizações.

Verificou-se que as diferenças nos fatores de risco modificáveis, nos antecedentes genéticos e na distribuição dos subtipos de tumores entre as populações podem explicar parcialmente as diferenças a nível mundial e mesmo regional na frequência dos cancros gastrointestinais; em particular, são evidentes grandes variações entre as populações ocidentais e asiáticas, especialmente para o CE e o CG. Isto pode afetar a aplicabilidade dos resultados e dados dos centros asiáticos às populações ocidentais e vice-versa. Alguns países asiáticos (como o Japão e a Coreia) têm programas nacionais estruturados de rastreio endoscópico para o CE e CG, cuja relação custo-eficácia foi demonstrada, dada a elevada incidência destes cancros. No entanto, muitas questões continuam por responder no contexto dos países ocidentais, nomeadamente: (i) a eficácia e a relação custo-eficácia do rastreio da neoplasia do trato gastrointestinal superior [particularmente em populações de alto risco, como os doentes com doença hepática crónica avançada compensada (DHCAC) e os doentes com neoplasia de cabeça e pescoço], (ii) a aplicabilidade e segurança de técnicas avançadas de RE e (iii) a abordagem a longo prazo após RE de neoplasias do trato gastrointestinal superior, especialmente no evento indesejável de uma ressecção não curativa, que pode ter um impacto significativo no processo de tomada de decisão.

Assim sendo, o principal objetivo desta tese foi apresentar estudos de caso sobre como melhorar o rastreio, a abordagem terapêutica e o tratamento a longo prazo da neoplasia do trato gastrointestinal superior no contexto Ocidental.

O primeiro estudo foi um trabalho retrospectivo no qual se avaliou a frequência de neoplasia gástrica em doentes com DHCAc submetidos a EGD para rastreio de varizes gastroesofágicas em comparação com indivíduos saudáveis que foram submetidos a EGD para rastreio de CG (ao mesmo tempo que a colonoscopia realizada para rastreio do cancro colorretal). Verificámos uma frequência aumentada de neoplasia gástrica em doentes com DHCAc em comparação com indivíduos saudáveis. Os nossos resultados suportam que, pelo menos em Portugal e noutros países europeus com incidência intermédia-elevado de CG, deve ser considerada a continuação da realização de EGD em doentes com DHCAc, ao invés de uma abordagem não invasiva para exclusão de varizes gastroesofágicas.

O segundo foi um estudo prospetivo unicêntrico que teve como objetivo avaliar o impacto clínico e a relação custo-eficácia de um programa de rastreio endoscópico para neoplasia esofágica (NE) e gástrica (NG) em doentes com neoplasia da cabeça e pescoço. Identificámos NE ou NG em um quinto dos doentes, a maioria apresentando-se em estadio inicial e passível de ressecção endoscópica. Na análise económica de saúde, a implementação do programa revelou-se custo-eficaz em Portugal. Estes resultados podem ser aplicáveis a outros países ocidentais de rendimento médio-elevado.

O terceiro estudo foi um estudo ocidental multinacional retrospectivo (10 centros europeus) que teve como objetivo comparar a eficácia e os resultados da ressecção endoscópica da mucosa subaquática (U-EMR) versus a ressecção endoscópica da mucosa convencional para o tratamento de lesões epiteliais duodenais superficiais não ampulares. A U-EMR surgiu recentemente como uma potencial alternativa na abordagem terapêutica destas lesões, mas estudos anteriores focaram-se em populações asiáticas e lesões pequenas. Verificámos que a U-EMR se associou a uma menor taxa global de eventos adversos e de lesão residual, independentemente do tamanho da lesão. Os nossos resultados confirmam o possível papel da U-EMR como

uma técnica eficaz e segura na gestão das lesões epiteliais duodenais superficiais não ampulares.

O quarto estudo foi uma análise retrospectiva multinacional (19 centros europeus e australianos) que teve como objetivo validar o sistema de pontuação eCura [previamente criado e validado no Japão para auxiliar na tomada de decisão após uma dissecação endoscópica da submucosa gástrica não curativa, estratificando doentes em risco baixo, intermédio e alto de metástase ganglionar]. Confirmámos que o eCura pode ser aplicado nos países ocidentais. Além disso, foi criada uma versão modificada do mesmo: W-eCura. O W-eCura apresentou uma maior precisão do que o sistema eCura original. Este novo score pode ser particularmente útil em doentes cirúrgicos de alto risco, evitando cirurgias desnecessárias, mantendo ao mesmo tempo uma sensibilidade muito elevada.

Esta tese fornece dados que podem contribuir para melhorar o diagnóstico, a abordagem terapêutica e a gestão a longo prazo das neoplasias do trato gastrointestinal superior; de facto, com a seleção personalizada dos doentes, a utilização criteriosa de técnicas de RE e a tomada de decisão guiada por sistemas de pontuação após RE, resultados semelhantes aos observados em países asiáticos, como o Japão, poderão ser alcançados no Ocidente.

3. Introduction

The gastrointestinal (GI) tract is the organ system with the highest cancer burden and cancer mortality. GI cancers account for one-fourth of cancer cases, with over 5.2 million cases of GI cancers diagnosed in 2021, and nearly one-third of cancer-related mortality globally (1, 2). From 2010 to 2021, while the incidence rates of colorectal cancer (CRC), pancreatic cancer and liver cancer (from metabolic dysfunction-associated steatotic liver disease and alcohol-related liver disease) have increased, esophageal, gastric and biliary tract cancer have decreased (2). There is a considerable variation in incidence and mortality rates across the world, but most cases are still diagnosed at advanced stages (3).

Upper GI neoplasia encompass esophageal cancer (EC), gastric cancer (GC) and duodenal cancer. There is a wide variation between these neoplasias regarding epidemiology, natural history, diagnostic and therapeutic management (4). Nevertheless, considering that their clinical burden may be significant, all of them will be considered in this thesis.

3.1. Epidemiology and pathogenesis of upper gastrointestinal neoplasia

EC and GC belong to the most commonly diagnosed malignancies worldwide, being associated with a high disease-related mortality (5, 6) (Fig. 1 and 2). Given their anatomic proximity, both sites share several risk factors and epidemiological features. However, EC and GC also display distinct geographical and temporal patterns in their incidence. Also, although most cases of duodenal neoplasia are diagnosed incidentally by esophagogastroduodenoscopy (EGD) performed for other reasons (7), duodenal precursor and invasive lesions are being increasingly detected and their epidemiological trends should also be addressed.

Figure 1. Age-standardized incidence rate (World) per 100 000 of EC and GC (combined), both sexes combined, 2022.

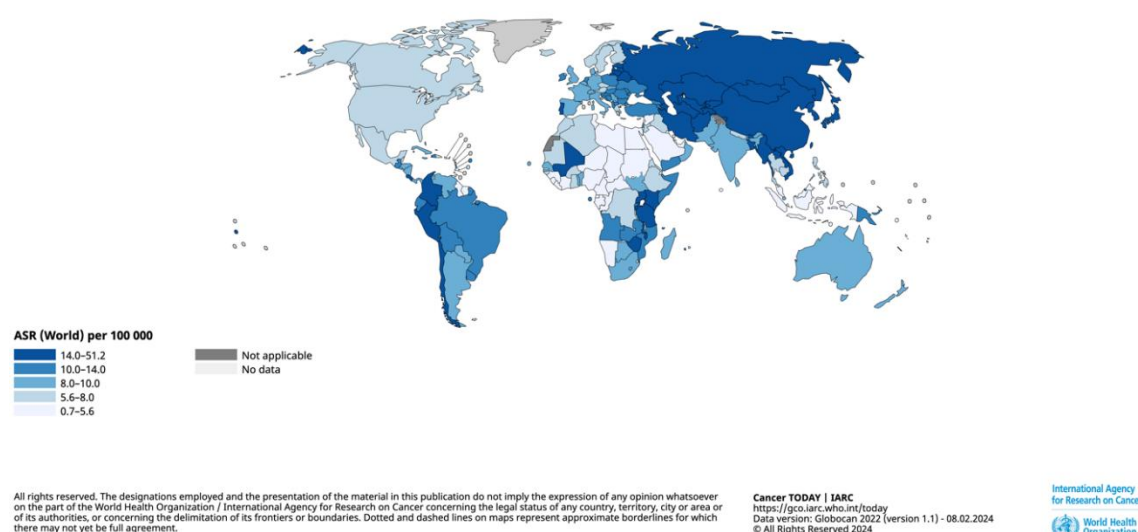
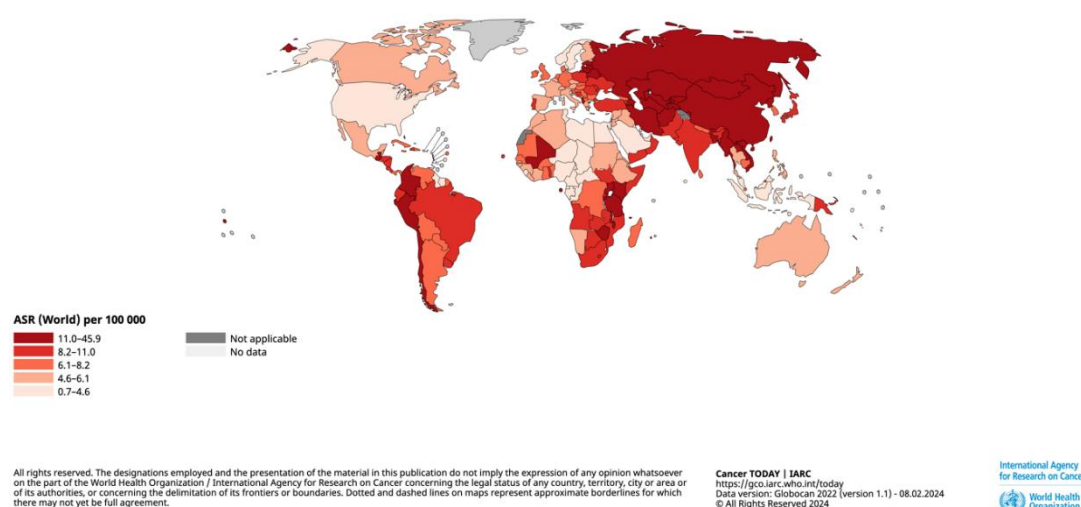


Figure 2. Age-standardized mortality rate (World) per 100 000 of EC and GC (combined), both sexes combined, 2022.



3.1.1. Esophageal neoplasia

EC is a complex disease whose etiological factors vary depending on the histologic type and the population in which it occurs. Typically, two main histological subtypes of EC are distinguished: squamous cell carcinoma (ESCC) and adenocarcinoma (EAC). While ESCC occurs primarily in stratified squamous epithelium lining the upper two-

thirds of the esophagus, EAC typically develops in the lower third of the esophagus and originates predominantly from the Barrett mucosa (8). ESCC and EAC have almost completely distinct geographic patterns, time trends, and primary risk factors (9).

Globally, there were more than 500,000 new cases and more than 400,000 deaths from EC in 2022, corresponding to age-standardized incidence and mortality rates of 5.0 and 4.3 per 100,000, respectively. Most cases (85%) were SCCs. Incidence and mortality rates were 2- to 3-fold higher in males compared with females (3). Although age-standardized incidence and mortality rates of EC have decreased worldwide over the past three decades, there has been an increase in (i) absolute numbers of new cases and deaths and (ii) disability-adjusted life years attributable to EC, in relation to population growth and ageing (10). These trends over time indicate that EC still causes a substantial disease burden across the world that may continue to rise. It is important to note that while globally ESCC remains the most common type of EC, recent studies have showed a changing landscape of EC, with decreases in ESCC and increases in EAC observed in high-income Western countries, most likely due to changes in risk factor profiles across these countries (6, 11).

The most important prognostic factor of EC is the disease stage at diagnosis, with most cases being diagnosed at an advanced stage. EC survival in most countries remains low, in the range of 10%–30% at 5 years after diagnosis (12). Nevertheless, there are promising results from some high-income countries, such as Japan, with a 5-year survival of 34% in the 2010-2014 period (12).

Esophageal squamous-cell carcinoma

ESCC remains the most common subtype of EC globally, with its highest incidence rates in Eastern Asia and Eastern Africa, particularly in areas such as Northern Iran, Central Asia and China (forming the so-called “esophageal cancer belt”) (6). This area was along the path of the Silk Road, which has led to hypotheses that some shared environmental and/or genetic risk factors along this route can be a possible explanation for the observed high risk (10).

The etiology of ESCC is multi-factorial and strongly population-dependent. Tobacco smoking and heavy alcohol consumption remain the two main risk factors for ESCC

and have been found to be responsible for the majority of ESCC cases in high-income countries (13, 14). These behaviors were historically more prevalent in men than in women. Nevertheless, in high-incidence areas, risk factors such as hot beverage drinking, opium use, low intake of fresh fruits, indoor air pollution, lack of access to piped water, poor oral health and low socioeconomic status seem to be the main contributors for this neoplasia (15, 16). These risk factors seem to be less sex-dependent than those reported in high-income countries. Other risk-factors include caustic injuries and radiotherapy (RT) for breast cancer (17, 18). Given these large differences in etiology, population-specific estimates are needed for all risk factors.

Precursor lesions and histopathological characterization

ESCC is generally believed to develop through a sequence of dysplastic precursor lesions, which can be detected endoscopically and diagnosed by histopathological evaluation (19). Squamous dysplasia of the esophagus is defined as an unequivocal neoplastic alteration of the esophageal squamous epithelium (with evident architectural and cytologic abnormalities) limited to the esophageal epithelium and not invading the lamina propria (20, 21). Squamous dysplasia results from clonal genetic alterations [e.g. *PT53* alterations, which occurs in approximately 90% of all cases (22, 23)] and is associated with a predisposition for progression to invasive carcinoma.

Risk factors for dysplasia are similar to those previously identified for ESCC. It is important to note that numerous studies have attempted to assess whether human papillomavirus (HPV) is an etiologic agent in esophageal carcinogenesis, possibly by acting synergistically with physical, chemical, and/or nutritional factors that have previously been described (24). However, evidence is controversial and contradictory. For example, there are studies reporting HPV positivity in 13% of subjects without squamous dysplasia, compared to 8% to 16% with squamous dysplasia, and 0% with invasive ESCC (25). Overall, this indicates that, if HPV is an etiologic agent, the number of cases caused by this virus is very low (9, 26-30).

Microscopically, squamous dysplasia is characterized by architectural and cytologic abnormalities that vary in extent and severity. Architectural abnormalities include loss of normal cell polarity, overlapping nuclei, and lack of surface maturation. Cytologic

abnormalities encompass nuclear changes, such as enlargement, hyperchromasia, pleomorphism, increased nuclear/ cytoplasmic ratio, as well as increased mitotic activity. The histopathologic characterization of squamous dysplasia is relevant for grading and diagnosis purposes. For example, the World Health Organization (WHO) classification adopted a two-tiered system [low-grade (LGD) and high-grade (HGD)] for the grading of squamous dysplasia, based on the vertical extent of epithelial involvement of the dysplastic cells and the severity of cytologic atypia (20). As another example, in Western countries, ESCC is diagnosed when the neoplastic epithelium invades the lamina propria or beyond. In contrast, most Japanese pathologists define HGD as “non-invasive” or “in situ” squamous-cell carcinoma. This is a consequence of differences in the diagnostic criteria for carcinoma, with Japanese pathologists considering nuclear atypia to be as important as the invasive depth of the tumor (31). Nevertheless, despite these differences in the histopathological characterization, the clinical management is similar in the Western and Japanese setting (32).

The natural history of esophageal squamous dysplasia may be influenced by local and systemic immune responses (33). Previous Asian studies showed that approximately two-thirds of cases of dysplasia have a regressive or stable status, with the remaining one-third having a progressive status (34). The risk of progression increases along with the histologic grading of dysplasia (35). A recent nationwide study from Netherlands showed that the annual risk of ESCC was 4.0% in patients with LGD and 8.5% in patients with HGD, with the rate of ESCC development increasing with the severity of the dysplasia and age (36). This suggest that endoscopic follow-up or treatment should be considered in all patients with esophageal squamous dysplasia. While for patients with LGD endoscopic surveillance with careful inspection with virtual chromoendoscopy [such as narrow-band imaging (NBI)] or dye-based chromoendoscopy of the esophageal mucosa may be applied, in patients with HGD and in case of suspected ESCC, endoscopic treatment should be performed (19).

Esophageal adenocarcinoma

Over the past 30 years, there has been a significant increase in the incidence of EAC in many Western countries (37). In 2012, an estimated 52,000 individuals (41,000 men and 11,000 women) developed EAC worldwide, resulting in a global incidence rate of

0.7 per 100,000 person-years (1.1 in men and 0.3 in women). Most patients (53%) were from Europe, Northern America, or Oceania (38). The incidence rate of EAC has surpassed that of ESCC in several Western countries, including the United Kingdom (UK), the Netherlands, Ireland, New Zealand, the United States of America (USA), Australia, Denmark, Canada, and Sweden (38, 39). According to recent projections, the incidence of EAC is set out to continue to increase, so that EAC is expected to become the predominant type of EC in a growing number of high-income and very high-income countries (40). EAC is characterized by a striking male predominance, probably reflecting differences in the prevalence of risk factors (41).

These trends have largely been attributed to increase levels of abdominal obesity, a major cause of gastro-esophageal reflux disease (GERD), and Barrett's esophagus (BE) (42, 43). GERD was first established as a risk factor for EAC in the late 1990s and later confirmed in population-based studies (with this association being stronger in adults younger than 50 years) (44, 45). According to the European Society of Gastrointestinal Endoscopy (ESGE) guidelines, individuals with BE and long-term GERD and additional risk factors should be screened by EGD for dysplastic BE or early-stage EAC (46). Nevertheless, EACs are missed in a large proportion of patients with BE because 40% do not report GERD symptoms (47). Regarding other factors, tobacco smoking is a well-established and moderately strong risk factor for EAC (48). By contrast, a recent pooled analysis from the International Barrett's Esophagus and Esophageal Adenocarcinoma Consortium confirmed no association between alcohol intake and an increased risk of EAC (49). At the same time, *Helicobacter pylori* (Hp) infection may reduce the risk of EAC due to lower acid production (50, 51). Meta-analyses of observational studies have reported a 40%–60% reduced risk of EAC associated with Hp (52, 53). However, eradication of Hp does not seem to pose an increased risk for EAC, as suggested by a recent Nordic study (54). Nevertheless, further data are necessary in order to evaluate the generalizability of this study to different geographic and socioeconomic backgrounds (55).

Precursor lesions and histopathological characterization

BE is the sole known precursor to the development of EAC and is characterized by changes of the distal esophagus to specialized columnar epithelium with intestinal

metaplasia (IM) (56). BE has been an area of controversy and its definition and practice have varied along time and across the world (57). As examples, (i) the ESGE, American Society for Gastrointestinal Endoscopy, and the American College of Gastroenterology define BE as IM lining in the distal esophagus with a minimum length of 1 cm, (ii) the American Gastroenterology Association defines it as any extent of IM, and (iii) the British Society of Gastroenterology as any columnar metaplasia (fundic type, cardiac type, and intestinal type) lining in the distal esophagus with a minimum length of 1 cm (46, 58-60).

BE progresses to EAC in a stepwise manner, transitioning from nondysplastic BE to LGD, HGD and EAC. The development of EAC is driven through progressive accumulation of genetic abnormalities such as mutational inactivation of *CDKN2A* and *TP53* genes, cell cycle abnormalities and aneuploidy (61).

Current guidelines require the confirmation of any dysplasia in BE by a second expert pathologist (46). This is especially important in the case of BE with LGD, whereby considerable inter-observer variability exists (62). While BE without dysplasia may benefit from endoscopic surveillance, therapy for the eradication of BE is appropriate in the presence of confirmed dysplasia or early EAC (46).

3.1.2 Gastric neoplasia

GC is a leading cause of global mortality (63). Worldwide, in 2022, 968,784 individuals were diagnosed and 660,175 died from GC, making GC the sixth-most common cancer and the seventh-leading cause of cancer-related death (3). There is marked worldwide variability in the incidence of GC (3, 63). Such incidence is highest in East Asia, Central Asia, and Latin America [age-standardized rates (ASR) >15 per 100,000 person-years] and lowest in eastern sub-Saharan Africa, the USA, Canada, Western Europe, Australia, and New Zealand (ASR <6 per 100,000 person-years). Nevertheless, it is important to note that, even within regions, significant heterogeneity in incidence can occur. Furthermore, it is important not to forget that even in countries with a relatively low incidence and mortality, the burden is typically higher among the most vulnerable populations, such as immigrants from not only high but also low-risk incidence regions (64).

In the European Union, while the incidence and mortality of GC are relatively low (6.5 and 4.1 per 100,000, respectively), substantial differences exist between countries. In fact, the burden of GC is particularly high in Portugal and the Baltic countries (65). Portugal is a paradigmatic example of a country that does not follow the epidemiological trends of its region, as it is a country with intermediate incidence of GC (defined as an ASR between 10-20 per 100,000 person-years). The current Portuguese ASR is of 12.8 per 100,000, being the highest among Western European countries (3). The incidence of GC is particularly high in the Northern Portugal, with a verified ASR between 25 and 30/100,000 (66). The reasons for this unexpectedly high incidence have not previously been elucidated but are most likely multifactorial, with a combination of genetic factors, familial aggregation, dietary habits (namely the high consumption of salted and smoked meat) and a high prevalence of Hp infection (67). Nevertheless, these results also show a large potential for a decrease in the burden of GC in Portugal, namely through primary prevention measures and adoption of screening strategies. In fact, a recent study by Libânio D et al showed that between 2007-2016, in Northern Portugal, the ASR decreased by 4.5%, while its mortality reduced 30.9% (66). Interestingly, in this period, the proportion of cases detected at a T1 stage increased by 5.9 percent points, the 1-year net survival increased from 57.2% to 60.6%, and the 5-year net survival increased from 33.8% to 38.3%. In Portugal, co-payment for colonoscopy sedation was introduced in 2010. The increase in the number of EGDs performed accompanied the rise in colonoscopies, supporting the hypothesis that greater availability of EGDs contributed to the increased detection of T1 cancers in the country.

The incidence and mortality from GC are typically decreasing across the globe, with this trend being mainly attributable to a decline in non-cardia GC (68, 69). At the same time, owing to changing patterns of the populations (namely advancing age), the absolute number of GC cases and deaths are expected to increase. If the current trends continue, a 62% rise in the number of cases within a 20-year period is expected (70). Data from the Global Cancer Observatory (GLOBOCAN, 2022) showed that, in Europe, the number of new GC cases has been estimated to increase from 136,000 in 2022 to 174,000 in 2050, and GC-related deaths from 95,400 to 128,000, respectively (3). It is important to note that countries with a higher GC-related mortality rate also tend to

be those with a higher incidence (10). However, Japan and South Korea are notable exceptions, due to structured, nationwide GC screening programs. In fact, GC 5-year survival in Japan and South Korea exceeds 60%, while in the rest of the world (including in North America and Western Europe) it does not surpass 35% (12). This situation can be explained by diagnosis of the disease at a relatively late stage, therefore indicating the importance of prevention and screening. Previous studies reported that the mortality might be reduced by 40%, with early detection by means of screening (71). Surprisingly, until a few years ago, the need for screening of GC has not been prioritized in the Western setting (including Europe) because of declining incidence and mortality indicators (65).

Typically, two subsites of GC can be distinguished: (i) cardia GC or proximal GC, and (ii) non-cardia GC or distal GC. Whereas cardia GC arises in the proximal stomach, non-cardia GC cancers occur in more distal regions of the stomach. Gastric carcinogenesis is a multistep and multifactorial process and is the result of the complex interplay between genetic susceptibility and environmental factors (72). While obesity has been associated with cardia GC, Hp infection remains the main causal risk factor for GC, being responsible for 90% of all non-cardia GC and 20% of all GC in 2018 (73). Of note, while approximately half of the world's population is infected with Hp, only a small fraction will end up developing GC, suggesting that other environmental or host-related factors may contribute to cancer development (74). These include (i) autoimmune gastritis (75); (ii) Epstein-Barr virus infection (76); (iii) microbial community modifications by long-term use of proton-pump inhibitors (77); (iv) smoking; (v) diets rich in salt/salt-preserved foods; and (vi) consumption of red and processed meat (78-81). In opposition, dietary fruit and vegetable intake and the consumption of nonsteroidal anti-inflammatory drugs were shown to be associated with a decreased risk of non-cardia GC (82, 83).

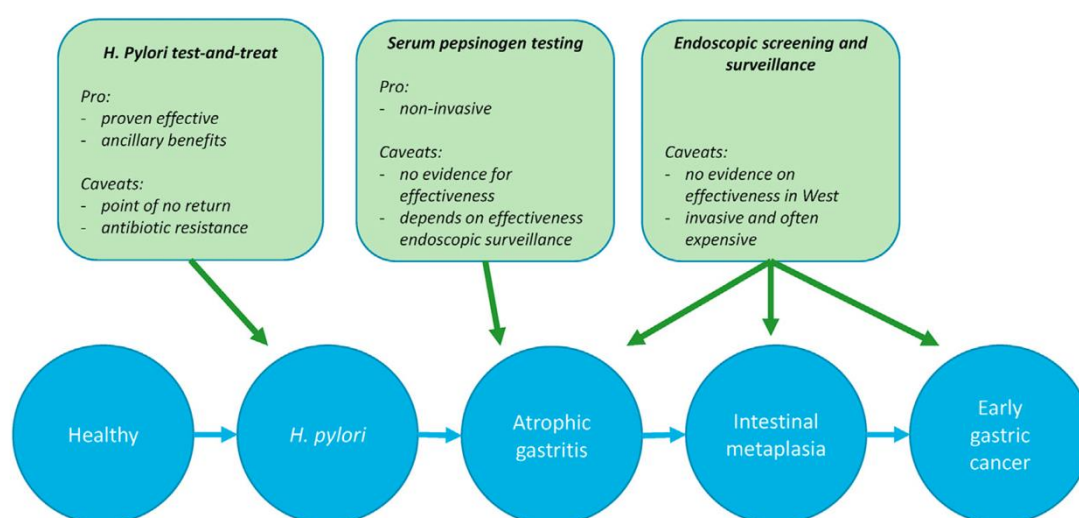
Most GC cases are sporadic, but familial aggregation is estimated to occur in approximately 10% of cases (84). Nevertheless, it is estimated that only up to 3% of worldwide GCs are truly hereditary, with three main syndromes occurring primarily in the stomach: (i) hereditary diffuse gastric cancer; (ii) gastric adenocarcinoma and (iii) proximal polyposis of the stomach, and familial intestinal gastric cancer (63, 84). Other hereditary cancer syndromes, including Lynch syndrome, familial adenomatous

polyposis (FAP) and Peutz-Jeghers syndrome have been associated with increased GC risk (85).

Precursor lesions and histopathological characterization

Several precancerous conditions have previously been recognized, such as chronic atrophic gastritis and IM, peptic ulcer disease, gastric stump after partial gastrectomy and gastric polyps. The typical mechanism of intestinal type cancer development, described by Pelayo Correa in 1988, is a multistep process which involves, in most cases, a progression from normal mucosa through chronic gastritis (chronic inflammation of the gastric mucosa), mucosal atrophy (loss of gastric glands) and IM (substitution of gastric epithelium by intestinal epithelium) to dysplasia and carcinoma (86). An overview of the Correa cascade, along with the possibilities for prevention and screening of GC is highlighted in Figure 3.

Figure 3. Overview of the Correa cascade.



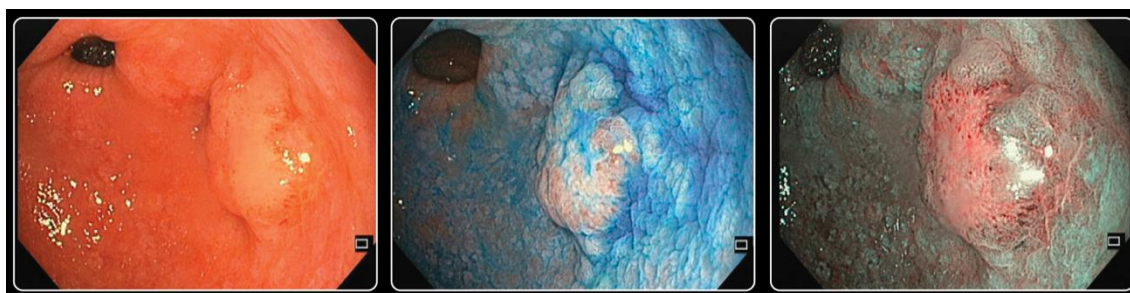
Used with permission from: Lansdorp-Vogelaar I et al. Cost-effectiveness of prevention and early detection of gastric cancer in Western countries. *Best Pract Res Clin Gastroenterol.* 2021 Mar-Apr;50-51:101735

According to this model, long standing inflammation is the primary pathogenic factor leading to GC development. The annual progression rate from IM to GC is estimated to be 0.1% per year, with the topographical extent of IM and the degree of incomplete-type IM being reliable indicators of GC risk (87, 88). Several classification

systems for chronic gastritis have been developed, including the Sydney classification system (89), the Operative Link on Gastritis Assessment (OLGA) (90), and the Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) (91). These systems have emerged as key tools in assessing the severity and extent of these mucosal changes and predictors for cancer risk (92). More recently, Pimentel-Nunes P *et al* proposed an Endoscopic Grading of Gastric Intestinal Metaplasia system, using virtual chromoendoscopy with NBI, which possibly allows a better staging of gastritis than histology alone since it takes into account a complete assessment of the gastric mucosa (93). This score has been further validated in the Western and Asian settings and may be an additional tool in the personalized management of gastric precancerous conditions (94, 95).

Gastric dysplasia is defined as unequivocal neoplastic changes in the gastric epithelium, without evidence of lamina propria invasion. The diagnostic criteria are based on the presence of cellular atypia, abnormal differentiation, architectural disorganization and increased mitotic activity. Gastric dysplasia can be graded as LGD or HGD (72) (Fig. 4).

Figure 4. Gastric lesion evaluated in white-light, dye chromoendoscopy with indigo carmine and virtual chromoendoscopy. Histopathological examination after ESD revealed HGD, with free lateral margins.



Author's own images.

On the contrary, gastric adenocarcinoma is a malignant epithelial neoplasm with glandular differentiation arising from the gastric mucosa. It represents a biologically heterogeneous group of tumors with respect to etiology, histogenesis, morphology, and molecular features. Early GC (EGC) is defined as a carcinoma limited to the mucosa or to the mucosa and submucosa, regardless of tumor size or the presence of lymph-node metastases (LNM) (96).

GC is very heterogenous from the morphological standpoint, and intratumor heterogeneity may also be evident (*i.e.* the coexistence of different morphological components within the same tumor) (97). Some of the histological classifications that have been proposed include those of Laurén (1965) (98), Nakamura (1968) (99), Carneiro (1995) (100), the WHO (2010) (20), and the Japanese Gastric Cancer Association (2011), which is mainly used by Asian pathologists (96). Noteworthy, Western and Asian pathologists with expertise on GC have made the effort of recognizing the similarities of different classification systems and proposed, in the last version of the Japanese Gastric Cancer Association and the WHO classifications, the publication of a comprehensive table showing corresponding entities. This highlights the effort for greater reproducibility and applicability of findings and studies between Western and Asian centers.

Besides morphological heterogeneity, multiple gene mutations, epigenetic and transcriptional changes have been detected in GC, highlighting its molecular heterogeneity (72). The landmark study of GC molecular-based stratification was carried out by The Cancer Genome Atlas research network, which defines four molecular subtypes: (i) Epstein-Barr virus-associated GC; (ii) microsatellite instability-high GC; (iii) genomically stable GC and (iv) GC with chromosomal instability (101). This classification has prognostic significance and may show predictive value in the response to conventional chemotherapy, as well as targeted therapies, being a prime example on the potential value of precision medicine in the therapeutic management of GI neoplasias (102).

3.1.3 Duodenal neoplasia

Superficial nonampullary duodenal epithelial tumors (SNADETs) are rare, with an estimated prevalence of 0.3% to 4.6% in patients referred to EGD (103-105). Nevertheless, in recent years, advances in endoscopic imaging devices and techniques, in association with an increased awareness among endoscopists, have led to an increased detection of these lesions (7, 106, 107).

SNADETs are defined as lesions that are limited to the mucosa or submucosa, and include adenomas and adenocarcinomas (108); most are located in the descending part of the duodenum (109, 110).

In contrast to ampullary tumors, duodenal adenomas are less often sporadic, being associated in 60% of cases with FAP (111). Another predisposing genetic syndrome is MUTYH-associated polyposis (112). Several other independent risk factors for sporadic SNADETs were identified in a recent study and may raise awareness to the cases in which a careful endoscopic examination of the whole duodenum must be carried out. These include current smoking, BE, fundic gland polyps and history of other GI malignant diseases (namely CRC and GC) (113). Hp infection has previously been identified as a risk factor for SNADETs, although the association between SNADETs and GC remains controversial (114). Finally, a meta-analysis and a recent case-control study have suggested an association between sporadic duodenal adenomas and colorectal adenomas (115, 116). Therefore, the ESGE recommends that all cases with duodenal adenomas should undergo colonoscopy (117).

Most SNADETs are diagnosed incidentally during an EGD, with an initial histopathological finding of LGD. Nonetheless, these lesions may progress to adenocarcinoma, which is associated with a poor prognosis (118-120). Taking this into account, all duodenal adenomas should be considered for ER, as progression to invasive carcinoma is highly likely in the long-term follow-up (117).

Precursor lesions and histopathological characterization

Both duodenal adenomas in FAP and sporadic SNADETs have the potential to progress to carcinomas based on the adenoma-carcinoma sequence theory, similar to colonic adenomas (118, 121-123). HGD diagnosis at first biopsy and a lesion diameter ≥ 20 mm are significant predictive factors for progression to adenocarcinoma (118). The progression from adenoma to adenocarcinoma may have two different pathways (124). In the first, intestinal-type lesions follow the adenoma–carcinoma sequence. The second pathway involves progression of a *de novo* gastric type, including gastric foveolar-type or pyloric gland adenoma. This pathway is independent of the usual Wnt/ β -catenin pathway and is associated with gastric duodenal metaplasia in duodenal bulb. The gastric-type lesion is more frequently diagnosed as carcinoma,

with an associated poorer prognosis (125). The intestinal-type progression is associated with adenomas with intestinal-type (adenomatous) dysplasia, most of which are located in the second part of the duodenum and are the most common form of presentation. Serrated lesions, with features reminiscent of colorectal traditional serrated adenomas, are also identifiable and are frequently associated with dysplasia or adenocarcinoma (126).

3.2. Current strategies to reduce the burden of upper gastrointestinal neoplasia

When detected at an advanced stage, upper GI neoplasia display a pronounced epidemiological impact, clinical burden and dismal prognosis. Therefore, serious efforts are ongoing to reduce the incidence and improve prognosis of these neoplasia, either by earlier detection or by improving the therapeutic management after the diagnosis.

3.2.1 Primary prevention measures

The primary mean of prevention for upper GI neoplasia is the elimination of identified risk factors. Regarding EC, GC and, to some extent, duodenal cancer, this includes well-known measures such as: (i) tobacco and alcohol abstinence; (ii) avoidance of hot beverages, salted meat, and processed foods; (iii) high fruit and vegetable intake; (iv) regular physical activity and (v) obesity treatment (127-129).

In the particular case of GC, several studies tried to evaluate the protective effect of Hp eradication therapy in GC incidence. A recent meta-analysis evaluated the effect of eradication therapy on subsequent occurrence of GC in healthy Hp-positive adults (130). A 46% reduced risk of subsequent GC after eradication therapy was observed, with no statistical heterogeneity detected despite considerable variations in the treatments administered. Reduced GC-related mortality – but not all-cause mortality – was also observed (relative risk=0.61). This systematic review also included three randomized controlled trials that evaluated the association of Hp eradication therapy on subsequent GC incidence among individuals with EGC and found a combined 51%

reduced risk (131-133). All these trials were performed in high-risk countries and many questions remain about the applicability and cost-effectiveness of these strategies in lower-incidence countries. The recent Maastricht VI/Florence consensus report states that a population-based Hp test and treat program (with massive Hp eradication) is cost-effective in populations with intermediate or high incidence of GC (134). Nevertheless, it is important to note that some retrospective studies suggest a protective effect of Hp eradication even in countries of low incidence of GC, such as the USA (135, 136).

3.2.2 Endoscopic screening

Most of upper GI cancers are preceded by slowly progressing precancerous conditions or lesions, providing opportunities for effective interventions. The use of endoscopic techniques in the GI tract allows not only for early detection and minimally invasive therapeutic management of neoplasias but also for long-term surveillance (4). Nevertheless, the distinct geographic disparities in the incidence of the different types of upper GI neoplasia may have a significant impact in the development of effective screening strategies. Tailoring screening methods to align with the predominant histological subtype in a specific population or region is critical for enhancing cost-effectiveness and early detection efficacy (137).

Esophageal squamous-cell carcinoma

A landmark study by Wei WQ *et al*, involving 3319 volunteers from a region with a high ESCC incidence in China, showed that the cumulative incidence and mortality rate of ESCC were significantly lower in the group that underwent one-time endoscopic screening (138). Other retrospective studies have demonstrated a significant cancer-survival benefit in patients living in high-risk regions in China undergoing endoscopic screening compared with controls, with economic analyses using Markov modeling suggesting that this approach is cost-effective (139-141). These results suggest that endoscopic screening and subsequent interventions can significantly diminish the incidence and mortality of EC. Remarkably, early detection of EC might also occur as a byproduct of screening for GC, as observed in Korea and

Japan. In these countries, the mortality rates for EC are much lower than in other countries with similar incidence (142). These findings probably reflect the long-standing national endoscopic screening programs for GC that are available in these countries, in association with heightened public awareness.

In lower incidence countries, the harms and risks of ESSC screening would surpass its benefits, so that a population screening program is not recommended (143, 144). The ESGE currently recommends endoscopic screening in small subgroups of patients at very high risk, such as: patients with (i) previous or concomitant diagnosis of head and neck neoplasia (HNN) (145); (ii) achalasia (146, 147); (iii) previous RT for breast cancer; (iv) previous caustic injury of the esophagus; (v) tylosis (148). Nevertheless, many questions remain regarding the specific timing to start screening, surveillance intervals and whether screening is cost-effective. Therefore, at the present time, organized screening for ESCC is not an option even in high-risk individuals in most European countries (4).

Esophageal adenocarcinoma

American and European Societies have independently published guidelines to select candidates for BE and EAC screening, mostly relying on demographic and clinical characteristics commonly found in patients with BE (4, 58, 149-151). Screening in the general population is not recommended due to the relatively low risk and lack of cost-effectiveness (152). Therefore, screening should be considered in high-risk individuals, such as in those with long-standing GERD symptoms (*i.e.* > 5 years) and multiple risk factors (age $\geq$ 50 years, white race, male sex, obesity, first-degree relative with BE or EAC) until the age of 75, if no dysplasia is found (4).

Nevertheless, most cases of EAC (>90%) continue to be diagnosed after the onset of alarm symptoms (47). Additionally, the low annual rate of progression from BE to EAC (0.1-0.5% per year) raises questions about the cost-effectiveness and impact of surveillance for incidental neoplasia (153). Nevertheless, in most countries, patients with BE are managed with endoscopic surveillance at regular intervals, since invasive EAC has a high lethality and treatment-associated morbidity. In all Western guidelines,

the surveillance intervals are based on the extent of BE and the diagnosis and degree of neoplastic lesions (46, 60).

Interestingly, in close relation to the slow rate of neoplastic progression, previous studies suggested that most patients with BE will die due to non-EAC related causes (154, 155). Therefore, evidence to show that BE screening and surveillance is not only cost-effective but also effective in reducing EAC-mortality is challenging to generate; a large prospective randomized controlled trial (BOSS trial) recently showed that surveillance did not improve overall survival or cancer-specific survival, as compared to 'at need' endoscopy; according to the authors, the later approach may potentially be a safe alternative for low-risk patients (156).

Gastric cancer

Currently, screening for GC is only performed in countries with a high disease incidence, defined as an ASR ≥ 20 per 100,000, such as Japan or South Korea (4). Both these countries have structured national screening programs for GC. Considering the growing evidence, the Japanese national guidelines currently recommend either EGD or radiographic screening on a biennial basis, beginning at age of 50 years, with no definite stopping age (157). Regarding South Korea, GC screening began in 2002 and guidelines recommend a biennial EGD between 40-75 years (158). In fact, the implementation of GC screening in these countries led to an increase in the diagnosis of EGC, lower GC-related mortality, and higher 5-year survival (159, 160).

Detection of GC at early stages is associated with an overall 5- year survival rate of 85–90%. However, populational-based GC screening programs are rare in Western countries, mainly due to concerns of low adherence, limited efficacy and questionable cost-effectiveness. Nevertheless, while endoscopic screening for the entire population is not recommended in low-risk regions (ASR < 10 per 100,000) (161), in intermediate-risk regions such as Portugal, EGD may play a role in primary screening, depending on local settings, the availability of endoscopic resources and evidence of cost-effectiveness (4).

A recent study by Areia *et al* proposed to perform a screening EGD concurrently with the initial screening colonoscopy for CRC in the Western setting (162). In a cost-

utility analysis study based on a Markov model, the authors compared three screening strategies and concluded that endoscopic GC screening was cost-effective if combined with a colonoscopy. This study suggests that, in Europe, if a CRC screening program is already in place, all countries with an intermediate incidence of GC might benefit by providing a screening EGD in conjunction with colonoscopy for their populations (4).

On the other hand, particularly in low-incidence regions, such as the USA and many European countries, identifying individuals with precancerous lesions and ensuring appropriate surveillance may represent a viable strategy by to improve EGC detection and management (63). The second European guideline on the Management of Epithelial Precancerous Conditions and Lesions in the Stomach (MAPS II) was published in 2019 and stratified individuals based on histologic extent and severity of gastritis, family history, and Hp status (163). More specifically, MAPS II recommends surveillance every 3-years for individuals with advanced atrophic gastritis/IM (both in antrum and corpus) or any grade of IM in the presence of risk factors such as family history of GC, incomplete IM and persistent Hp infection; in patients with advanced atrophic gastritis/IM and a family history of GC, a more intensive endoscopic follow-up is advocated (every 1 to 2 years). A previous study confirmed the cost-utility of this approach in Portugal (164). Nevertheless, many question remain about the optimal surveillance interval for gastric precancerous lesions, with both the current American Gastroenterology Association (75, 165) and ESGE guidelines (163) basing their recommendations on expert opinions or modeling studies. Although Asian studies suggest that screening intervals less than 3 years can be associated with an increased diagnosis of EGC, the applicability of these results in the Western setting is still unknown (166-169).

To make a further progress in reducing GC morbidity and mortality, risk stratification among selected asymptomatic individuals has previously been highlighted as a key area of future focus (63). Although Japan and South Korea are the most prominent examples of national screening programs targeting the asymptomatic general population, smaller-scale screening programs may be applied, particularly in the context of “opportunistic” screening in subgroups of patients that undergo EGD for other reasons. For example, as previously described, patients with HNN may have an increased risk of not only EC but also GC due to shared risk factors

(170) and may represent a specific group of patients that may benefit from an endoscopic screening program. Another subgroup of patients that may benefit by “opportunistic” screening for GC is those with compensated advanced chronic liver disease (cACLD). Previous studies suggested that these patients may have an increased risk of GC, especially those with hepatitis B virus infection and alcoholic liver disease (ALD) (171-176). All patients with cACLD were previously indicated to be screened for gastroesophageal varices (GOEV), primarily using EGD (177). More recently, the Baveno VI and the Baveno VII guidelines sought to identify patients who could safely avoid screening with EGD because of reduced risk of having GOEV (178, 179). According to these recommendations, only patients with liver stiffness measurement by transient elastography ≥ 20 kPa and platelet count $\leq 150 \times 10^9/L$ should undergo EGD. Over the years, several studies have confirmed the value of the criteria proposed by the Baveno guidelines in predicting GOEV (180-182), but the possible impact of these guidelines in missing GC cases in cACLD patients has not been yet addressed.

3.3. Treatment and outcomes after endoscopic resection

Endoscopic resection (ER) is nowadays the treatment of choice for most early GI malignancies with no or limited submucosal invasion and no additional risk factors for LNM (183-185). Nevertheless, ensuring endoscopic and histological completeness of ER is of paramount importance to accurately identify patients who can be referred for close surveillance and those who would benefit from additional treatments (*i.e.* surgery with lymphadenectomy, chemotherapy, RT).

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are the mainstays endoscopic treatments for early GI lesions. However, EMR is unsuitable for *en-bloc* resection of lesions >20 mm or non-lifting lesions. On the other hand, especially when used in a *piecemeal* fashion, EMR may hinder optimal histological examination of early GI cancers, especially regarding R *status*, and may be associated with a higher rate of residual lesion and recurrence. This may significantly impact patients’ prognosis, potentially leading to unnecessary additional interventions (185). Recently, underwater EMR (U-EMR), first described by Professor

Kenneth Binmoeller, has emerged as a potential alternative to conventional EMR (C-EMR). This technique aims to overcome some of the limitations of C-EMR, particularly in the treatment of SNADETs, by potentially allowing *en-bloc* resection of larger lesions, while maintaining a similar rate of adverse events (AEs) (186).

However, it was the introduction of ESD in Japan in the 90's for the treatment of EGC that revolutionized the endoscopic management of early GI neoplasia (187-190). ESD enables *en-bloc* resection regardless of lesion size, allowing precise histopathological evaluation and accurate assessment of the risk of LNM. Nevertheless, it is technically demanding and associated with a higher risk of AEs compared with EMR (185). In the two decades following its introduction, ESD became the treatment of choice for EGC in Japan and other Asian countries. In these settings, national consensus guidelines were carefully designed and established within an evidence-based risk stratification framework (191, 192). Accumulating evidence on the success of ESD in the treatment of EGC emerged, being associated with lower procedural time, risk of AEs and costs, and with better health-related quality of life, as compared with gastrectomy and lymphadenectomy (184, 193-197). This led to its use in other parts of the GI tract, including the esophagus, colon, rectum and duodenum. Despite the different epidemiological context, ESD progressively gained more attention in Europe, Australia and North America. Further effort is being made particularly regarding training and development of new devices (*i.e.* traction devices) that can make the procedure easier, faster and more effective, with the ultimate goal to achieve results comparable with Asian endoscopists (198-203). With increasing experience, ESD was proven to be safe and effective for the treatment of EGC in high-volume Western centers with *en-bloc* and R0 resection rates of >95% and 85%, respectively (204-207); this eventually led to its inclusion in the current Western guidelines for treatment of early GI neoplasias (184, 208, 209).

As ER of early GI malignancies became more popular, the focus was shifted toward the indications and the criteria for a curative local resection of invasive GI neoplasias (183). When facing the undesired outcome of a non-curative (NC) resection, physicians and patients must decide whether further treatment is required. For adequate decision-making, an accurate estimation of the risk of parietal recurrence and LNM, according to the adverse prognostic factors, is paramount and needs to be balanced

with surgical risk, patient's physical status and preference. Indeed, for some patients (e.g. advanced age and severe comorbidities), the recurrence risk may be lower than the surgical risk and surveillance may be an option, (with similar disease-specific survival) between surveillance and surgery (210-218).

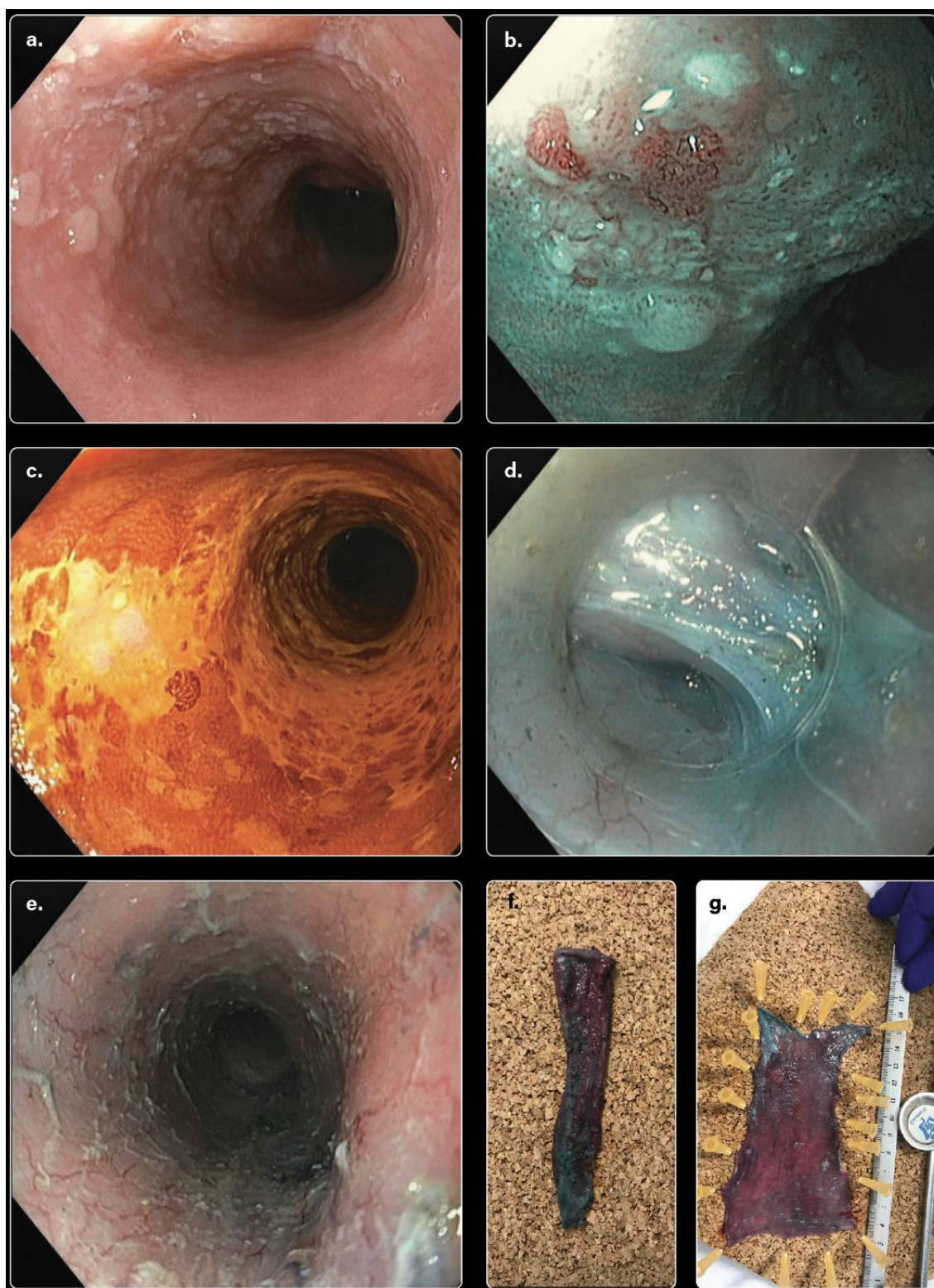
3.3.1 Esophageal squamous-cell carcinoma

Treatment

Current ESGE guidelines recommend ESD as the treatment of choice for early ESCC (184) (Fig. 5). Lesions limited to the epithelium (m1) or the lamina propria (m2) represent absolute indications for ER, with a 5-year disease-specific survival and 5-year overall survival (OS) of 98-100% and 85-95%, respectively (219). Compared with EMR, ESD is associated with higher *en-bloc* and curative resection rate and a lower local recurrence rate (220). Compared with surgery, a recent systematic review and meta-analysis showed that there was no significant differences between ESD and esophagectomy regarding OS, disease-specific survival and recurrence-free survival, with ESD being associated with fewer AEs (221). Therefore, ESD is recommended as first-line therapy for selected T1 lesions.

It is important to note that two issues remain under debate regarding T1 ESCC. The first concerns lesions that have preoperatively been clinically staged as cT1a-m3/T1b-sm1 (N0M0) and the second regarding circumferential clinically staged T1a-m1/m2 ESCC. The ESGE suggests that ESD can be considered in these particular cases. Regarding the latter, a recent multicenter study by Rodríguez de Santiago E *et al* assessed the outcomes of circumferential ESD for early ESCC in the Western setting and showed that, although feasible, the resection was curative in only approximately half of the lesions (222). These results highlight the need to improve selection for ER.

Figure 5. Example of an ESD performed for an esophageal SCC



a. white-light; b. narrow band imaging; c. lugol staining; d. submucosal dissection; e. final eschar, after circumferential dissection; f. cylinder of ESD specimen; g. fixation of the specimen in a cork plate.

Used with permission from: Santos-Antunes J.

Outcomes after endoscopic resection

ESGE guidelines suggest that an *en-bloc* R0 resection of an m3 or sm1 ESCC that is well to moderately differentiated and with no lymphovascular invasion, should be considered a low risk (curative) resection and no further treatment is generally recommended (184). This contrasts with the Japanese practice guidelines, which recommend additional treatment for all lesions with submucosal invasion, regardless of the presence of lymphovascular invasion (223), despite insufficient evidence to fully support this approach (224). In fact, in a recent retrospective Chinese study, no single patient with m3/sm1 cancer, high tumor differentiation, no lymphovascular invasion, and tumor length < 20 mm had LNM (225). Nevertheless, in lesions >20 mm there is a real risk of LNM and the risk for further therapy should be balanced against the risk of LNM after complete staging and multidisciplinary discussion (184). In these cases, complementary RT or chemoradiotherapy may be considered.

In the case of patients meeting high risk criteria (NC resection) such as deeper (> 200 μ m) invasion into the submucosa or lymphovascular invasion, surgery should be the preferred approach for young fit patients, given the better OS as compared with other approaches (218). It is important to note that currently there is no evaluation system for NC esophageal ESD, contrarily to what happens for gastric lesions (see below) (191). Considering the significant morbimortality associated with esophageal surgery, the design and validation of a tool to evaluate the risk of LNM and residual cancer after NC esophageal ESD may be helpful for selecting patients who are more likely to benefit from additional therapies and avoiding unnecessary salvage surgery (226).

3.3.2 Esophageal adenocarcinoma

Treatment

Contrarily to ESCC, for BE-associated lesions, the ESGE recommends using EMR for $\leq$ 20 mm visible lesions with low probability of submucosal invasion. This recommendation is based on a recent randomized controlled trial that found no significant differences between EMR and ESD in terms of the need for surgery,

neoplasia remission, or recurrence (227). ESD should be preferred for lesions suspicious for submucosal invasion, malignant lesions >20 mm or for lesions in scarred/fibrotic areas (228). In these cases, compared with surgery, ESD appears to be as effective but with a better safety profile and overall quality of life (229-231).

Outcomes after endoscopic resection

The decision between (i) close surveillance after ER of a T1 EAC or (ii) referral for additional surgery is guided by the assumed risk of LNM (232). This risk is based on the presence of histological high-risk factors in the ER specimen (233). The distinction between low-risk T1 EAC and high-risk T1 EAC usually drives the decision for additional esophagectomy with lymphadenectomy. These high-risk features include submucosal invasion, poorly or undifferentiated cancer, and/or presence of lymphovascular invasion. The presence of at least one of these high-risk criteria increases the risk for LNM and may negatively impact survival of patients (217, 234, 235).

Interestingly, the risk of LNM in high-risk lesions appears to be lower than previously assumed and may result in overtreatment for the majority of patients (233). The last ESGE guidelines on BE state that even in high-risk T1b EAC (submucosal invasion >500 µm and/or lymphovascular invasion and/or poor differentiation), consideration for additional treatments (chemotherapy, RT, surgery) or strict endoscopic follow-up could be undertaken on an individual basis (guided by patient characteristics and individual risk), after multidisciplinary discussion (46). The ongoing multicenter prospective PREFER trial (NCT03222635) aims to evaluate the safety of a watchful waiting approach instead of surgery in patients after ER of high-risk T1 EAC without signs of metastasis at baseline (N0M0). Interim results showed LNM in 6 out of 120 patients (5%), with all being still eligible for curative treatment (236). These promising results suggest that a watchful waiting strategy after ER of high-risk T1 EAC might prevent patients from undergoing more invasive but unnecessary treatments.

3.3.3 Gastric neoplasia

Treatment

As previously stated, ESD is the first-line treatment for EGC with a low risk of LNM (<1%). When compared to surgery, ESD is associated with similar long-term outcomes and lower risk of AEs (184, 237).

The selection of patients for ESD is based on the lesion size, presence of ulceration, morphology and other specific histological parameters. The Japanese guidelines (192, 238) define as absolute indications for ER: (i) dysplastic lesions regardless of size; (ii) non-ulcerated differentiated intramucosal (cT1a) lesions of any size or ≤ 30 mm if ulcerated; and (iii) undifferentiated cT1a lesions with ≤ 20 mm without ulcerative findings. The ESGE guidelines also consider the first two criteria as absolute indications for ER; however, the third criteria is considered an expanded indication (defined as a lesion presumed to have a 1-3% risk of LNM) (184). Interestingly, the American Gastroenterology Association guidelines, in parallel with Japanese recommendations, have defined even stricter absolute criteria for ER, including in this group only non-ulcerated differentiated cT1a lesions with ≤ 20 mm (209). An overview of indications for gastric ESD from different guidelines can be seen in Table 1.

Table 1. Clinical staging: absolute and expanded indications for endoscopic resection according to European, Japanese, and American guidelines.

TYPE OF LESION		GUIDELINES		
		European	Japanese	American
Adenocarcinoma	Dysplasia, any size			
	cT1a, differentiated, non-ulcerated, ≤ 20 mm			
	cT1a, differentiated, non-ulcerated, > 20 mm			
	cT1a, differentiated, ulcerated, ≤ 30 mm			
	cT1a, undifferentiated, non-ulcerated, ≤ 20 mm			
	eCuraC1 recurring cT1a lesions			
	cT1b, differentiated, submucosally invasive (< 500 μ m)			
	<i>En-bloc</i> resected lesions at risk for submucosally invasive cancer			

 Absolute indication
 Expanded indication

cT1a: adenocarcinoma clinically staged as intramucosal

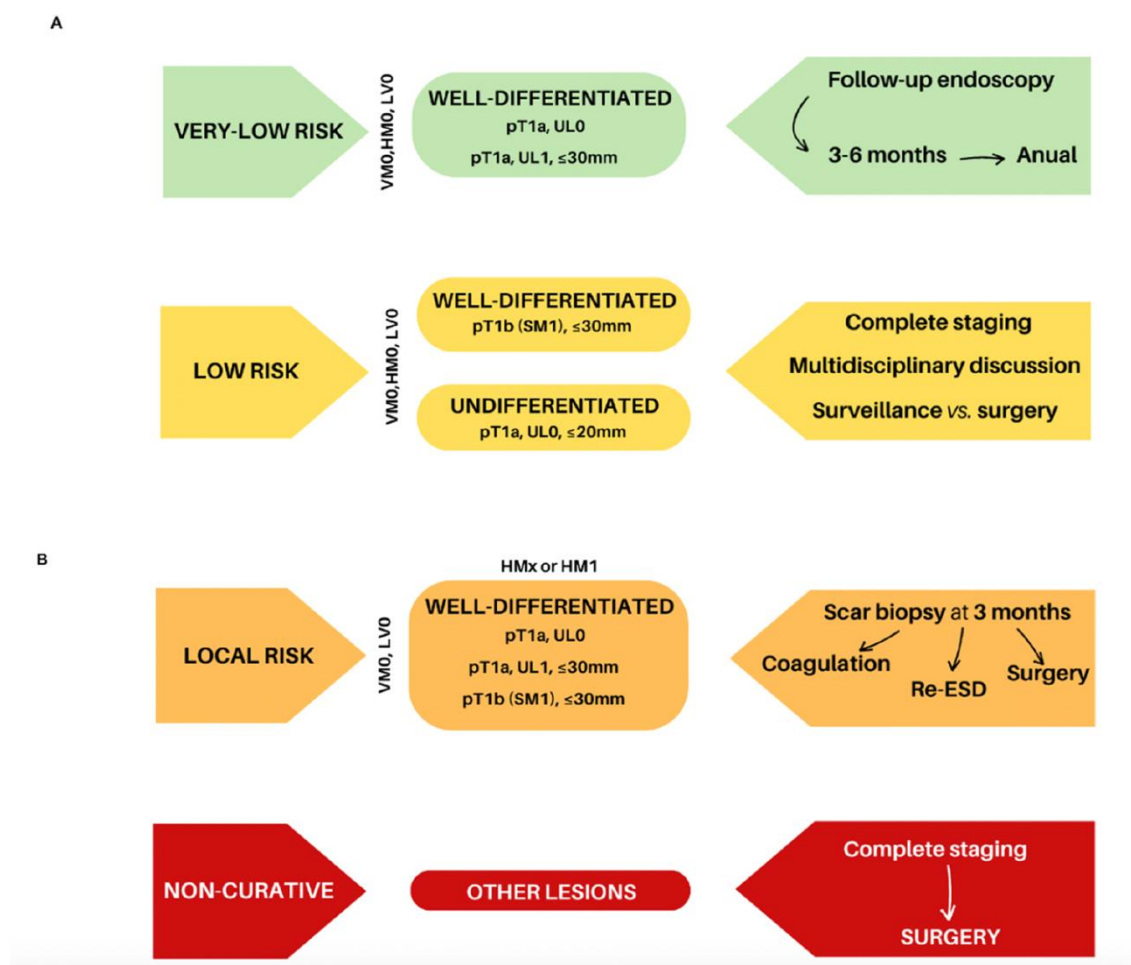
cT1b: adenocarcinoma clinically staged as submucosal

Adapted and used with permission from: Cunha Neves JA et al. Curative criteria for endoscopic treatment of gastric cancer. Best Pract Res Clin Gastroenterol. 2024 Feb;68:101884.

Outcomes after endoscopic resection

To define the management after ER, histopathological assessment of the specimen is required to classify the resection as curative or NC. Although endoscopic evaluation is the most accurate method to predict curability, up to 20% of ESDs are considered NC after the evaluation of the resected specimen; nevertheless, the risk may be minimal when certain conditions are met (239-241). Current ESGE guidelines (184) recommend the use of the terminology “very-low risk resection” and “low-risk resection” for those considered “curative”. Among NC-ESDs, local-risk resections are those with a higher risk of having parietal residual lesion (in the ESD site), such as those piecemeal-resected or with positive (benign) horizontal margin, without other risk factors for LNM. High-risk resections are those with features indicative of a high risk for LNM, warranting complementary treatment. These features include lymphatic permeation, positive vertical margins, large (>3 cm) submucosal or ulcerated intramucosal adenocarcinomas, large (>2 cm) undifferentiated carcinomas or lesions with deep (>SM1) submucosal invasion. Post-resection management according to ESGE guidelines is resumed in Fig. 6.

Figure 6. Post-resection management according to the European ESD guidelines.



HM0: negative horizontal margin; HMx: piecemeal resection; HM1: positive horizontal margin; LV0: no lymphovascular invasion; pT1a: intramucosal adenocarcinoma; pT1b (SM1): adenocarcinoma with superficial submucosal invasion ($\leq 500 \mu\text{m}$); UL0: non-ulcerated; UL1: ulcerated; VM0: negative vertical margin.

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In order to identify NC resections that may require further surgical therapy, Hatta *et al* designed the eCura score system, stratifying Asian patients based on the risk of LNM (191). The eCura system evaluated five risk factors for the development of LNM and weighted them according to the relative risk: 3 points for lymphatic permeation, and 1 point each for (i) lesion size $>30 \text{ mm}$, (ii) positive vertical margins, (iii) venous invasion and (iv) submucosal invasion $\geq 0.5 \text{ mm}$. Patients were then further categorized in three groups: low-risk group (0–1 point, 2.5% risk of LNM), intermediate-risk group (2–4 points, 6.7% risk) and high-risk group (5–7 points, 22.7% risk). This score was validated in the Asian setting, where the high-risk category was found to display significantly

higher risk of recurrence and LNM rates (242, 243). Nevertheless, to date no previous studies have assessed the adequacy of this score in the Western setting, being unclear whether there are additional prognostic variables that could be helpful in the estimation of recurrence and LNM risk.

Although the risk of LNM is low or very low after a curative ER, there is a moderate risk of metachronous lesions during follow up (10-20%) (244-246). A recent prediction score (FAMISH) included six clinical predictors (scored 0-3): (i) positive family history of GC, (ii) older age, (iii) male sex, (iv) corpus IM, (v) synchronous gastric lesions, and (vi) persistent Hp infection (247). This score, already externally validated in the Asian Setting (248), might be a useful tool to accurately identify patients with low-to-intermediate risk for metachronous lesions at 3 years of follow-up, who could have surveillance intervals extended to reduce the burden of care.

3.3.4 Duodenal neoplasia

Treatment

Despite being rarely diagnosed, 30% to 85% of SNADETs have the potential to progress to malignancy, making their surgical or endoscopic removal mandatory (249). Pancreaticoduodenectomy is the primary treatment for duodenal cancer but is associated with significant morbidity and mortality (30-40% and 1-4% respectively) and is considered too invasive for SNADETs (7, 250). Therefore, ER has been established as the main treatment modality.

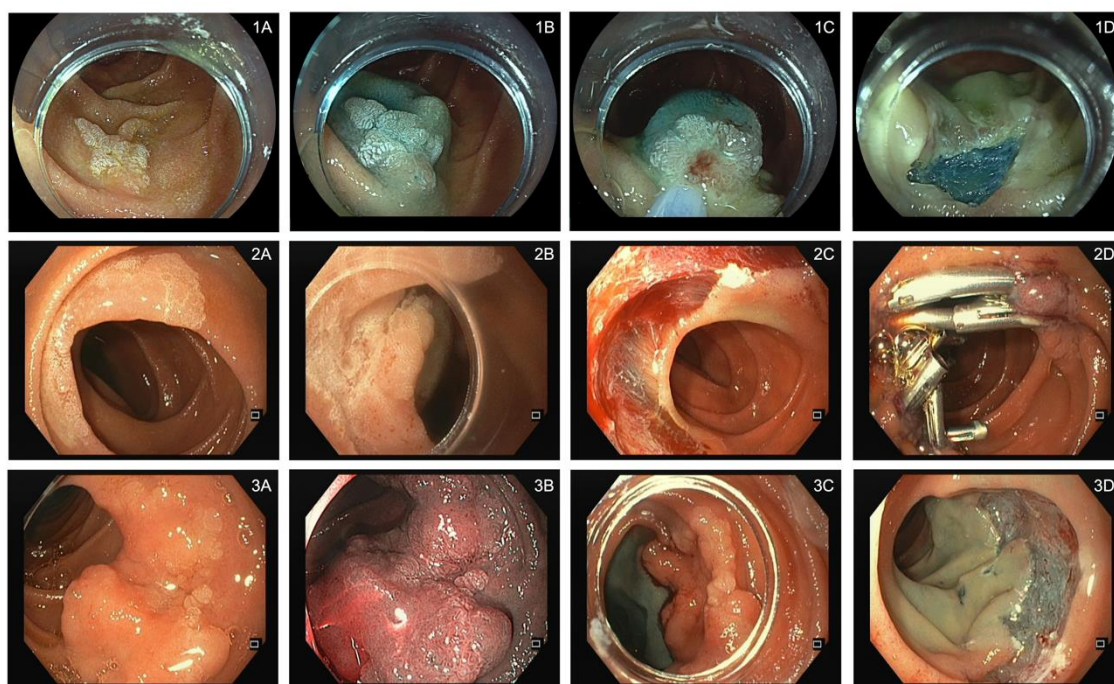
It is important to note that ER in the duodenum is technically more difficult than its execution in other organs owing to the poor maneuverability of the endoscope, fibrous submucosal layer, rich vascularity and thin muscularis propria layer (7). These features, together with the exposure to bile and pancreatic juice from the duodenal papillae, increase the risk of immediate and delayed AEs (such as bleeding and perforation), even when the treatment is completed safely (251).

Although current ESGE guidelines recommend cold-snare polypectomy for small lesions ≤ 5 mm, C-EMR is recommended as the first-line ER technique for SNADETs,

including large lesions >20 mm (117). In these lesions, despite a lower rate of *en-bloc* resection and higher risk of recurrence, piecemeal C-EMR is an appropriate treatment.

More recently, potentially effective alternatives to C-EMR have emerged, trying to overcome some of the limitations of C-EMR, namely the significant risk of AEs and recurrence. These alternatives include (i) ESD; (ii) cold-snare EMR; (iii) U-EMR (Fig. 7).

Figure 7. Overview of different endoscopic techniques in the management of SNADETs.



1. C-EMR; 2. U-EMR; 3. U-EMR after partial injection of the distal border.

Author's own images.

U-EMR implies an antigravity floating effect of the mucosa and submucosa as a result of saline/water immersion after air/CO₂ suctioning, with a reduced risk of muscular propria entrapment within the snare and thermal injury (7). Previous Asian studies did not show differences in recurrence rates between U-EMR and C-EMR, despite a higher *en bloc* resection rate and shorter procedure time for lesions ≤20 mm in the former (252, 253). Nonetheless, the potential benefits and drawbacks of U-EMR in the Western setting and for larger lesions >20 mm are yet to be evaluated.

Outcomes after endoscopic resection

ESGE recommends endoscopic surveillance 3 months after index treatment, bearing in mind that most of the recurrences can be managed by ER (117). Further

endoscopic follow-up should be done 1 year later. Subsequent surveillance intervals should be the individualized to the lesion site, *en bloc* resection status and initial histological result.

4. Rationale

Gastrointestinal cancer burden may be affected by the changing trends of preventable risk factors such as alcohol consumption, metabolic syndrome, infection and dietary risk factors (254-256). The decline of EC, GC and biliary tract cancer, and the higher decrease in mortality rates at a greater extent than incidence rates suggest glimpses of cautious optimism for the efforts put into controlling risk factors. For example, the decreasing trends of EC and GC (5, 257, 258) could be due to improved food preservation and reduced prevalence of Hp (142, 259). While primary prevention strategies are paramount, the evolving landscape of screening strategies for early diagnosis and minimally invasive therapeutic management may also have a significant effect on the global impact of these cancers.

Even though the majority of the GI tract cancers arise sporadically, genetic factors also play a significant role in their risk (260). Differences not only in the modifiable risk factors and genetic background but also in the distribution of tumor subtypes across populations have been found to partly explain the worldwide and even regional differentials in the burden from GI cancers; more particularly, wide variations between Western and Asian populations are evident, especially for EC and GC (38, 261). This may significantly impact on the applicability of the results and data from Asian centers to Western populations and vice-versa. The encouraging result of declining incidence rates of some types of GI cancers should be interpreted with caution and there is a need to take distinct geographical regions and socioeconomic development into account when trying to address public health policies to tackle cancer. In particular, lower sociodemographic index countries need to pay greater focus and commit resources to address the rising trend of GI cancers and its associated societal burden (2). Therefore, a personalized and tailored approach is of paramount importance in the holistic management of these conditions.

Regional differences in the incidence and burden of GI tract cancers can also have implications in the implementation of screening strategies and therapeutic management. CRC is uniquely suited for screening programs compared with other GI cancers, since the detection and resection of its precursor lesions (adenomatous and

serrated polyps) decreases the incidence and prevalence of CRC, with a consequent reduction in mortality (4, 262). In fact, according to the European Union screening report, most countries have implemented organized invitational screening programs for CRC, primarily based on fecal immunochemical testing. In this context, ER is established as the first-line modality in the therapeutic management of non-malignant colorectal polyps and early-CRC (184, 208, 263). Regarding upper GI neoplasia, as previously stated, some Asian countries (such as Japan and Korea) have structured, nationwide endoscopic screening programs for EC and GC, whose cost-effectiveness has been demonstrated, given the high incidence of these cancers (157, 264-266). Consequently, these countries have been pioneers in the therapeutic endoscopic and long-term management after ER of early upper GI, being responsible for technical and disruptive innovations such as ESD (267). Nevertheless, many questions remain to be answered in the context of Western countries, namely: (i) the efficacy and cost-effectiveness of screening for upper GI neoplasia, given its significantly lower incidence compared with Asian countries (and whether specific subpopulations should be targeted); (ii) the applicability and safety of advanced ER techniques, given their long-learning curve and significantly less experience of Western endoscopists in lesion characterization and prediction of histology, as compared with Asian endoscopists; (iii) the long-term management after ER of upper GI neoplasia, especially in the undesirable event of a NC resection, given the significant differences in specimen handling and histopathological analysis between Western and Asian centers, which could have a significant impact in the decision-making process (239).

Taking all these factors into consideration, a research project was conducted by addressing specific issues of our clinical practice, which currently lacks sufficient evidence, regarding the diagnosis and management of upper GI neoplasia.

5. Aims

The main aim of this thesis was to present case studies on how to improve the screening, diagnostic, therapeutic approach and long-term management of upper GI neoplasia in the Western setting. Four original research studies were designed taking into consideration (i) previously identified research gaps in this field, and (ii) the diversity of upper GI neoplasias.

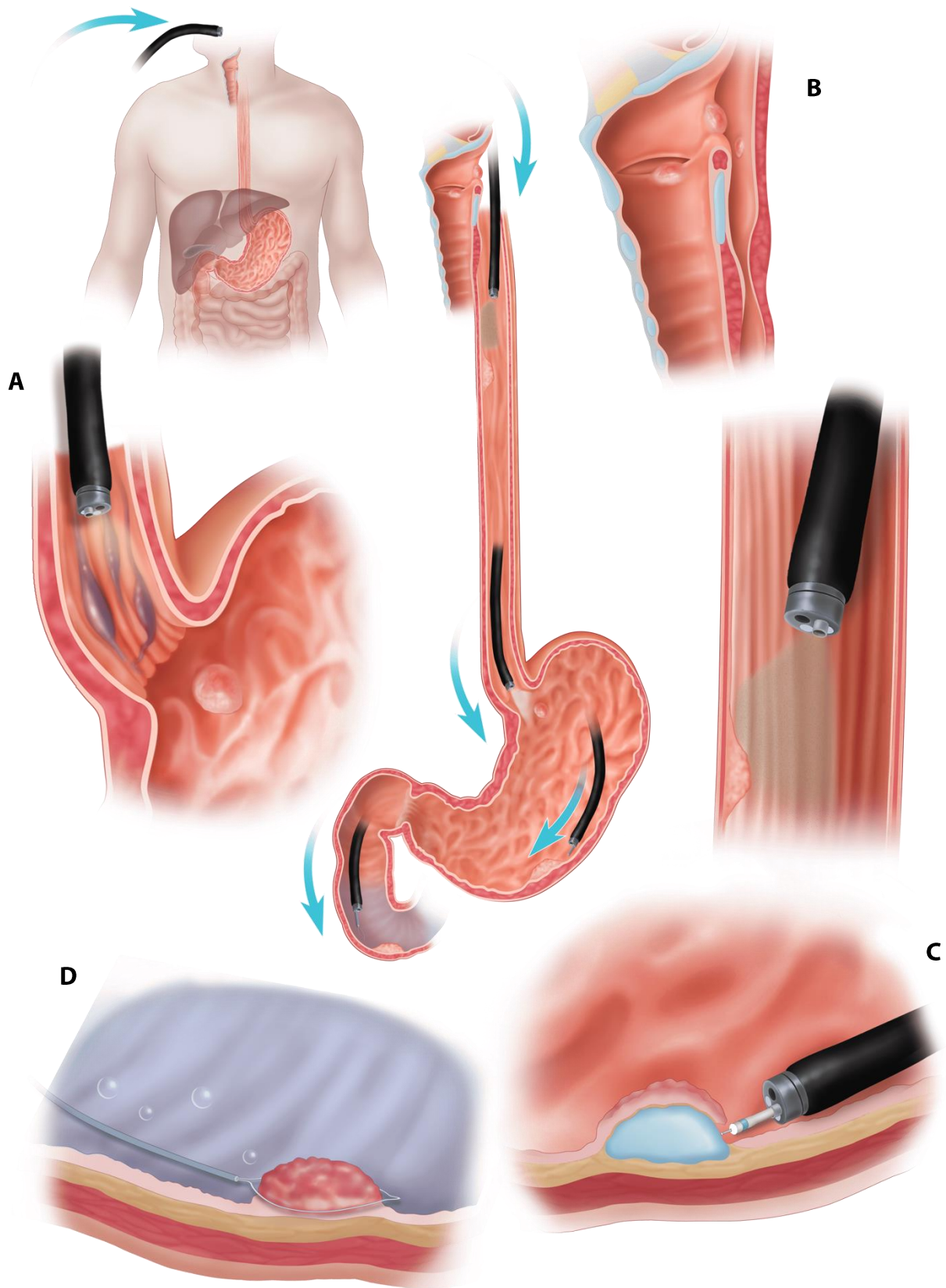
As specific aims, this thesis intended to:

1. Evaluate the frequency of gastric neoplasia (GN) in patients with ACLD who underwent endoscopic screening for GOEV and the miss-lesion rate if the Baveno VII-criteria had been strictly applied.
2. Evaluate the clinical impact and cost-effectiveness of an endoscopic screening program for EN in patients with HNN.
3. Compare the efficacy and outcomes of U-EMR compared with C-EMR for SNADETs in the Western setting.
4. Validate and refine the eCura scoring system after a NC gastric ESD in the Western setting.

As secondary aims, this thesis intended to:

1. Evaluate the frequency of GN in a cohort of asymptomatic healthy individuals who underwent screening EGD concurrently with colonoscopy performed for CRC screening in a country of intermediate-high risk of GC.
2. Perform a detailed histopathological characterization of GN in the cohort of patients harboring ACLD, in order to identify potential etiopathogenic factors (beyond the etiology of ACLD) that may contribute to the increased risk of GC in this population.
3. Evaluate the frequency of GN in patients with HNN undergoing endoscopic screening.
4. Evaluate the potential contribution of viral-related pathogenesis for the co-occurrence of gastro-esophageal neoplasia (GEN) in HNN patients.
5. Evaluate risk factors for parietal residual lesion and LNM after a NC ESD for GN.

Figure 8. Graphical overview of the thesis outline.



A. Endoscopic screening in cACLD patient for GOEV and GN; B. Screening for EN in patient with HNN; C. Gastric ESD; D. U-EMR of a SNADET

6. Results

6.1. Study 1

Higher frequency of gastric neoplasia in advanced chronic liver disease patients:
Impact of screening endoscopy in an intermediate-high risk country

6.2. Study 2

Cost-utility and clinical impact of endoscopic screening for esophageal
and gastric neoplasia in patients with head and neck neoplasms

6.3. Study 3

Underwater Endoscopic Mucosal Resection Vs Conventional Endoscopic
Mucosal Resection for Superficial Nonampullary Duodenal Epithelial Tumors
in the Western Setting

6.4. Study 4

Predicting residual neoplasia after a non-curative gastric ESD: validation and
modification of the eCura system in the Western setting: the W-eCura score

6.1.

Study 1

Higher frequency of gastric neoplasia in advanced chronic liver disease patients: Impact of screening endoscopy in an intermediate-high risk country

Morais R, Moreira J, Gaspar R, Santos-Antunes J, Marques M, Coelho R, Alves R, Ferreira-Silva J, Dias E, Pereira P, Lopes S, Cardoso H, Sousa-Pinto B, Faria-Ramos I, Gullo I, Carneiro F, Liberal R, Macedo G.

Dig Liver Dis. 2024 Dec;56(12):2133-2142

DOI: 10.1016/j.dld.2024.04.035

Epub 2024 May 28

PMID: 38811247

Cited by 2 articles

(Google Scholar, 2025, April 24)

Impact factor 4

(Thomson-Reuters, 2023)

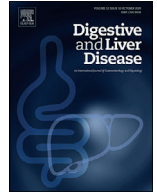
Rank 52 of 164 on Gastroenterology journals (Q2)

(Scimago Journal & Country Rank, 2023)



Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Oncology

Higher frequency of gastric neoplasia in advanced chronic liver disease patients: Impact of screening endoscopy in an intermediate-high risk country ☆

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ARTICLE INFO

Article history:

Received 30 December 2023

Accepted 29 April 2024

Available online xxx

Keywords:

Gastric neoplasia

Advanced chronic liver disease

Gastric cancer screening

ABSTRACT

Background: The Baveno VII guidelines were proposed to identify which patients could safely avoid screening esophagogastroduodenoscopy (EGD) for gastroesophageal varices. We aimed to evaluate the frequency of gastric neoplasia in compensated advanced chronic liver disease (cACLD) patients who underwent EGD for screening of gastroesophageal varices (GOEV) compared to a healthy population.

Methods: Retrospective study that enrolled all cACLD patients who underwent EGD for GOEV screening (January 2008-June 2018) in a tertiary reference center. cACLD patients were compared with asymptomatic healthy individuals who underwent EGD in a private hospital setting (April 2017-March 2018).

Results: We evaluated 1845 patients (481 cACLD patients, 1364 healthy individuals). A significantly higher frequency of gastric neoplasia was observed in patients with cACLD compared to healthy individuals (4.0% vs. 1.0%; $p < 0.001$). Rare histopathological subtypes (WHO Classification) accounted for 28.7 % of gastric carcinoma cases in the cACLD cohort. Seven cases of gastric neoplasia (36.8 % of gastric neoplasia cases in the cACLD patients) were diagnosed in patients who, according to the Baveno VII criteria, would have not been submitted to EGD.

Conclusion: We found an increased frequency of gastric neoplasia in patients with cACLD in comparison with healthy individuals. In countries with intermediate-high risk for GC, continuing to perform EGD could be beneficial.

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1. Introduction

Gastric cancer (GC) is a major worldwide health concern, being the fifth most commonly diagnosed cancer in the world and the fourth-leading cause of cancer-related deaths [1]. GC is most fre-

quently diagnosed in advanced stages, having a five-year survival rate of around 20 % [2]. There is a considerable worldwide variation in GC incidence and mortality [1,3]. Despite that, there is no clear geographical pattern of GC incidence [4,5]. For example, although the most affected European regions are Central and Eastern Europe (11.3 per 100,000 people in 2020), Portugal is considered an intermediate-high incidence country [6–8].

Considering the delay in diagnosis and the poor prognosis of advanced-stage GC, some strategies have been proposed for early detection and prevention, such as eradication of *Helicobacter pylori* (Hp) infection, serum biomarkers and endoscopic screening [9].

☆ Financial disclosure: None to report.

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Endoscopic screening for GC, already established in Japan [10] and other high-incidence regions, is associated with improved survival and has proved to be cost-effective [11].

For countries with intermediate risk of GC, more evidence is needed to understand if GC screening by esophagogastroduodenoscopy (EGD) might also be cost-effective. In the context of early detection and prevention strategies, attempts have been made to consider potential risk factors. Among environmental causes, Hp infection is the most important established risk factor for non-cardia GC [12]. Some other well-established risk factors include tobacco smoking, alcohol consumption, salted food intake and genetic predisposition [2,13]. Previous studies also suggested other potential factors including hepatitis B virus (HBV) infection, alcoholic liver disease (ALD) and advanced chronic liver disease (ACLD) [14–19]. Regarding the latter, all patients with compensated ACLD (cACLD) were indicated to be screened for gastroesophageal varices (GOEV), primarily using EGD [20]. More recently, the Baveno VI and the Baveno VII guidelines sought to identify patients who could safely avoid screening with EGD [21,22] because of reduced risk of having GOEV. According to these recommendations, only patients with liver stiffness measurement (LSM) by transient elastography (TE) ≥ 20 kPa and platelet count $\leq 150 \times 10^9/L$ should undergo EGD [21]. Over the years, several studies have confirmed the value of the criteria proposed by the Baveno guidelines in predicting GOEV, but none have acknowledged the possible impact of EGD screening in cACLD patients, regarding the risk of developing upper gastrointestinal neoplasia [22–25], particularly in intermediate incidence countries.

The main objective of this study was to evaluate the frequency of gastric neoplasia in cACLD patients who underwent EGD for screening of GOEV compared to a healthy population. In this context, we estimated the missed-lesion rate if the Baveno VII criteria had been strictly followed.

Further, we aimed to achieve two specific objectives: 1. conducting a detailed histopathological analysis of gastric neoplasia among individuals with cACLD, and 2. evaluating clinical outcomes following surgery and/or endoscopic resection (ER) of gastric neoplasia in this population.

2. Materials and methods

2.1. Study design

We performed a retrospective study at Centro Hospitalar Universitário São João (Porto, Portugal). We enrolled all asymptomatic cACLD patients who underwent EGD for GOEV screening from January 2008–June 2018. These patients were compared with asymptomatic healthy individuals who underwent EGD for GC screening (at the same time as colonoscopy performed for colorectal cancer screening) in a private hospital setting (Hospital da Luz Póvoa do Varzim, Porto, Portugal) between April 2017–March 2018.

2.2. cACLD cohort

The Baveno VII criteria were used to identify cACLD cases among all patients who attended the Hepatology outpatient clinic. Patients were considered to have cACLD if any of the following criteria were fulfilled: (a) LSM by TE > 12.5 kPa [21]; (b) stage of cirrhosis in liver biopsy (F4 score) [26].

We only included cases with at least one EGD performed for GOEV screening and at least one clinical evaluation after EGD. Patients were excluded if any of the following were present: (a) clinical signs suggestive of decompensated ACLD (b) prior history of organ transplantation; (c) surveillance of previous gastric neoplasia; (d) gastrointestinal bleeding or iron deficiency anemia.

2.3. Asymptomatic healthy individuals cohort

Individuals for whom screening with EGD was proposed by the general practitioner at the same time of colonoscopy were selected. Before the procedure, a survey was performed with questions regarding demographics, personal and family history of gastrointestinal cancer and presence of symptoms. Patients were excluded if any of the following were present: (a) surveillance of previous gastric neoplasia; (b) alarm symptoms such as gastrointestinal bleeding, anorexia or weight loss; (c) iron deficiency anemia; (d) clinical history suggestive of CLD.

2.4. Endoscopic procedures

In the cACLD cohort, all EGDs were performed by senior endoscopists or fellows-in-training under supervision. In the healthy individuals cohort, all EGDs were performed by two senior endoscopists (SL, GM).

Olympus® gastroscopes (GIF-Q165, GIF-Q180, GIF-H190) were used in the cACLD cohort, while Pentax® gastroscopes (EG-2990i) were used in the asymptomatic healthy individuals group. Virtual chromoendoscopy with narrow band imaging/i-SCAN was used for additional assessment, depending on the endoscopist's preference. Biopsies were located in a separate vial in the presence of suspicious lesions. If no suspicious lesions were identified, random biopsies from the antrum and gastric body using separate vials were obtained.

2.5. Histopathological examination

All the specimens collected were analyzed by board-certified pathologists. GC cases in the cACLD cohort were reviewed by pathologists with experience in gastrointestinal pathology (IG, FC) and classified according to the World Health Organization (WHO) and Laurén classifications [27,28].

Modified Giemsa staining was performed in tissue sections obtained from formalin-fixed paraffin-embedded blocks of the gastric endoscopic biopsies for screening of Hp infection. In cACLD patients with a diagnosis of gastric neoplasia that were Hp negative, immunohistochemistry using primary monoclonal antibody against Hp (clone SP48) was performed (Ventana Medical Systems, 1910 E. Innovation Park Drive, Tucson, Arizona 85755 USA). Samples were processed and evaluated in the automatic Ventana Benchmark Ultra platform using the OptiView Universal DAB detection kit.

For the evaluation of gastritis, the severity of inflammation, activity, atrophy, and intestinal metaplasia were graded as “absent,” “mild,” “moderate,” and “severe” [29]. In patients in which at least two biopsies from both the antrum and gastric body were obtained in separate vials, the Operative Link on Gastritis Assessment (OLGA) and the Operative Link on Gastritis/Intestinal Metaplasia Assessment (OLGIM) were retrospectively calculated for the purpose of gastritis staging [30,31], using the information available in the database of the Department of Pathology. As previously reported, OLGA/OLGIM=0 was defined as absence of atrophic gastritis (AG)/intestinal metaplasia (IM). Extensive AG/GIM was defined as OLGA/OLGIM III–IV and non-extensive/focal AG/IM as OLGA/OLGIM I–II.

2.6. Management after EGD

For evaluating clinical outcomes after the diagnosis of gastric neoplasia, only cACLD cases were considered. After EGD, patients were guided according to the MAPS I and II guidelines in the presence of pre-malignant lesions and according to the ESMO guidelines if diagnosed with GC [13,32,33]. In the latter, after complete

staging, cases were discussed by the Esophagogastric Multidisciplinary Team at CHUSJ for decision and pursuit of treatment [34]. Immediate and post-procedure adverse events (AEs), disease recurrence, mortality and survival (defined as the time from the treatment date to either death or the last follow-up contact) were evaluated. Surgery AEs were classified according to the Clavien-Dindo classification [35].

2.7. Statistical analysis

We aimed to compare the cACLD cohort and asymptomatic healthy individuals regarding the risk of gastric neoplasia. In addition, we compared these two groups on demographic characteristics, Hp infection status and gastritis staging.

Categorical variables were described through absolute and relative frequencies and continuous variables using means and standard deviations or medians, interquartile ranges (IQR), and minimum and maximum values. Continuous variables with normal distribution were tested using the independent samples *t*-test or the one-way ANOVA test, while continuous variables with non-normal distribution were tested using the Mann-Whitney and Kruskal-Wallis tests. The Fisher's exact test or the Pearson chi-square test,

as appropriate, were used to compare groups on categorical variables.

We assessed the association between cACLD and gastric neoplasia using logistic regression models. In particular, we built logistic regression models (i) having either gastric carcinoma or the presence of overall gastric neoplasia as the dependent variable, and (ii) considering the presence of cACLD as the independent variable. For each dependent variable, we built unadjusted and adjusted regression models. In adjusted models, the inverse probability of treatment weighting using the propensity score was applied to balance exposure groups for baseline characteristics (i.e., to account for a set of potential confounders). Propensity scores were built for the independent variable using multivariable logistic regression models, including the sex, age, family history of GC, presence of Hp infection, OLGA ≥ 3 , and OLGIM ≥ 3 as covariates.

In the cACLD cohort, overall survival (OS) in the follow-up was estimated using the Kaplan-Meier method, and the differences among the risk groups (considering the diagnosis or not of gastric neoplasia) were assessed using the log-rank test.

All data was analyzed with SPSS® v.28.0, with all significance levels being set at $p < 0.05$.

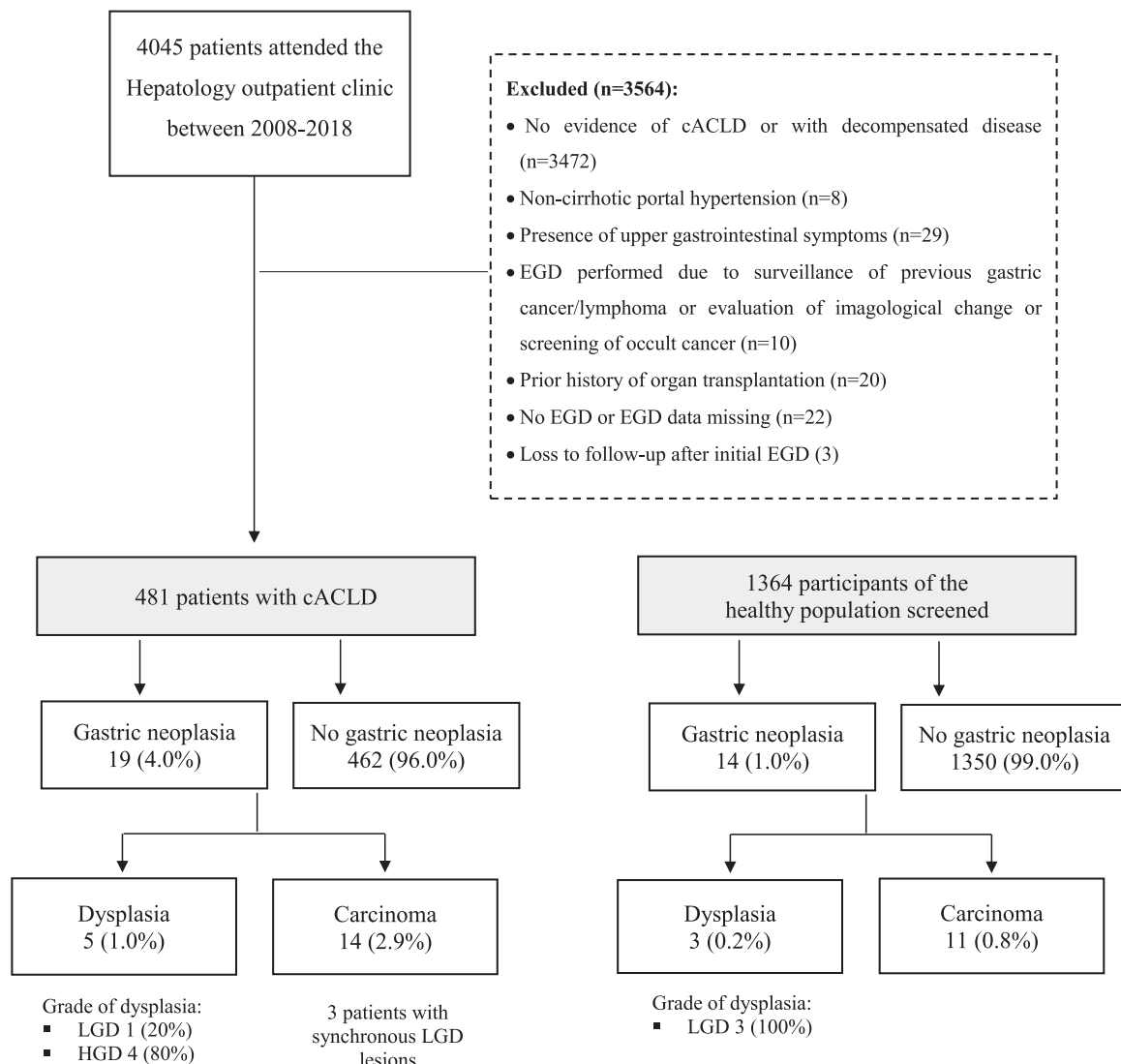


Fig. 1. Study flowchart.

cACLD, compensated advanced chronic liver disease; EGD, esophagogastrroduodenoscopy; HGD, high grade dysplasia; LGD, Low-Grade Dysplasia.

Table 1
Demographic data.

	Total <i>n</i> = 1845	cACLD cohort <i>n</i> = 481	Healthy individuals cohort <i>n</i> = 1364	<i>p</i> value
Gender, <i>n</i>(%)				
Female	892 (48.3 %)	150 (31.2 %)	742 (54.4 %)	0.001
Male	953 (51.7 %)	331 (68.8 %)	622 (45.6 %)	
Age, median (IQR), years	58 (49–66)	58 (49–66)	57 (49–66)	0.492
Family history of gastric cancer, <i>n</i>(%)	27 (1.5 %)	4 (0.8 %)	23 (1.7 %)	0.268

IQR, interquartile range; cACLD, compensated advanced chronic liver disease.

Table 2
Characterization of the cACLD population.

	Total <i>n</i> = 481
Active alcohol consumption, <i>n</i> (%)	148 (30.8 %)
Smoking, <i>n</i>(%)	
Active smoker	70 (14.5 %)
Ex-smoker	72 (15 %)
Non-smoker	339 (70.5 %)
Etiology, <i>n</i>(%)	
Alcohol	213 (44.3 %)
HCV	59 (12.3 %)
Alcohol and HCV	29 (6 %)
HBV	26 (5.4 %)
Alcohol and HBV	7 (1.5 %)
NAFLD	40 (8.3 %)
Alcohol and NAFLD	39 (8.1 %)
AIH	18 (3.7 %)
PBC	14 (2.9 %)
AIH and PBC	10 (2.1 %)
PSC	1 (0.2 %)
Hemochromatosis	11 (2.3 %)
Wilson disease	2 (0.4 %)
Alfa-1 antitrypsin deficiency	1 (0.2 %)
Cryptogenic	11 (2.3 %)
ALD	288 (59.9 %)
Hepatocellular carcinoma, <i>n</i>(%)	53 (11 %)
Fibrosis staging in liver biopsy (METAVIR), <i>n</i>(%) F4	141 (29.3 %)
Transient elastography liver stiffness measurement, median (IQR), kPa	19.0 (10.2–35.3)
LSM by TE_{≤20} kPa, <i>n</i>(%)	192 (39.9 %)
Platelets, median (IQR), /mm³	136,000 (86,000–194,000)
Platelets_{≥150,000/mm³}, <i>n</i>(%)	190 (39.5 %)
Number of EGDs, median (IQR)	3 (2–5)
Gastro-esophageal varices on at least one EGD, <i>n</i>(%)	198 (41.2 %)
Time of follow-up after initial EGD, median (IQR), months	63 (33–97)

cACLD, compensated advanced chronic liver disease; ALD, alcoholic liver disease; AIH, autoimmune hepatitis; HBV, hepatitis B virus; HCV, hepatitis C virus; LC, liver cirrhosis; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; EGD, esophagogastroduodenoscopy; LSM, liver stiffness measurement; TE, transient elastography; IQR, interquartile range.

2.8. Ethical considerations

This study was conducted according to the Declaration of Helsinki. Informed consent to perform EGD was obtained before the procedure. The study was approved by the Ethics Department of CHUSJ (reference number 313/2022).

3. Results

Of the 4045 patients who attended the Hepatology outpatient clinic between 2008 and 2018, we identified 481 cACLD patients who met the eligibility criteria. These 481 patients were compared with 1364 healthy participants (Fig. 1).

Among assessed participants, 51.7 % were males and the median age was 58 years old (IQR=49–66 years) (Table 1). There was a positive GC family history in 1.5 % of the patients. We observed a male predominance in the cACLD cohort compared to the asymptomatic healthy individuals group (68.8 % vs. 45.6 %, respectively; $p = 0.001$), with no significant differences between groups regarding age and family history of GC.

3.1. Characterization of the cACLD population

ALD was the most common cause of CLD ($n = 288$, 59.9 % when considering patients with multiple etiologies), followed by hepatitis C virus infection ($n = 59$, 12.3 %) and non-alcoholic fatty liver disease ($n = 40$, 8.3 %) (Table 2). One hundred and fifteen patients (23.9 %) had simultaneously LSM by TE ≤ 20 kPa and platelet count $\geq 150 \times 10^9/L$.

The patients underwent a median number of 3 EGDs (IQR 2–5) for screening of GOEV. The median follow-up time after EGD was 63 months (IQR 33–97).

3.2. Hp infection and gastritis staging

The frequency of Hp infection was significantly higher in healthy individuals compared to patients with cACLD (47.2% vs. 30.2 %; $p < 0.001$) (Table 3). Regarding the evaluation and staging of gastritis, in the cACLD cohort, there was a significantly higher frequency of both OLGA and OLGIM stages $\geq III$ compared to healthy individuals (12.1% vs. 1.6 %; $p < 0.001$; 14.5% vs. 1.9 % $p < 0.001$, respectively).

Table 3Frequency of *H. pylori* infection and gastritis staging among patients with cACLD and healthy individuals.

	Total n = 1845	cACLD cohort n = 481	Healthy individuals cohort n = 1364	p value
Hp infection, n(%)				<0.001
Yes	734 (44.2 %)	90 (30.2 %)	644 (47.2 %)	
No	928 (55.7 %)	208 (69.8 %)	720 (52.8 %)	
No data	183 (9.9 %)	183 (38.0 %)	-	
Gastric atrophy, n(%)				<0.001
Antrum				
No	1177 (71.5 %)	190 (67.1 %)	987 (72.4 %)	
Mild	304 (18.5 %)	55 (19.4 %)	249 (18.3 %)	
Moderate	141 (8.5 %)	24 (8.5 %)	117 (8.6 %)	
Severe	25 (1.5 %)	14 (5.0 %)	11 (0.8 %)	
No data	198 (10.7 %)	198 (41.2 %)	-	
Body				<0.001
No	1367 (87.0 %)	164 (79.2 %)	1203 (76.6 %)	
Mild	97 (6.2 %)	19 (9.2 %)	78 (5.0 %)	
Moderate	95 (6.0 %)	15 (7.2 %)	80 (5.9 %)	
Severe	12 (0.8 %)	9 (4.4 %)	3 (0.2 %)	
No data	274 (14.9 %)	274 (57.0 %)	-	
OLGA, n(%)				<0.001
0	1022 (65.0 %)	127 (61.4 %)	895 (65.6 %)	
I	309 (19.7 %)	37 (17.9 %)	272 (20.0 %)	
II	193 (12.3 %)	18 (8.7 %)	175 (12.8 %)	
III	32 (2.0 %)	13 (6.2 %)	19 (1.4 %)	
IV	15 (1.0 %)	12 (5.8 %)	3 (0.2 %)	
No data	274 (14.9 %)	274 (57.0 %)	-	
OLGA≥III, n(%)				<0.001
No data	274 (14.9 %)	274 (14.9 %)	22 (1.6 %)	
Intestinal metaplasia, n(%)				<0.001
Antrum				
No	1283 (77.9 %)	183 (64.7 %)	1100 (80.7 %)	
Mild	224 (13.6 %)	42 (14.8 %)	182 (13.3 %)	
Moderate	102 (6.2 %)	41 (14.5 %)	61 (4.5 %)	
Severe	38 (2.3 %)	17 (6.0 %)	21 (1.5 %)	
No data	198 (10.7 %)	198 (41.2 %)	1290 (92.7 %)	
Body				<0.001
No	1457 (92.8 %)	167 (80.7 %)	65 (4.1 %)	
Mild	65 (4.1 %)	16 (7.7 %)	32 (2.0 %)	
Moderate	32 (2.0 %)	13 (6.3 %)	17 (1.1 %)	
Severe	17 (1.1 %)	11 (5.3 %)	-	
No data	274 (14.9 %)	274 (57.0 %)	-	
OLGIM, n(%)				<0.001
0	1185 (75.4 %)	123 (59.4 %)	1062 (77.9 %)	
I	239 (15.2 %)	33 (16.0 %)	206 (15.1 %)	
II	91 (5.8 %)	21 (10.1 %)	70 (5.1 %)	
III	38 (2.4 %)	19 (9.2 %)	19 (1.4 %)	
IV	18 (1.2 %)	11 (5.3 %)	7 (0.5 %)	
No data	274 (14.9 %)	274 (57.0 %)	-	
OLGIM≥III, n(%)				<0.001
No data	274 (14.9 %)	274 (57.0 %)	26 (1.9 %)	

cACLD, compensated advanced chronic liver disease; Hp, *Helicobacter pylori*; OLGA, Operative Link on Gastritis Assessment; OLGIM, Operative Link on Gastritis/Intestinal-Metaplasia Assessment.

3.3. Frequency of gastric neoplasia

The overall frequency of gastric neoplasia was 1.8 % (Table 4). The frequency of gastric neoplasia in the cACLD cohort was significantly higher than that observed in healthy individuals [$n = 19$ (4.0 %; 95 %CI=2.2–5.7 %) vs. $n = 14$ (1.0 %; 95 %CI=0.5–1.6 %); $p < 0.001$].

The frequency of gastric dysplasia was 0.4 % ($n = 8$), being significantly different between cACLD patients and asymptomatic healthy individuals [$n = 5$ (1.0 %; 95 %CI=0.1–1.9 %) vs. $n = 3$ (0.2 %; 95 %CI=0–0.5 %); $p = 0.019$]. Histological grading was significantly higher in the cACLD cohort (high-grade dysplasia 80% vs. 0 %; $p = 0.028$). The frequency of gastric carcinoma was also more common among patients with cACLD [$n = 14$ (2.9 %; 95 %CI=1.4–4.4 %) vs. $n = 11$ (0.8 %; 95 %CI=0.3–1.3 %), $p = 0.002$].

In unadjusted models, cACLD was positively associated with the occurrence of gastric carcinoma (OR=8.9; 95 %CI=4.0–19.9; $p < 0.001$) and overall gastric neoplasia (OR=9.8; 95 %CI=4.8–

19.8; $p < 0.001$). Positive associations were also found after adjustment for the propensity score both for gastric carcinoma (OR=3.2; 95 %CI=1.7–6.1; $p < 0.001$) and gastric neoplasia (OR=3.2; 95 %CI=1.8–5.6; $p < 0.001$).

3.3.1. Subanalysis according to the Baveno VII criteria

We evaluated patients that, according to the Baveno VII criteria, would not need EGD for the diagnosis of GOEV ($n = 115$, 23.9 % of cases). In this subgroup, 7 cases of gastric neoplasia (36.8 % of the total cases identified in the cACLD population; 95 %CI=15.2–58.5 %) were diagnosed (including 4 cases of gastric carcinoma).

3.4. Gastric carcinoma histological characterization

Gastric carcinomas were classified according to Laurén's and WHO classifications. Most carcinomas [$n = 15$ (60.0 %)] were of the intestinal and tubulo-papillary subtypes, with no significant differences between cACLD and asymptomatic healthy individuals

Table 4
Frequency and characterization of gastric neoplasia.

	Total n = 1845	cACLD cohort n = 481	Healthy individuals cohort n = 1364	p value
Gastric neoplasia, n(%)	33 (1.8 %)	19 (4.0 %)	14 (1.0 %)	<0.001
Gastric dysplasia, n(%)	8 (0.4 %)	5 (1.0 %)	3 (0.2 %)	0.019
Location				0.315
Body	1 (12.5 %)	1 (20.0 %)	-	
Antrum	6 (75.0 %)	4 (80.0 %)	2 (66.7 %)	
Antrum+body ⁺	1 (12.5 %)	-	1 (33.3 %)	
Histological grading				0.028
LGD	4 (50.0 %)	1 (20.0 %)	3 (100 %)	
HGD	4 (50.0 %)	4 (80.0 %)	-	
Gastric carcinoma, n(%)	25 (1.4 %)	14 (2.9 %)*	11 (0.8 %)	0.002
Location				0.164
Cardia	2 (8.0 %)	2 (14.3 %)	-	
Fundus	1 (4.0 %)	-	1 (9.1 %)	
Body	9 (36.0 %)	7 (50.0 %)	2 (18.2 %)	
Incisura	4 (16.0 %)	2 (14.3 %)	2 (18.2 %)	
Antrum	9 (36.0 %)	3 (21.4 %)	6 (54.5 %)	
Histological subtype – Laurén classification				0.078
Intestinal	15 (60.0 %)	7 (50.0 %)	8 (72.7 %)	
Diffuse	4 (16.0 %)	1 (7.1 %)	3 (27.3 %)	
Mixed	1 (4.0 %)	1 (7.1 %)	-	
Not defined	5 (20.0 %)	5 (35.7 %)	-	
Histological subtype – WHO classification				0.147
Gastric adenocarcinoma				
Tubulo-papillary	15 (60.0 %)	7 (50.0 %)	8 (72.7 %)	
Poorly-cohesive	4 (16.0 %)	1 (7.1 %)	3 (27.3 %)	
Mixed	1 (4.0 %)	1 (7.1 %)	-	
Rare histopathological subtypes	4 (16.0 %)	4 (28.7 %)	-	
Large cell neuroendocrine carcinoma	1 (4.0 %)	1 (7.1 %)	-	

⁺ Patient with two synchronous lesions.

* Three patients had a synchronous lesion with LGD in the antrum.

cACLD, compensated advanced chronic liver disease; LGD, low-grade dysplasia; HGD, high-grade dysplasia, WHO, World Health Organization.

cohorts. In the cACLD cohort, there were 4 cases of gastric carcinomas belonging to rare histopathological subtypes (28.7 %), according to the 5th Edition of the WHO classification, including two cases of gastric adenocarcinoma with enteroblastic differentiation (GAED) and two cases of gastric carcinoma with lymphoid stroma (GCLS), one associated with Epstein-Barr virus infection (patient with Primary Biliary Cirrhosis. Endoscopic ultrasound at diagnosis suggestive of a T3N2 lesion. Underwent neoadjuvant chemotherapy and was submitted to total gastrectomy - pT1bN0R0) and the other associated with microsatellite instability status (Patient with a previous diagnosis of ALD. Submitted to total gastrectomy (pT1bN3a) and adjuvant chemotherapy). A detailed histological and morphological characterization of these cases is shown in Fig. 2.

3.5. Clinical outcomes and management after diagnosis of gastric neoplasia in the cACLD population

The clinical outcomes and management approaches of cACLD patients after the diagnosis of gastric neoplasia are described in Supplementary Table 1 and 2.

Regarding the etiology of cACLD in patients diagnosed with gastric neoplasia, ALD was present in 57.9 % of cases. Nevertheless, while ALD was present in 100 % of the gastric dysplasia cases, in patients with gastric adenocarcinoma non-ALD was responsible for more than half of the cases (57.1 %). A subanalysis comparing patients with versus without ALD did not show significant differences in the frequency of Hp infection, gastritis staging and frequency of gastric neoplasia. (Supplementary Table 3).

3.5.1. Gastric carcinoma

Regarding gastric carcinoma cases in the cACLD cohort ($n = 14$), 7 (50.0 %) were diagnosed in the first screening EGD. The frequency of gastric adenocarcinoma was higher among non-ALD patients, albeit without statistical significance (4.1% vs. 2.1 % in ALD

patients; $p = 0.187$). The OS after the diagnosis of gastric carcinoma was 38 months (IQR 6–69), with a 3-year mortality rate of 42.9 %. There were no significant differences in OS estimate in cACLD patients with and without a diagnosis of gastric carcinoma (mean 92 ± 12 vs. 115 ± 3 months; $p = 0.359$).

4. Discussion

In our study, we found a 4-times higher frequency of gastric neoplasia in patients with cACLD compared to a healthy population, with this difference being observed even after adjustment to demographic and clinical variables. Few previous studies from the 90's addressed this matter, reporting a higher prevalence of precursor lesions and GC in patients with cACLD, compared to the expected prevalence for the general population [14–17]. More recently, Tae Hoon Ha et al. have found a significantly higher frequency of GC in patients with ALD compared to healthy individuals. They suggested that part of this increased risk is due to mechanisms related to and dependent on liver disease [18].

Hp infection corresponds to one of the most important risk factors for the development of GC [12]. In our study, the frequency of Hp infection was significantly higher in healthy individuals than in the cACLD cohort. The higher exposure of cACLD patients to antibiotics and proton-pump inhibitors can explain this difference [36]. Interestingly, despite a lower incidence of Hp infection, the frequency of advanced gastritis stages was significantly higher in the cACLD cohort compared to the asymptomatic healthy individuals cohort. A possible interpretation for our findings may be the spontaneous disappearance of Hp in the context of severe atrophy and intestinal metaplasia, as previously reported [37–39].

Interestingly, in the cACLD population, the frequency of special types of GC (according to the WHO Classification) was particularly high (28.7 %). According to the WHO, GCLS and GAED are

rare histopathological subtypes that account for 1–7 % and 2.6–5.4 % of GC cases [40], respectively. GAED has been noted to produce alpha-fetoprotein (AFP), being recognized as a variant of AFP-producing gastric carcinoma, which is associated with a poor prognosis and advanced-stage disease [41,42]. This was evident in our cohort, with both cases being diagnosed in an advanced stage with lymph node involvement, with need for (neo)adjuvant chemotherapy. The putative association between these rare histopathological subtypes and ACLD has not been addressed, in the literature. The interesting relationship between GAED, one of the AFP-producing gastric carcinomas and hepatocellular carcinoma deserves further

attention and should be addressed in future studies. Regarding the relative higher frequency of GCLS in comparison with other GC cohorts, it might be speculated that liver cirrhosis associated-immune dysfunction may contribute, to some extent [43], to the association with this peculiar histopathological subtype characterized by abundant lymphoplasmacytic infiltrate and immune suppressive biomarkers [44]. It is important to notice that the majority of cACLD patients in our study had ALD and that may also pose a bias, given that alcohol consumption is an established risk-factor for GC. Nevertheless, while ALD was present in 100 % of the gastric dysplasia cases, in patients with gastric adenocarcinoma, non-ALD

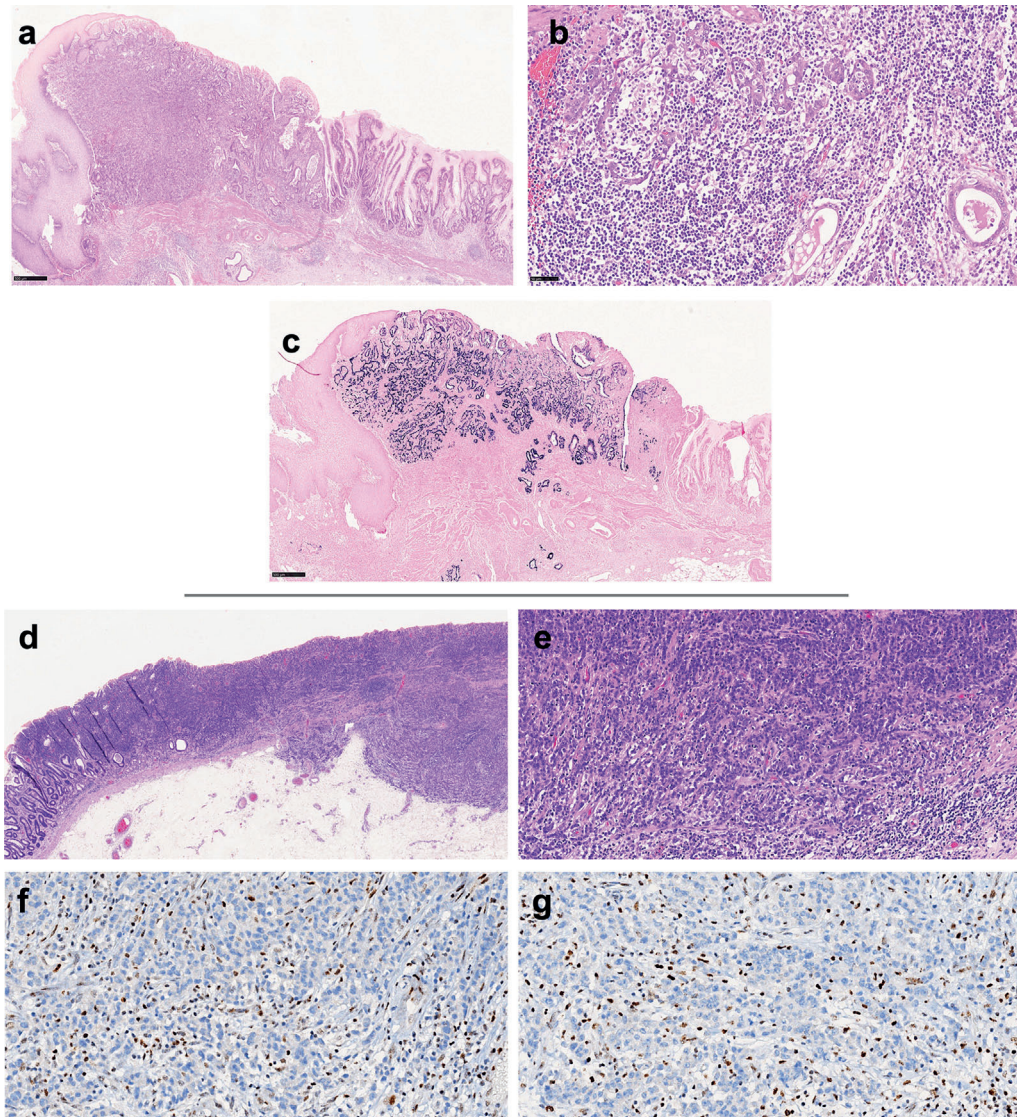


Fig. 2. – Case 1 (a-c). Adenocarcinoma of the ECG (a, HE, 40x amplification) composed of anastomosing glands and tubular structures with abundant inflammatory stroma composed predominantly of lymphocytes and plasma cells (b, HE, 400x amplification). Epstein-Barr encoding region (EBER) in situ hybridization showed EBV infection (c, EBER-ISH, 40x amplification).

Case 2 (d-g). Gastric adenocarcinoma (d, HE, 40x amplification) with abundant peri-tumoral and intra-tumoral lymphoid stroma (e, HE, 200x amplification). Immunohistochemistry for mismatch repair proteins (MMR) showed MMR-deficiency with loss of expression of MLH1 (f, MLH1, 400x amplification) and PMS2 (g, MLH1, 400x amplification) in tumour cells (note the positive internal control in stromal cells).

Case 3 (h-k). Fungating gastric adenocarcinoma (h, HE, 20x amplification) of predominant tubular architecture showing comedonecrosis and tumour cells with glassy eosinophilic and clarified cytoplasm (i, HE, 200x amplification). This case was diagnosed as gastric adenocarcinoma with enteroblastic differentiation. Accordingly, immunohistochemistry showed multifocal expression of SALL4 (j, 200x) and focal expression of glypican-3 (k, 250x). Patient with a previous diagnosis of HBV infection. Submitted to total gastrectomy (pT1bR0).

Case 4 (l-p). Fungating gastric adenocarcinoma (l, HE, 20x amplification) of tubular and papillary architecture showing comedonecrosis and tumour cells with clarified cytoplasm (m, HE, 200x amplification). This case was diagnosed as gastric adenocarcinoma with enteroblastic differentiation. Accordingly, immunohistochemistry showed expression of SALL4 (n, 200x), glypican-3 (o, 200x) and alpha-fetoprotein (p, 200x).

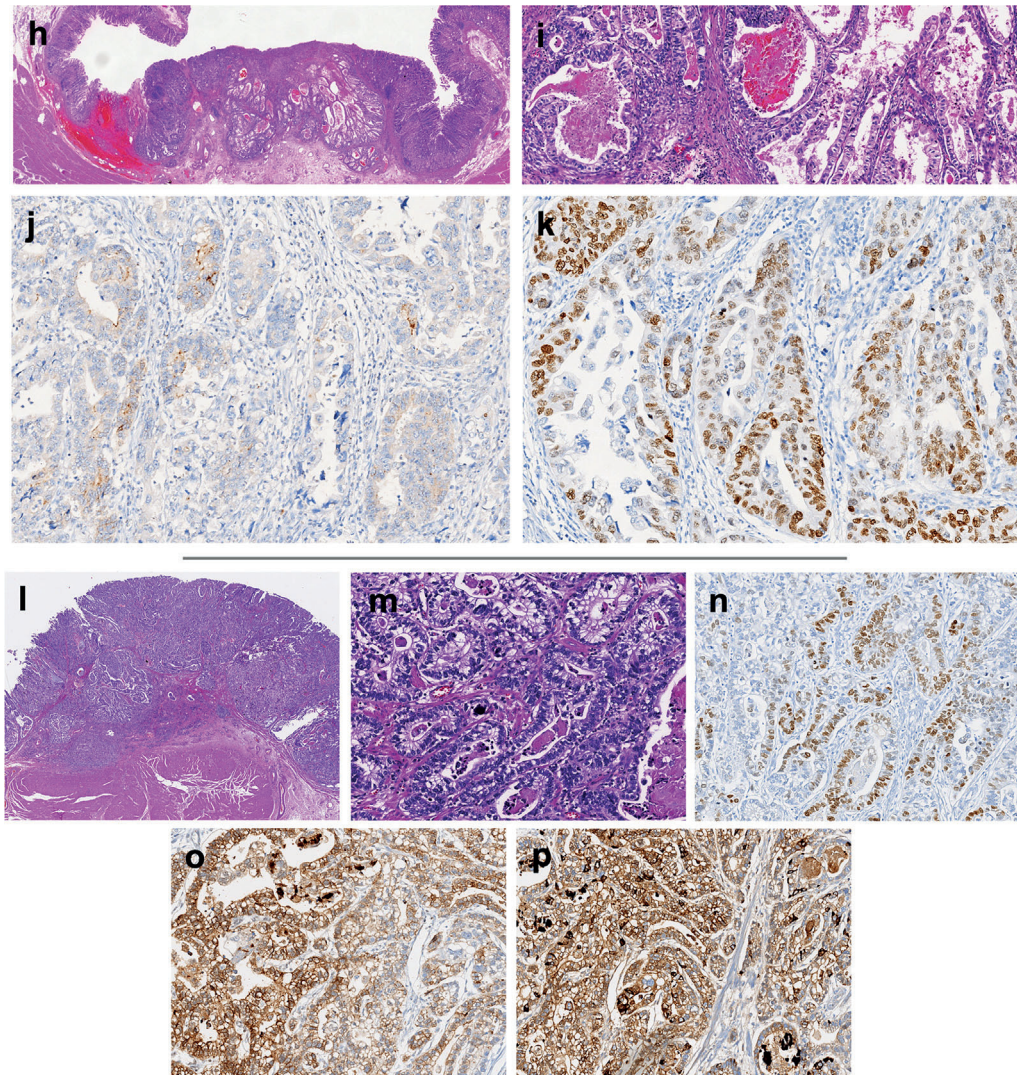


Fig. 2. Continued

patients accounted for more than half of cases. Our results suggest that other factors beside the etiology of ACLD may be associated with an increased risk of GC in this population.

Areia et al. proposed to perform a screening EGD at the same time as the first screening colonoscopy for colorectal cancer in Portugal. Using a Markov cost-utility analysis, they compared three screening strategies and concluded that endoscopic GC screening was cost-effective if combined with a colonoscopy [11]. More recently, a review article sought to understand the applicability of screening methods usually adopted in countries with high-risk of GC in countries of intermediate and low risk [45]. One of the recommended strategies for countries with intermediate risk may be to perform EGD after a positive fecal occult blood test [45]. Therefore, according to our results that demonstrate an overall higher frequency of gastric neoplasia in patients with ACLD compared to healthy individuals, screening these patients appears even more relevant than in the general population. According to the proposed Baveno VII criteria [21], a significant proportion of the patients included in the study (23.9 %) would not be submitted to EGD to diagnose high-risk varices. Nevertheless, we found that 36.8 % of the gastric neoplasia cases in the cACLD population would have been missed if these criteria had been strictly followed. These results highlight the possible role of EGD as an opportunistic screening method for an early diagnosis of gastric neoplasia in this pop-

ulation, especially considering that regular follow-up endoscopic surveillance for GOEV is indicated in a significant proportion of these patients.

Our study has some limitations inherent to the study design that should be addressed. The evaluation period was different for patients with cACLD (2008–2018) compared with healthy individuals (2017–2018). This may be a significant limitation, especially considering that, for a considerable period, in patients with cACLD, high definition endoscopes with the possibility of performing virtual chromoendoscopy were not used and, besides, the brand of the scopes used was different in both groups. Another limitation concerns the fact that in our study there was a significant male predominance in cACLD patients compared to healthy individuals. This could have led to an overestimation of GC frequency in the cACLD group. In the propensity scores analysis, we observed a significant positive association between cACLD and gastric neoplasia after adjustment of potential confounders. Nevertheless, it is important to stress that alcohol consumption and smoking status were not evaluated in healthy individuals, thus impairing the possibility of adjusting for these variables. Also, it was not possible to collect data regarding the status of Hp infection and gastritis staging in a large number of cACLD patients. Since all of these are established risk factors for GC, the possibility of confounding in the association between cACLD and gastric neoplasia cannot not be ex-

cluded. Future studies may continue to assess whether cACLD is an independent risk factor for gastric neoplasia.

Our study has strengths that bring valuable knowledge regarding this topic. This is the largest study conducted so far that evaluated and demonstrated an increased frequency of gastric neoplasia in cACLD patients. In addition, patients were carefully assessed regarding eligibility criteria and there was a long follow-up in the cACLD patients, that allowed a detailed evaluation of the management and outcomes after the diagnosis of gastric neoplasia. This is also the first study to suggest that EGD for GOEV screening can lead to an opportunistic detection of gastric neoplasia. Considering the previously reported efficacy and safety of ER in this population [46–48], early detection may lead to better outcomes in a population that is very difficult to treat. Although the reduced number of patients in our cohort did not allowed us to perform a detailed analysis, the majority underwent ER/surgery with curative intent, with a reasonable overall survival. We believe that these data provide additional important information to be considered in the approach of cACLD patients in specific countries, especially the ones with an intermediate GC risk where screening indications are not so clear.

In conclusion, we found a higher frequency of gastric neoplasia in patients with cACLD than in healthy individuals who were undergoing an already scheduled screening colonoscopy. The Baveno VII criteria suggest that EGD screening for GOEV may be preventable in certain patient groups. Based on our results, we suggest that in countries with intermediate-high risk for GC, continuing to perform EGD could be beneficial, as patients with cACLD may be at higher risk for GC, and its early detection may be associated with better outcomes.

Conflict of interest

None.

Acknowledgments

None to report.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.dld.2024.04.035](https://doi.org/10.1016/j.dld.2024.04.035).

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Supplementary Table 1

Etiology of cACLD, outcomes and management after diagnosis of gastric neoplasia in cACLD population

Total n=19	
Etiology of cACLD, n(%)	
Alcohol	7 (36.8 %)
Alcohol and NAFLD	3 (15.7 %)
Alcohol and HCV	1 (5.3 %)
HCV	1 (5.3 %)
HBV	2 (10.5 %)
NAFLD	2 (10.5 %)
PBC	1 (5.3 %)
AIH and PBC	1 (5.3 %)
Hemochromatosis	1 (5.3 %)
ALD, n(%)	
Yes	11 (57.9)
No	8 (42.1)
Gastric dysplasia (n=5)	
Etiology of cACLD, n(%)	
Alcohol	2 (40.0 %)
Alcohol and NAFLD	3 (60.0 %)
ALD	
Yes	5 (100.0 %)
No	0 (0.0 %)
Type of treatment	
Endoscopic	
- ESD	4 (80 %)
- EMR	3 (75 %)
- EMR	1 (25 %)
Surgery (subtotal gastrectomy)	
Gastric carcinoma (n=14)	
Etiology of cACLD, n(%)	
Alcohol	5 (35.7 %)
Alcohol and HCV	1 (7.1 %)
HCV	1 (7.1 %)
HBV	2 (14.3 %)
NAFLD	2 (14.3 %)
PBC	1 (7.1 %)
AIH and PBC	1 (7.1 %)
Hemochromatosis	1 (7.1 %)
ALD, n(%)	
Yes	6 (42.9 %)
No	8 (57.1 %)
TNM staging, n(%)	
T	
T1a	4 (28.6 %)
T1b	5 (35.7 %)
T2	1 (7.1 %)
T3	0 (0 %)
T4a	3 (21.5 %)
No data	1 (7.1 %)
N	
N0	10 (71.5 %)
N1	2 (14.3 %)
N3a	1 (7.1 %)
No data	1 (7.1 %)
M	
M0	12 (85.8 %)
M1	1 (7.1 %)
No data	1 (7.1 %)
AJCC Stage, n(%)	
IA	8 (57.3 %)
IB	1 (7.1 %)
IIB	1 (7.1 %)
IIIA	2 (14.3 %)
IV	1 (7.1 %)
No data	1 (7.1 %)
Type of treatment, n(%)	
Endoscopic	
- ESD	2 (14.3 %)
- ESD	2 (100 %)
Resection/ margins (R0)	2 (100 %)
Curative resection	1 (50 %)
Adverse events	0 (0 %)
Re-intervention	0 (0 %)
Number of days of hospitalization, median (IQR)	2
Tumor recurrence	0 (0 %)
Surgical	
- Total gastrectomy	11 (78.6 %)
- Total gastrectomy	8 (72.7 %)
- Subtotal gastrectomy	3 (27.3 %)
Resection/ margins (R0)	11 (100 %)
Adverse events	5 (54.5 %)
Surgical re-intervention	2 (18.2 %)
Number of days of hospitalization, median (IQR)	10 (9-21)
Additional treatment	3 (27.3 %)
- Neoadjuvant chemotherapy	1 (9.1 %)
- Adjuvant chemotherapy	2 (18.2 %)
Tumor recurrence	0 (0 %)
Palliative care	1 (7.1 %)
Mortality rate in the follow-up, n(%)	
Cause of death	
Related	3 (42.9 %)
-Tumor	1 (33.3 %)
-Complication	2 (66.7 %)
Unrelated	4 (57.1 %)
30-days mortality, n(%)	1 (7.1 %)
6-months mortality, n(%)	3 (21.4 %)
3-years mortality, n(%)	6 (42.9 %)
Overall survival, median (IQR), months	38 (6-69)

cACLD, compensated advanced chronic liver disease; ALD, alcoholic liver disease; AIH, autoimmune hepatitis; HBV, hepatitis B virus; HCV, hepatitis C virus; LC, liver cirrhosis; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; AJCC, American Joint Committee on Cancer; ESD, Endoscopic Submucosal Dissection; EMR, Endoscopic Mucosal Resection; HGD, high grade dysplasia; LGD, Low-Grade Dysplasia; IQR, interquartile range

Supplementary Table 2

Surgery adverse events classified according to the Clavien-Dindo classification.

	Number of events	Clavien-Dindo	Management
Local complications			
Wound infection	1	II	Antibiotherapy
Anastomotic dehiscence	1	V	Surgery
Bleeding	1	V	Surgery; Blood transfusion
Systemic complications			
Heart failure decompensation	1	I	Conservative
Paroxysmal atrial fibrillation	1	II	Rhythm control therapy
Acute on chronic kidney disease	1	I	Fluid therapy
Nosocomial pneumonia	1	II	Antibiotherapy
Hemoptysis	1	I	Conservative

Supplementary Table 3Subanalysis of patients with *versus* without ALD

	Total n=481	ALD n=288	Non-ALD n=193	p value
Hp infection, n(%)				
Yes	90 (30.2 %)	53 (29.6 %)	37 (31.1 %)	0.785
No	208 (69.8 %)	126 (70.4 %)	82 (68.9 %)	
No data	183 (38.0 %)	109 (37.8)	74 (38.3 %)	
OLGA≥III, n(%)				
Yes	25 (12.1 %)	15 (12.4 %)	10 (11.6 %)	0.867
No data	274 (14.9 %)	167 (58.0)	107 (55.4 %)	
OLGIM≥III, n(%)				
Yes	30 (14.5 %)	20 (16.5 %)	10 (11.6 %)	0.324
No data	274 (57.0 %)	167 (58.0)	107 (55.4 %)	
Gastric neoplasia, n(%)				
Yes	19 (4.0 %)	11 (3.8 %)	8 (4.1 %)	0.857
Gastric dysplasia, n(%)				
Yes	5 (1.0 %)	5 (1.7 %)	0 (0%)	0.086
Gastric carcinoma, n(%)				
Yes	14 (2.9 %)	6 (2.1 %)	8 (4.1 %)	0.187

Hp, *Helicobacter pylori*; OLGA, Operative Link on Gastritis Assessment;

OLGIM, Operative Link on Gastritis/Intestinal-Metaplasia Assessment; ALD, alcoholic liver disease

6.2.

Study 2

Cost-utility and clinical impact of endoscopic screening for esophageal and gastric neoplasia in patients with head and neck neoplasms

Morais R, Afonso J, Sousa N, Sousa-Pinto B, Libânio D, Marinho B, Sacramento M, Simplício M, Faria-Ramos I, Azevedo L, Marques M, Silveira H, Gullo I, Carneiro F, Santos-Antunes J, Macedo G.

European Journal of Gastroenterology and Hepatology
Accepted for publication

Impact factor 2.3
(Thomson-Reuters, 2023)

Rank 78 of 164 on Gastroenterology journals (Q2)
(Scimago Journal & Country Rank, 2023)

Cost-utility and clinical impact of endoscopic screening for esophageal and gastric neoplasia in patients with head and neck neoplasms

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Objective Patients with head and neck neoplasms (HNN) are at an increased risk of esophageal neoplasia (EN) and gastric neoplasia (GN). We aimed to assess the clinical impact and cost-utility of endoscopic screening in this population in the Western setting.

Methods In this single-center study HNN patients eligible for curative treatment underwent screening esophagogastroduodenoscopy. We assessed the frequency, clinical, and pathological outcomes of EN and GN. The cost-effectiveness of an annual endoscopic screening for EN was evaluated from a societal perspective, using a Markov model and probabilistic sensitivity analysis. In addition, we performed a sensitivity analysis using data on the prevalence of detected EN lesions in the four largest previous Western studies on this topic.

Results Forty-six HNN patients met the inclusion criteria and underwent endoscopic screening. Six EN were detected in five patients (10.9%, 95% confidence interval: 1.9–19.9%). Additionally, five GN were detected in five patients. Most patients had early-stage EN or GN (90%) and were treated with endoscopic resection (80%). Endoscopic screening strategy had an incremental cost-effectiveness ratio of 39 357.8 €/quality-adjusted life years gained, being cost-effective at a willingness-to-pay threshold of two times the Portuguese gross domestic product per capita. In the sensitivity analysis, it remained cost-effective when considering the prevalence of EN reported in Germany, France, and Brazil.

Conclusion An endoscopic screening program identified EN or GN in a fifth of HNN patients, most presenting at an early stage. The program implementation appears to be cost-effective in Portugal. These results may be applicable to other medium-to-high-income Western countries. Eur J Gastroenterol Hepatol XXX: XXXX–XXXX
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Introduction

Esophageal and gastric cancers are among the most prevalent and lethal malignancies worldwide [1]. Screening

for gastroesophageal neoplasia (GEN) is recommended and was found to be cost-effective in high-incidence Asian countries [2]. In Western countries, according to the European Society of Gastrointestinal Endoscopy, gastric neoplasia (GN), screening by esophagogastroduodenoscopy (EGD) may be considered in intermediate-to-high-risk regions, depending on local settings and availability of endoscopic resources [2]. Screening for esophageal neoplasia (EN), namely squamous cell carcinoma (SCC), however, has only been suggested in high-risk populations such as patients with achalasia or with head and neck neoplasms (HNN) [2].

Patients with HNN are at increased risk for a second primary EN (either synchronous or metachronous), due to shared risk factors including smoking and alcohol consumption. The role of human papillomavirus (HPV) infection in this context is controversial, especially in the absence of additional risk factors [3,4]. The co-occurrence of an EN is associated with a poor prognosis of HNN, regardless of how appropriately the latter is managed [5]. Therefore, early detection and management of concurrent EN by minimally invasive endoscopic resection may potentially improve patients' outcomes.

Several studies, mainly from Asia, have evaluated the diagnosis and management of EN in patients with HNN [6–12]. The applicability of these results in Western

European Journal of Gastroenterology & Hepatology XXX, XXX:XXXX–XXXX

Keywords: cost-effectiveness analysis, cost-utility analysis, esophageal neoplasia, esophagogastroduodenoscopy, gastric neoplasia, head and neck neoplasms, screening

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Received 21 January 2025 **Accepted** 30 March 2025.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.eurojgh.com.

populations is, however, uncertain due to differences in the incidence of HNN and EN. Studies conducted in the Western setting showed contradictory results, and a wide debate is still ongoing regarding (1) the impact of screening programs on patients' outcomes, (2) the timing and frequency of screening, and (3) the cost-effectiveness of screening all HNN patients vs. selected high-risk individuals [13–20].

Therefore, we aimed to evaluate the clinical impact and cost-effectiveness of an endoscopic screening program for EN in HNN patients, in a Western setting. Besides, we sought to evaluate the additional diagnosis of GN and to perform a complete histopathological characterization of all detected GEN and matched HNN.

Materials and methods

Study design

This study is a retrospective analysis of prospectively collected data that evaluated an endoscopic screening program for HNN patients in a tertiary referral center (Unidade Local de Saúde São João - ULSSJ, Porto, Portugal). The study was reported according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [21].

Eligibility criteria

We included all adult patients with HNN (from the oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, and paranasal sinus) diagnosed between June 2020 and December 2023 and proposed for curative-intent treatment.

HNN diagnosis and staging were obtained by flexible transnasal endoscopy and computed tomography scan (including chest scan), which were performed in all patients. MRI (depending on the location) and PET were also performed when deemed necessary [22].

We excluded patients (1) with nonepithelial HNN or (b) with clinical or imaging suspicion of GEN before the first EGD.

Study endpoints

The main endpoints were (1) the frequency of EN in patients with HNN undergoing endoscopic screening and (2) the cost-utility of an endoscopic screening strategy for EN vs. no screening strategy in patients with HNN.

Additional endpoints included (1) evaluation of the frequency of GN, (2) assessment of the treatment and clinical outcomes after the diagnosis of GEN, and (3) histopathological characterization of the detected GEN and matched HNN.

Screening and follow-up

The strategy consisted of the performance of a screening EGD in all included patients, within 12 months since the HNN diagnosis. Whenever possible, a synchronous strategy (≤ 6 months) was conducted. Careful inspection of the esophageal mucosa with white light imaging, narrow-band imaging (NBI), and Lugol's staining chromoendoscopy [20 ml of Lugol's staining (1.2% iodine solution)] was performed in all patients.

Visible lesions were characterized using the Paris Classification [23]. The surface and vascular patterns were carefully evaluated using NBI and magnification to assess the possibility of endoscopic resectability. Targeted biopsies were performed and located in separate vials in all suspicious lesions.

Random biopsies of the antrum and gastric body using separate vials were obtained at the endoscopist's discretion.

When no lesion was identified, annual endoscopic screening was proposed. Treatment was pursued in the cases with histopathological confirmation of GEN [esophagus: low-grade dysplasia (LGD), high-grade dysplasia (HGD), SCC, or adenocarcinoma; stomach: LGD, HGD, or adenocarcinoma]. After GEN detection, staging and treatment ensued, according to a multidisciplinary team and patient decision.

Endoscopic submucosal dissection (ESD) was used to manage lesions amenable to endoscopic resection and curativeness of the resection was defined according to current guidelines [24].

Histopathological analysis

A full description of the histopathological analysis can be found in Supplementary Table 1, Supplemental digital content 1, <http://links.lww.com/EJGH/B159>. All HNN and GEN cases were reviewed by at least two expert pathologists (I.G. and F.C.). A detailed histopathological characterization of the detected GEN and matched HNN in each patient was performed, with evaluation of biomarkers of viral infections, namely p16 immunohistochemistry for HPV and *in situ* hybridization for Epstein–Barr virus (EBER-ISH). This analysis aimed to assess if an infection by one (or both) of these oncogenic viruses could explain the presence of synchronous or metachronous neoplasias, besides the traditional risk factors common to both tumor models.

Cost-utility analysis

Target population and model structure

A health economic analysis was performed to evaluate the cost-utility of an endoscopic screening program (vs. no screening) for the diagnosis of EN in patients with HNN in Portugal. The societal perspective was adopted in agreement with the recommendations for reporting cost-effectiveness analyses [25]. We opted for a cost-utility analysis to simultaneously account for the life years gained and the quality of life associated with the corresponding health states. The consequences of the strategies being compared were expressed in quality-adjusted life years (QALY). The Consolidated Health Economic Evaluation Reporting Standards 2022 was followed for reporting the present analysis [26].

The target population included patients ≥ 18 years with stage I–III HNN. A Markov state-transition cost-utility model was designed (Fig. 1 and Supplementary Figure 1, Supplemental digital content 1, <http://links.lww.com/EJGH/B159>). The screening strategy consisted of the performance of an EGD within 12 months of the HNN diagnosis. In the case of a negative initial examination, follow-up EGD was proposed yearly for 5 years (time horizon). The nonscreening strategy implied that patients

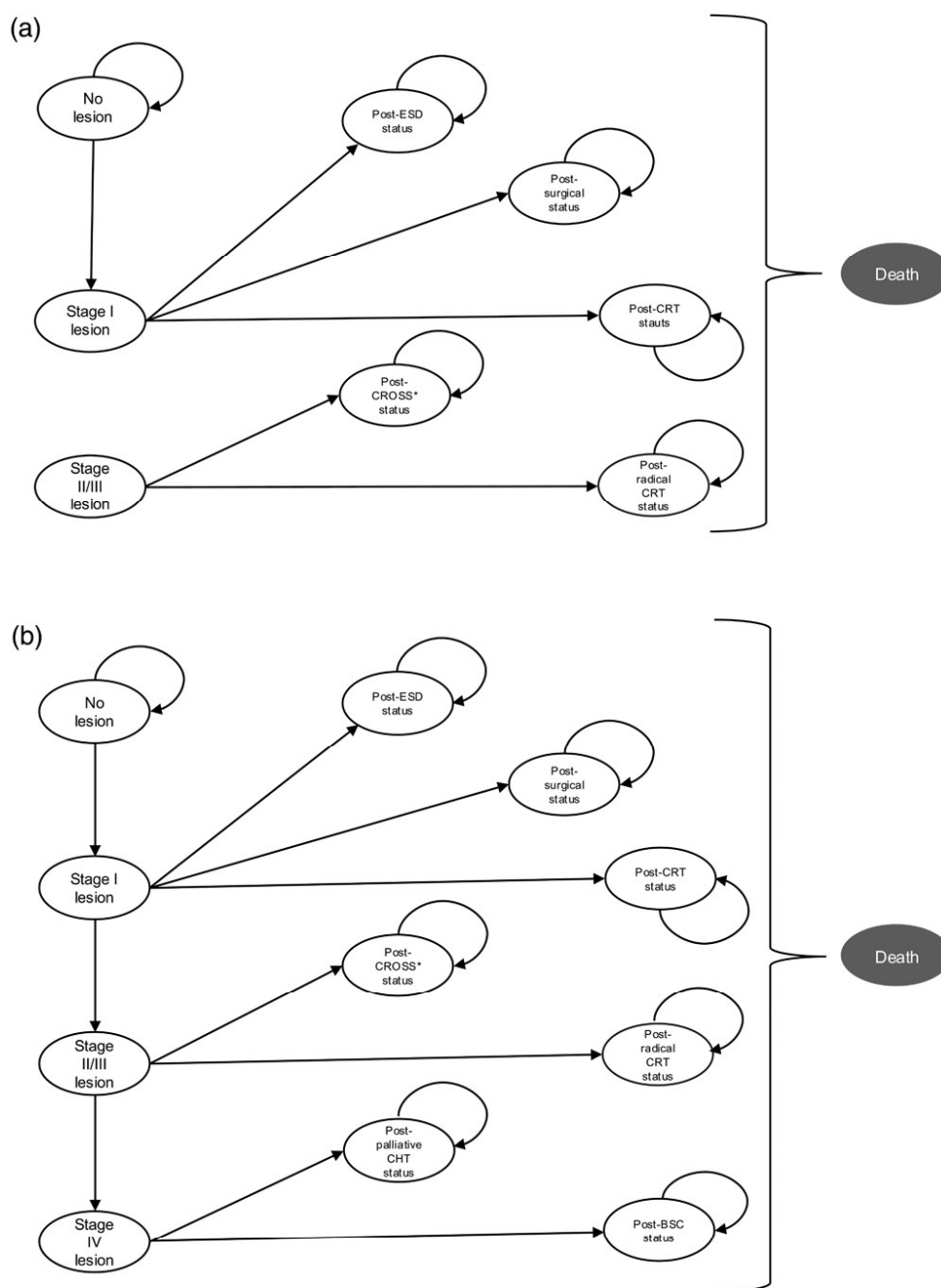


Fig. 1. Markov model illustration of a screening (a) vs. no screening strategy (b) in HNN patients, for the diagnosis of esophageal neoplasia (EN). A Markov model was used to project the costs and clinical outcomes for a time horizon of 5 years. The state-transition model simulated EN natural history as annual transitions between different health status. We assumed death as an absorbing state. *Preoperative chemoradiotherapy followed by surgery according to the CROSS study [Supplementary Table 2]. BSC, best supportive care; CHT, chemotherapy; CRT, chemoradiotherapy; ESD, endoscopic submucosal dissection; HNN, head and neck neoplasia.

were nonroutinely screened for EN. In this case, EN was diagnosed following (1) an EGD performed due to other reasons or (2) a complete evaluation following after EN signs or symptoms.

Costs were calculated using data from our center's Financial Department (ULSSJ, Porto, Portugal) and, whenever necessary, from national sources (Ministry of Health, Portugal).

Costs were calculated in 2023 Euros (€), with inflation adjustment as necessary. In accordance with published recommendations, a discount rate of 3% was incorporated for both costs and effectiveness results [25].

Supplementary Table 2, Supplemental digital content 1, <http://links.lww.com/EJGH/B159> summarizes the model inputs for the computation of costs, utilities, and transition probabilities. Modeling assumptions are described in Supplementary Table 3, Supplemental digital content 1, <http://links.lww.com/EJGH/B159>.

Outcomes and analysis

The effect size used to present our results was the incremental cost-effectiveness ratio (ICER). The main willingness-to-pay (WTP) threshold was set at 50 000 €/QALY

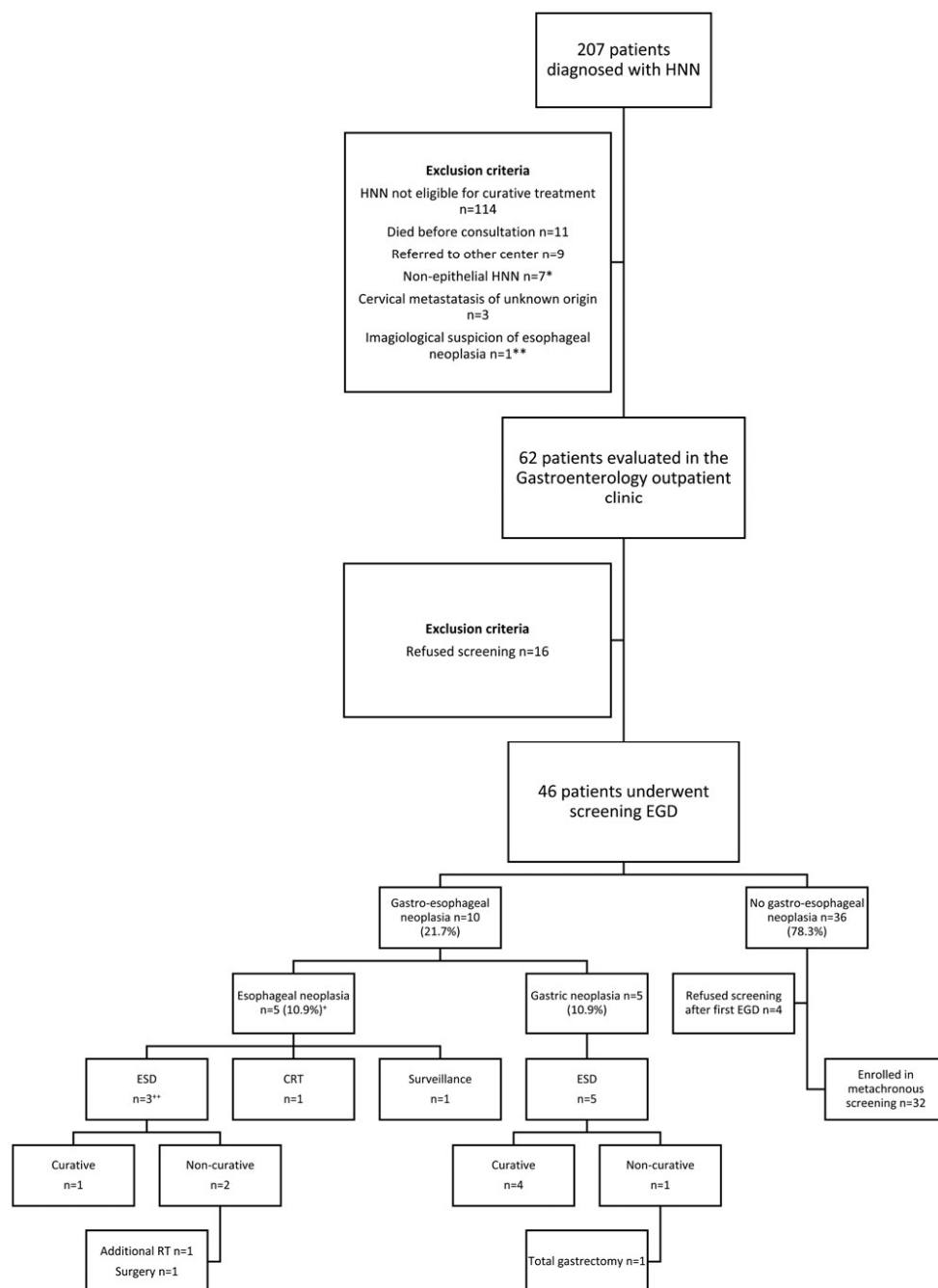


Fig. 2. Flow diagram of participant selection and clinical outcomes. CRT, chemoradiotherapy; EGD, esophagogastroduodenoscopy; ESD, endoscopic submucosal dissection; HNN, head and neck neoplasia; RT, radiotherapy. *Melanoma $n = 3$, central giant cell granuloma $n = 2$, ameloblastoma $n = 1$, and non-Hodgkin lymphoma $n = 1$. **Confirmed diagnosis of esophageal squamous cell carcinoma after EGD. +One patient had two synchronous esophageal neoplasias (one lesion with high-grade dysplasia, other with squamous cell carcinoma). ++The patient with two synchronous esophageal neoplasias underwent ESD of both lesions, with the one with squamous cell carcinoma being a noncurative resection. Note: None of the patients that underwent endoscopic screening had clinical or imaging suspicion of esophageal or gastric neoplasia.

gained, as it approximately corresponds to two times the Portuguese gross domestic product (GDP) per capita ($2 \times 24\,646 = 49\,292$ €). In addition, we considered WTP of one or three times the Portuguese GDP per capita as recommended by the WHO [27].

We performed a probabilistic sensitivity analysis using Monte Carlo simulation methods, with 10 000 simulations run per model. From the probabilistic sensitivity analyses performed, we retrieved the proportion of simulations identifying screening as cost-effective.

Additionally, we performed a sensitivity analysis considering the frequency of detected EN (at each oncological stage) in the four largest Western studies on this topic [13–16]. Results were expressed following probabilistic sensitivity analyses.

Statistical analysis

Categorical variables were described through absolute and relative frequencies, while continuous variables were

reported as means and standard deviations or medians, interquartile ranges (IQR), and minimum and maximum values. The Fisher's exact test or the chi-square test was used to compare categorical variables. Continuous variables with normal distribution were tested using the independent samples *t* test or the one-way ANOVA test, while continuous variables with nonnormal distribution were tested using the Mann–Whitney or the Kruskal–Wallis tests. All data were analyzed using SPSS v.28.0, IBM, Chicago, Illinois, USA and TreeAge Pro 2023 Healthcare Version, TreeAge Software, LLC, Williamstown, Massachusetts, USA.

Ethical considerations

Each patient gave written informed consent before EGD. The Ethics Committee of ULSSJ approved the study (project number 375/2023).

Results

During the study period, 207 patients diagnosed with HNN were evaluated in our institution, with 62 (30%) being evaluated in the gastroenterology outpatient clinic (median referral time since HNN diagnosis = 37 days, IQR = 8–82) (Fig. 2). The most common reason for nonreferral was the HNN not being eligible for curative treatment. After referral, 16 patients (25.8%) refused to undergo screening EGD. Forty-six patients underwent screening EGD after a median time of 4 months (IQR = 1–9) since HNN diagnosis [≤ 6 months ($n = 31$, 67.4%); 6–12 months ($n = 15$, 32.6%)].

Screened patients' baseline characteristics

Most patients were male ($n = 38$, 82.6%) and had a history of tobacco use ($n = 39$, 84.8%) and alcohol consumption ($n = 25$, 54.3%), or both. The median age was 61 years (IQR = 60–67). We did not observe significant differences between patients with or without a diagnosis of GEN regarding demographic data, family history of GEN, or functional status (Table 1).

Head and neck neoplasms characteristics

The most frequent HNN location was the larynx ($n = 19$, 41.3%), with the majority being SCC ($n = 42$, 91.3%). All patients underwent treatment, with the most common strategies being chemoradiotherapy ($n = 15$, 32.6%) and surgery plus chemoradiotherapy ($n = 14$, 30.4%).

At endoscopic screening, 31 patients (67.4%) were already in HNN remission, while the remaining ($n = 15$, 32.6%) were being treated with curative intent. Most patients underwent one screening EGD ($n = 38$, 82.6%), with the remainder undergoing two ($n = 7$; 15.2%) or three ($n = 1$; 2.2%) screening EGDs.

Gastroesophageal neoplasia detected with endoscopic screening

An EN or GN was detected in 10/46 patients (21.7%, 95% confidence interval (CI): 9.8–33.6%). All of these patients had a current or previous history of drinking,

smoking or both. Histopathological characterization of these cases is reported in Table 2. Supplementary Table 4, Supplemental digital content 1, <http://links.lww.com/EJGH/B159> describes a detailed individual analysis of each patient with GEN.

Esophageal neoplasia

A total of six EN were detected in 5/46 patients (10.9%, 95% CI: 1.9–19.9%). The median lesion size was 12 mm (IQR: 10–30). All cases were identified in the index EGD, ≤ 6 months after HNN diagnosis. Histopathological characterization revealed three cases of SCC, one of squamous HGD, and two of squamous LGD.

One patient with an SCC not amenable to endoscopic resection (T2N0M0) was referred for chemoradiotherapy. In one patient with an LGD lesion, surveillance was decided due to the metastatic progression of HNN. In the remaining three patients, ESD of the lesions ($n = 4$) was performed, being noncurative in two: one received subsequent treatment with adjuvant radiotherapy and the other underwent esophagectomy (with evidence of residual lesion with HGD in the surgical specimen).

No adverse events (AEs) were reported after endoscopic/surgical resection. No patient had evidence of recurrence/progression of the EN during the follow-up. One patient died (20.0%) in the follow-up due to an unrelated cause (pneumonia).

Histopathological analysis – p16 and Epstein–Barr virus encoding region evaluation

One patient had diffuse p16 expression in the esophageal SCC but not in the matched HNN (Supplementary Figure 2, Supplemental digital content 1, <http://links.lww.com/EJGH/B159>). One patient showed simultaneous focal p16 expression in both the EN and HNN. No p16 expression was observed in the remaining EN ($n = 3$), with the correspondent HNN being also p16 negative. No esophageal neoplasms were positive for EBER-ISH.

Gastric neoplasia

A total of five GN were detected in 5/46 patients (10.9%, 95% CI: 1.9–19.9%). Four lesions were identified in the index EGD (≤ 6 months after HNN diagnosis) while one lesion was detected in the second follow-up EGD (14 months after HNN diagnosis). Histopathological characterization revealed four cases of adenocarcinoma and one of LGD.

All five GN underwent ESD, with four being curative. One patient with a noncurative ESD underwent total gastrectomy, without evidence of residual disease in the surgical specimen. No significant differences between groups were observed regarding the staging of gastritis when comparing patients with or without GN (Supplementary Table 5, Supplemental digital content 1, <http://links.lww.com/EJGH/B159>).

No AEs were reported after endoscopic/surgical resection. No recurrence or progression of the GN was observed and no patient died in the follow-up.

Table 1. Demographic data and baseline head and neck neoplasms characteristics and staging of screened patients

	Total (N = 46)	GEN (n = 10)	No GEN (n = 36)	P
Demographic data				
Sex, n (%)				0.055
Female	8 (17.4)	4 (40)	4 (11.1)	
Male	38 (82.6)	6 (60)	32 (88.9)	
Age, median (IQR), minimum–maximum, years	61 (60–67), 43–80	63 (63–64), 55–73	56 (54–74), 43–80	0.423
Family history of GEN, n (%)				
Esophageal neoplasia	1 (2.2)	0 (0)	1 (2.8)	0.594
Gastric neoplasia	2 (4.3)	0 (0)	2 (5.6)	0.446
Personal history of cancer, n (%)*	6 (13)	2 (20)	4 (11.1)	0.598
CRC	2 (4.3)	2 (20)	0 (0)	
Lung cancer	1 (2.2)	0 (0)	1 (2.8)	
Bladder cancer	1 (2.2)	1 (10)	1 (2.8)	
Non-Hodgkin lymphoma	1 (2.2)	1 (10)	1 (2.8)	
Prostate cancer	1 (2.2)	1 (10)	0 (0)	
Basal cell carcinoma	1 (2.2)	0 (0)	1 (2.8)	
Tobacco use, n (%)				0.398
Current	20 (43.5)	3 (30)	17 (47.2)	
Former	19 (41.3)	6 (60)	13 (36.1)	
No	7 (15.2)	1 (10)	6 (16.7)	
Tobacco pack years, median (IQR)	40 (29–50)	30 (20–40)	40 (30–50)	0.373
Alcohol consumption, n (%)				0.758
Current	14 (30.4)	4 (40)	10 (27.8)	
Former	11 (23.9)	2 (20)	9 (25.0)	
No	21 (45.7)	4 (40)	17 (47.2)	
Alcohol grams per day, median (IQR)	50 (26–83)	26 (19–53)	50 (40–90)	0.199
Gastroesophageal reflux disease, n (%)	3 (6.5)	1 (10)	2 (5.6)	0.530
ECOG status				0.515
0	30 (65.2)	8 (80)	22 (61.1)	
1	15 (32.6)	2 (20)	13 (36.1)	
2	1 (2.2)	0 (0)	1 (2.8)	
HNN characteristics and staging				
Location of HNN, n (%)				0.853
Nasopharynx	1 (2.2)	0 (0)	1 (2.8)	
Hypopharynx	7 (15.2)	2 (20)	5 (13.9)	
Oral cavity	15 (32.6)	2 (20)	13 (36.1)	
Larynx	19 (41.3)	5 (50)	14 (38.9)	
Paranasal sinus	4 (8.7)	1 (10)	3 (8.3)	
Histology, n (%)				0.134
Squamous cell carcinoma	42 (91.3)	8 (80)	34 (94.4)	
Adenocarcinoma	3 (6.5)	1 (10)	2 (5.6)	
High-grade squamous dysplasia	1 (2.2)	1 (10)	0 (0)	
Stage†				0.190
I	8 (17.4)	3 (30)	5 (13.9)	
II	8 (17.4)	2 (20)	6 (16.7)	
III	11 (23.9)	1 (10)	10 (27.8)	
IVa	18 (39.1)	3 (30)	15 (41.7)	
NA	1 (2.2)	1 (10)	0 (0)	
T				0.326
T1	10 (21.7)	3 (30)	7 (19.4)	
T2	9 (19.6)	2 (20)	7 (19.4)	
T3	12 (26.1)	2 (20)	10 (27.8)	
T4	14 (30.4)	2 (20)	12 (22.2)	
NA	1 (2.2)	1 (10)	0 (0)	
N				0.044
N0	20 (43.5)	7 (70)	13 (36.1)	
N1	7 (15.2)	1 (10)	6 (16.7)	
N2	14 (30.4)	0 (0)	14 (38.9)	
N3	4 (8.7)	1 (10)	3 (8.3)	
NA	1 (2.2)	1 (10)	0 (0)	
M				0.217
M0	45 (97.8)	9 (90)	36 (100)	
M1	0 (0)	0 (0)	0 (0)	
NA	1 (2.2)	1 (10)	0 (0)	
HNN treatment, n (%)				0.480
CRT	15 (32.6)	2 (20)	13 (36.1)	
Surgery	7 (15.2)	3 (30)	4 (11.1)	
Surgery + RT	10 (21.7)	2 (20)	8 (22.2)	
Surgery + CRT	14 (30.4)	3 (30)	11 (30.6)	

Bold value indicates $P < 0.005$.

CRC, colorectal cancer; CRT, chemoradiotherapy; GEN, gastroesophageal neoplasia; HNN, head and neck neoplasms; IQR, interquartile range; NA, nonapplicable; RT, radiotherapy.

*More than one cancer in two patients. All neoplasms were under remission at the beginning of follow-up.

†Eighth edition of the American Joint Committee on Cancer/International Union Against Cancer TNM staging system.

Table 2. Characterization of esophageal and gastric neoplasia

Esophageal neoplasia (n = 5)	
Histological grading, n (%)	
Low-grade squamous dysplasia	2 (40)
Squamous cell carcinoma*	3 (60)
Lesion size, median (IQR), mm	12 (10–30)
Morphology, n(%)	
Polypoid	0 (0)
Nonpolypoid, nondepressed	3 (60)
Depressed	2 (40)
p16 expression	
Negative	3 (60)
Focal/heterogeneous	1 (20)
Positive†	1 (20)
EBER-ISH	
Negative	5 (100)
Positive	0 (0)
Esophageal SCC (n = 3)	
Histological subtype – WHO classification, n (%)	
Esophageal squamous cell carcinoma, NOS	3 (100)
T staging, n (%)	
T1b	2 (66.7)
SM1	1 (50)
>SM1	1 (50)
T2	1 (33.3)
Lymphovascular permeation, n (%)	0 (0)
Differentiation, n (%)	
Poor	1 (33.3)
Well/moderate	2 (66.7)
Gastric neoplasia (n = 5)	
Histological grading, n (%)	
Low-grade dysplasia	1 (20)
Adenocarcinoma	4 (80)
Lesion size, median (IQR), mm	13 (15–24)
Location, n (%)	
Antrum	1 (20)
Body	1 (20)
Cardia	3 (60)
Morphology, n (%)	
Polypoid	1 (20)
Nonpolypoid, nondepressed	2 (40)
Depressed	2 (40)
p16 expression	
Negative	3 (75)
Focal/heterogeneous	1 (25)
Positive*	0 (0)
NA	1 (20)
EBER-ISH	
Negative	3 (75)
Positive	1 (25)
NA	1 (20)
Gastric adenocarcinoma (n = 4)	
Histological subtype – Laurén classification	
Intestinal	3 (75)
Undetermined	1 (25)
Histological subtype – WHO classification, n (%)	
Gastric adenocarcinoma	
Tubular	3 (75)
Gastric carcinoma with lymphoid stroma	1 (25)
T staging, n (%)	
Tis	1 (25)
T1b	3 (75)
SM1	2 (66.7)
>SM1	1 (33.3)
Lymphovascular permeation, n (%)	1 (25)
Differentiation, n (%)	
Poor	0 (0)
Well/moderate	4 (100)

EBER-ISH, Epstein–Barr virus encoding region *in situ* hybridization; IQR, inter-quartile range; NA, nonapplicable; NOS, not otherwise specified; SCC, squamous cell carcinoma.

*One patient had a synchronous esophageal lesion with squamous high-grade dysplasia.

†Cases were considered positive when block-positive p16 staining was observed in dysplastic lesions and when moderate to strong nuclear and cytoplasmic p16 staining was observed in at least 70% of cells in invasive lesions.

Histopathological analysis – p16 and Epstein–Barr virus encoding region evaluation

Focal p16 expression was observed in one patient with gastric adenocarcinoma, whose matched HNN was negative for p16 expression. One case of gastric adenocarcinoma, showing the morphologic features of gastric carcinoma with lymphoid stroma, was associated with Epstein–Barr virus (EBV) infection, with the corresponding HNN being negative for EBER-ISH (Supplementary Figure 3, Supplemental digital content 1, <http://links.lww.com/EJGH/B159>).

Clinical outcomes of the screened patients

The median follow-up after EGD was 13 months (IQR = 5–20). Three patients (6.5%) were diagnosed with additional neoplasms during follow-up (pancreatic cancer = 1, lung cancer = 2).

Four patients (8.7%) refused to be enrolled in subsequent screening after the first EGD. Eleven patients (23.9%) died during follow-up, with no significant differences in the mortality rate between patients with or without GEN (10.0 vs. 27.8%, $P = 0.244$) – six (54.5%) due to progression of the HNN and five (45.5%) from causes unrelated to HNN or GEN.

Cost-utility analysis

Main analysis

Screening would be associated with an average increased cost of €1327.2 per patient and an average gain of 0.03 QALY (Table 3). This corresponds to an ICER of 39 357.81 €/QALY, rendering screening cost-effective at the WTP threshold of 50 000 €/QALY gained (as well as the WTP of three times the Portuguese GDP per capita). Supplementary Figure 4, Supplemental digital content 1, <http://links.lww.com/EJGH/B159> depicts the overall survival, cumulative QALYs, and cumulative costs associated with the screening and no screening strategies.

In the probabilistic sensitivity analysis using data from the current study, screening would be associated with an average increased cost of €1580.52 per patient, as well as with an average gain of 0.05 QALY (ICER = 35 044.79 €/QALY) (Table 3).

Screening would have a 63% probability of being cost-effective at a WTP threshold of 50 000 €/QALY gained (Fig. 3a). For the WTPs of one and three times the Portuguese GDP per capita, the probabilities would respectively be of 34 and 72% (Fig. 3b).

Sensitivity analysis with data from other Western series

Probabilistic sensitivity analysis using data from other Western series showed that the screening strategy remained cost-effective at a WTP of 50 000 €/QALY gained if the prevalence of EN lesions was the same as reported in Germany, France, and Brazil (but not in the Netherlands) (Table 3).

Discussion

This study aimed to evaluate the impact and cost-utility of an endoscopic screening program in patients with HNN in

Table 3. Deterministic one-way sensitivity analysis and probabilistic sensitivity analysis results of the screening strategy for esophageal neoplasia vs. no screening

Country of origin of the study	Frequency of esophageal neoplasia*, n (%)	Patients with dysplastic lesions/ stage I esophageal cancer, n (%)	Costs screening (Euro)	Costs no screening (Euro)	Differences in costs (screening vs. no screening) (Euro)	Effective-ness of screening (QALY)	Effective-ness of no screening (QALY)	Differences in effec-tiveness (QALY – screening vs. no screening)	ICER
Deterministic one-way sensitivity analysis									
Portugal (current study)	5/46 (10.9)	4/5 (80)	3205.08	1327.15	1877.92	1.68	1.64	0.0337	39 357.81
Probabilistic sensitivity analysis									
Portugal (current study)	5/46 (10.9)	4/5 (80)	4008.16	1580.52	2427.64	1.65	1.61	0.0451	35 044.79
Sensitivity analysis with data from other Western countries									
Netherlands [18]	13/202 (6.4)	12/13 (92.3)	2536.89	1354.28	1182.61	1.69	1.66	0.022	52 839.41
Brazil [20]	181/1888 (9.6)	148/181 (81.8)	3067.62	1748.30	1319.32	1.66	1.63	0.031	42 854.96
Germany [21]	12/148 (8.1)	7/15 (46.7)	3421.74	1975.10	1446.64	1.66	1.63	0.033	43 360.71
France [19]	39/392 (9.9)	22/39 (56.4)	3934.92	2356.83	1578.09	1.64	1.64	0.042	37 514.43

An additional sensitivity analysis was performed taking into consideration the data from the main Western studies on this topic. GDP, gross domestic product; ICER, incremental cost per QALY gained; QALY, quality-adjusted life years.
*Besides lesions with esophageal squamous cell carcinoma includes also lesions with low-grade/high-grade dysplasia and esophageal adenocarcinoma.

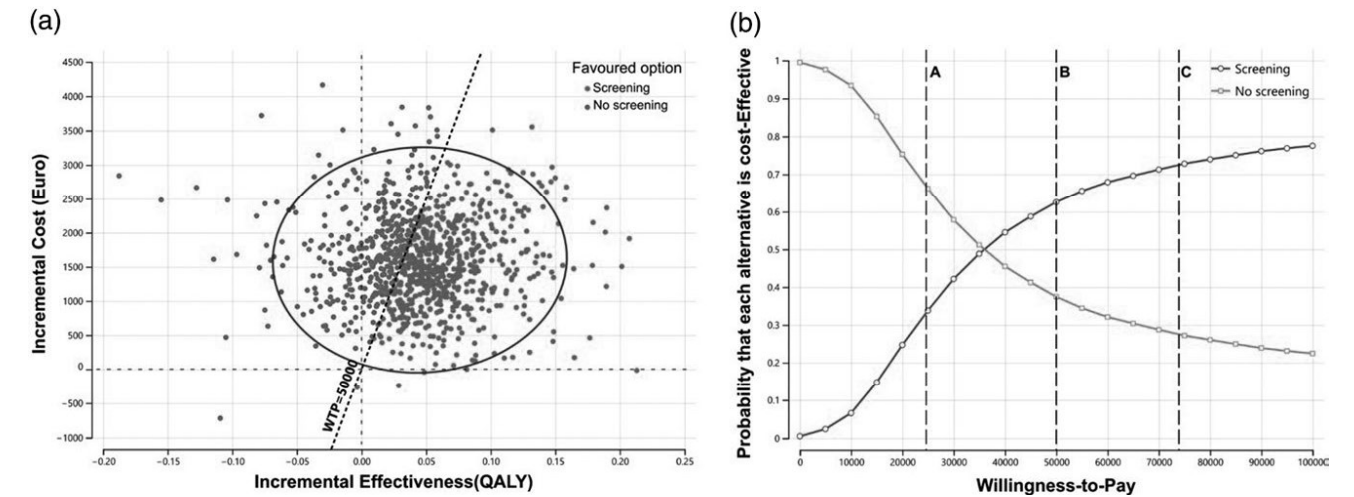


Fig. 3. (a) Scatter plot for probabilistic Monte Carlo sensitivity analysis of the endoscopic screening vs. no screening strategy. The scatter plot represents 10 000 simulated iterations in a Monte Carlo probabilistic sensitivity analysis where the x-axis represents incremental effectiveness in terms of quality-adjusted life years (QALY) and the y-axis represents incremental costs in Euros. The oval represents the confidence ellipse, in which 95% of the results of the simulations are present. Cost-effective simulations are in green and below the dotted line representing the willingness-to-pay threshold, set at €50 000/QALY gained. (b) Acceptability curve of the endoscopic screening vs. no screening strategy. The vertical lines represent the thresholds of acceptability [1–3 times the Portuguese gross domestic product (GDP) per capita]. The x-axis represents the willingness-to-pay in Euros per QALY and the y-axis represents the probability that screening is cost-effective.

a Western country with intermediate-to-high risk for GN. Our results showed an overall frequency of EN of 10.9%. The health economic analysis indicated that endoscopic screening for EN, performed within 12 months since diagnosis in stage I–III HNN patients, is cost-effective in Portugal. In addition, an unexpectedly high frequency of GN was evident.

Routine endoscopic screening in patients with HNN has yet to be implemented in most Western countries [2]. Our study showed a higher frequency of EN than previously reported in the other prospective Western studies (ranging between 1.8 and 10%) [13–20]. Nevertheless, many of these studies were performed before the advent of image-enhanced endoscopy, which is associated with a better diagnostic performance for detecting early EN, without a significant increase in cost per procedure [28]. In our study, all procedures were performed under

sedation, with a standardized inspection of the esophageal mucosa using both virtual and conventional chromoendoscopy, which can partly explain our higher detection rates. Moreover, while the role of endoscopic screening for the diagnosis of EN has been extensively studied, very few studies addressed the opportunistic diagnosis of GN in patients with HNN (with rates ranging between 0.5 and 1.8%) [13,19,29], but in our cohort, it was unexpectedly high (10.9%). Portugal is a country with an intermediate-to-high risk for GN, and endoscopic screening for this neoplasia in the general population was found to be cost-effective [30]. A recent study from our group recently compared the frequency of GN among healthy individuals who underwent EGD at the same time of screening colonoscopy with that of patients with compensated advanced chronic liver disease who underwent EGD for screening of gastroesophageal varices. The frequency

of GN was 1 and 4%, respectively [31]. In the present study, the synergic presence of additional risk factors for GN in patients with HNN, within a susceptible population may partially explain our findings. Interestingly, all patients with GN were negative for *Helicobacter pylori* infection. Unfortunately, systematic gastric biopsies were not performed in this cohort, and missing data prevented us from evaluating the relationship between GN frequency and gastritis stages.

To the best of our knowledge, no previous study has evaluated the cost-utility of an endoscopic screening program in HNN patients in the Western setting. Recently, a study from Taiwan reported EN screening among patients with oral cavity cancer (OCC) to be cost-effective [32]. In this study, four different strategies (annual, annual for 3 years, annual for 10 years, annual for life) were compared, with the latter being the most favorable from the payer's perspective, particularly in patients with early-stage OCC. Nevertheless, it should be acknowledged that these findings may not be applicable in the Western setting for several reasons: (1) this study focused only on OCC excluding other HNN in which the risk of EN may be significantly higher (e.g. piriform sinus); (2) differences in the incidence of EN; (3) significant divergence in costs (e.g. the cost of EGD in Taiwan is 47.42 € vs. 142.81 € in Portugal). In our analysis, an annual endoscopic screening program for the diagnosis of EN in patients with HNN was found to be cost-effective, for a WTP corresponding to between 2–3 times the Portuguese GDP per capita. Of note, while the gains in QALY associated with screening were relatively small, it is important to note that these patients (1) have a high risk of mortality in the follow-up due not only to the baseline HNN but also due to other risk factors such as second primary tumor (other than EN) and comorbidities and (2) tend to display a low quality of life. The probabilistic sensitivity analysis using data from other Western centers confirmed that the screening strategy remained cost-effective if the prevalence of detected lesions would be the same as the one detected in Brazil, Germany, and France. We, however, did not use specific cost data from these countries, so we cannot conclude whether screening would be cost-effective in those countries. The generalizability of the results to other Western countries should warrant further research. In the near future, screening may become even more cost-effective as a consequence of (1) the application of artificial intelligence tools [33] or (2) increased survival of HNN patients with novel targeted immunotherapies [34].

Many questions remain unsolved regarding patient selection, timing, and frequency of endoscopic screening in patients with HNN. A recent study conducted in the Netherlands evaluated screening for EN in HNN patients [13]. Compared with van Tilburg *et al.*, we had almost twice the prevalence of EN (10.9 vs. 6.0%), if we account for the LGD cases in their work. The authors evaluated different timings for EGD, but most lesions were detected at the index EGD with the highest yield observed in synchronous screening (7.1%). Most of the patients (80%) were amenable to endoscopic treatment. Regarding our results, all the EN were detected at the index EGD and 66.7% underwent ESD. In our sample, 8.7% of patients refused subsequent screening and 23.9% died during our short follow-up period of 13 months. Nonetheless, 15.2%

performed two more EGD and 2.2% performed three additional EGD with no additional lesion detection. This data suggests that at least one screening EGD should be recommended following an HNN diagnosis. Ideally, this index EGD should be performed within 6 months but may be acceptable up to 12 months. A clear definition of timing is crucial, as our findings, in line with those of van Tilburg, indicate that a significant proportion of patients in remission from HNN have a window of opportunity during which they are willing to undergo further procedures, like screening EGD. Delaying initial screening for 1–2 years should be discouraged because a lesion could progress to a stage where it is not amenable to endoscopic resection anymore [15]. Regarding long-term follow-up, previous studies reported metachronous EN rates ranging between 1.5 and 5.1%, which may continue to rise even after 10 years [18,35]. The decision to recommend follow-up EGD should be based on further studies that assess the yield of subsequent metachronous screening and the outcomes associated with therapeutic options that ensue. Therefore, taking all these factors into account, together with the findings of our study, follow-up EGD should be considered on a year-to-year basis, considering the natural history and location of HNN (particularly in those with a piriform sinus involvement, which is a known risk factor for EN [36]) and patients' functional status and preferences.

In this study, we aimed to explore the role of viral infection as a driving factor of the co-occurrence of HNN and GEN, with the potential aim of more precisely selecting patients for screening. The viral-related pathogenesis associates high-risk HPV infection to oropharyngeal SCC and EBV infection to gastric carcinoma, particularly to the histological subtype of gastric carcinoma with lymphoid stroma [37,38]. Nevertheless, a previous study has suggested that patients with HPV-positive HNN have a lower risk of second primary tumors [4]. In our study, no significant matching between EBV or HPV infection in HNN and GEN was found, supporting that viral infection plays a limited role in the field cancerization phenomenon. Therefore, we are not able to suggest targeted recruitment of patients for EGD based on EBV/HPV status of the HNN tumor.

Our study has some limitations. A selection bias cannot be excluded since the screening program was implemented in a single tertiary reference center, which may limit the generalization of these results. Furthermore, the series included a small number of patients with HNN. While this is a consequence of the strict inclusion and exclusion criteria (which may have contributed, at least partially to an overestimation of the frequency of GEN), this also shows the difficulties of implementing a screening program in a difficult-to-manage population with significant comorbidities and frequent social issues. Finally, the short follow-up and the possible lead time bias limit our ability to assess the long-term impact on the patients' prognosis. Regarding the cost-utility analysis, while we tried to evaluate all possible clinically relevant scenarios, the simultaneous presence of two neoplasias with distinct behaviors implied some model simplifications and assumptions. Nonetheless, it is important to highlight that a conservative approach was used in the estimations performed. In addition, the model did not consider EN recurrences in the follow-up. Considering that

the risk of recurrence is higher in more advanced stages and is associated with additional costs and loss of productivity, this may have led to an underestimation of the cost-effectiveness of the model.

In conclusion, our study showed that the implementation of endoscopic screening led to the identification of EN or GN in one-fifth of HNN patients, mostly discovered at an early stage, allowing a curative-intent treatment. Annual endoscopic screening for EN may be considered cost-effective in the Portuguese setting. Future studies should focus on the optimization of patient selection, evaluation of the long-term clinical impact of screening, and assessment of its cost-effectiveness in other Western countries and of alternative strategies, such as one-time screening.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

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Supplementary material and methods

Supplementary tables

Supplementary Table 1

Description of the performed histopathological analysis

Tumor morphology

- Tumor morphology of HNN and GEN, including histological classification and degree of differentiation were classified according to the World Health Organization classification and, in the case of gastric neoplasia, Laurén classification [1,2].

Immunohistochemistry and EBV In Situ Hybridization

- In patients harboring both HNN and GEN, serial 3-µm sections were prepared from a representative formalin-fixed paraffin-embedded block from each tumor location.
- Immunohistochemistry staining was performed with antibody directed against p16 (clone CINtec® p16 Histology, prediluted; Roche-Mannheim, Germany). Samples were processed in the automatic Ventana Benchmark Ultra platform using the OptiView Amplification DAB detection kit.
- The presence of EBV infection was investigated by EBV-encoded small RNAs (EBER) *in situ* hybridization (EBER-ISH; INFORM EBER probe, Ventana Medical Systems) using the same equipment, with enzymatic digestion (ISH protease) and the iViewBlue detection kit.

Evaluation of p16 expression

- We evaluated p16 expression as a surrogate biomarker of HPV infection. For dysplastic lesions, p16 staining was evaluated using the same criteria proposed for lower anogenital HPV-associated lesions, according to the CAP [3].
- For invasive neoplasias, p16 was considered positive when at least 70% of neoplastic cells showed moderate to strong nuclear and cytoplasmic staining, according to the CAP algorithm for HNN [4].

CAP, Consensus Recommendations from the College of American Pathologists; EBV, Epstein-Barr virus; GEN, gastro-esophageal neoplasia; HNN, head and neck neoplasia; HPV, human papillomavirus

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Supplementary Table 2

Model parameters and inputs for the cost-effectiveness analysis study

Variable	Distribution	Mean (SD)	Likeliest value (min-max)	Data used for parameter definition – number of events (number of participants)	Source
Proportion of patients with no lesion at baseline	beta	0.89 (0.05)	NA	41 (46)	Present study
Proportion of patients in stage I at baseline	beta	0.09 (0.05)	NA	4 (46)	Present study
Proportion of patients in stage II/III at baseline	beta	0.02 (0.03)	NA	1 (46)	Present study
Probability of maintaining no lesion status (annual)	beta	0.76 (0.07)	NA	31 (41)	Present study
Probability of developing a stage I lesion in a patient with no lesion (annual)	triangular	NA	0.02 (0.00 – 0.05)	NA	Present study
Probability of having an ESD in a patient with a stage I lesion	beta	0.75 (0.17)	NA	3 (4)	Present study
Probability that the ESD is done with curative intent in a patient with stage I lesion undergoing ESD	beta	0.33 (0.20)	NA	1 (3)	Present study
Probability of having a non-curative ESD followed by surgery in a patient with a stage I lesion	beta	0.50 (0.22)	NA	1 (2)	Present study
Probability of surgery complications (Clavien-Dindo grade 3 to 4)	NA	NA	0.40	NA	[5]
Probability of surgery-related deaths	beta	0.02 (0.004)	NA	20 (1160)	[[6]
Probability of having a non-curative ESD followed by CRT in a patient with a stage I lesion	beta	0.50 (0.22)	NA	1 (2)	Present study
Probability of CRT complications in the setting of non-curative ESD, CTC grade 3 to 4)	NA	NA	0.31	NA	[7]
Yearly probability of death in a patient with an esophageal neoplasm	beta	0.24 (0.07)	NA	10 (41)	Present study
Probability of undergoing neoadjuvant CRT followed by surgery in a patient with stage II/III lesion	beta	0.36 (0.004)	NA	4877 (13480)	[8]
Probability of complications from neoadjuvant CRT (CTC grade 3 to 4)	beta	NA	0.22	NA	[9]
Additional probability of death from neoadjuvant CRT followed by surgery	beta	0.18 (0.02)	NA	66 (366)	[9]
Probability of complications from definitive CRT (CTC grade 3 to 4)	beta	NA	0.42	NA	[9,10]
Additional probability of death from definitive CRT	beta	0.02 (0.02)	NA	2 (95)	[10]
Probability of detection of a lesion at stage I in the no screening context †	beta	0.08 (0.03)	NA	6 (78)	[11]
Probability of detection of a lesion at stage II/III in the no screening context	beta	0.51 (0.06)	NA	41 (78)	[11]
Probability of undergoing palliative chemotherapy in a patient with a stage IV lesion	beta	0.22 (0.004)	NA	2207 (9948)	[12]
Probability of complications from palliative chemotherapy (CTC grade 3 to 4)	NA	NA	0.47	NA	[13]
Probability of death in a patient undergoing palliative chemotherapy (annual)	beta	0.66 (0.01)	NA	1457 (2207)	[10]
Probability of death in a patient undergoing best supportive care (annual)	triangular	NA	0.95 (0.90 – 1.00)	NA	Expert opinion
Cost (in Euro) ‡	Distribution	Mean (SD)	Likeliest value (min-max)		Source
Working day	gamma	34.98 (0.89)	NA	NA	[14]
Travelling to and from the hospital, unit (fuel and other expenses)	gamma	9.99 (0.26)	NA	NA	Expert opinion
Daily stay at the internal medicine ward	gamma	454.19 (11.59)	NA	NA	Hospital data
Daily stay at the general surgery ward	gamma	583.16 (14.89)	NA	NA	Hospital data
Daily stay at the palliative care ward	gamma	325.80 (8.32)	NA	NA	Hospital data
EGD (including biopsy)	gamma	142.81 (3.64)	NA	NA	Hospital data
Cost of travel associated with EGD	gamma	9.99 (0.26)	NA	NA	Expert opinion
Staging after neoplastic lesion detection (includes thoraco-abdomino-pelvic CT scan and endoscopic ultrasound)	gamma	322.60 (8.24)	NA	NA	Hospital data
Cost of travel associated with staging, with CT scan and endoscopic ultrasound performed on the same day	gamma	9.99 (0.26)	NA	NA	Expert opinion
Endoscopic submucosal dissection (ESD)	gamma	1636.06 (41.76)	NA	NA	Hospital data
Bleeding following ESD	gamma	36.58 (0.93)	NA	NA	[15], Hospital data
Perforation following ESD	gamma	203.87 (5.20)	NA	NA	[15], Hospital data
Cost of travel associated with ESD performance and possible AEs	gamma	9.99 (0.26)	NA	NA	Expert opinion
Surgery	gamma	14813.60 (378.16)	NA	NA	Hospital data
Surgery AEs	gamma	8745.90 (223.26)	NA	NA	[5], Hospital data
Cost of travel associated with surgery and possible AEs	gamma	9.99 (0.26)	NA	NA	Expert opinion
Chemo-radiation following non-curative ESD	gamma	10841.56 (276.76)	NA	NA	Hospital data
AEs from chemo-radiation following non-curative ESD	gamma	985.59 (25.16)	NA	NA	[7], Hospital data
Cost of travel associated with chemo-radiation after non-curative ESD plus possible AEs	gamma	289.82 (7.40)	NA	NA	[7], Expert opinion
Neoadjuvant chemo-radiation	gamma	20539.99 (524.34)	NA	NA	Hospital data
Complications from neoadjuvant chemo-radiation	gamma	699.47 (17.86)	NA	NA	[9], Hospital data
Cost of travel associated with neoadjuvant chemo-radiation and eventual AEs	gamma	229.86 (5.87)	NA	NA	[9], Expert opinion
Definitive chemo-radiation	gamma	8632.62 (220.37)	NA	NA	Hospital data
AEs from definitive chemo-radiation	gamma	1335.31 (34.09)	NA	NA	[9,10], Hospital data
Cost of travel associated with definitive chemo-radiation and eventual AEs	gamma	249.84 (6.38)	NA	NA	[10,16], Expert opinion
Palliative chemotherapy	gamma	25055.06 (639.60)	NA	NA	[13], Hospital data
AEs from palliative chemotherapy	gamma	1494.29 (38.14)	NA	NA	[13], Hospital data
Cost of travel associated with palliative chemotherapy and eventual AEs	gamma	139.91 (3.57)	NA	NA	[13], Hospital data, Expert opinion
Best supportive care	gamma	2280.59 (58.22)	NA	NA	Hospital data, Expert opinion
Cost of travel to the palliative care unit	gamma	5.00 (0.14)	NA	NA	Expert opinion
Utility data	Distribution	Mean (SD)			
Base utility for a patient who survived a HNN	beta	0.70 (0.20)			[17]
Stage I, ESD, additional disutility	beta	0.09 (0.15)			[18,19], Expert opinion
Stage I, surgery, additional disutility	beta	0.13 (0.15)			[20]
Stage II/III, neoadjuvant chemotherapy followed by surgery or definitive CRT, additional disutility	beta	0.19 (0.17)			[20]
Stage IV, palliative chemotherapy, additional disutility	beta	0.26 (0.19)			[20]
Stage IV, best supportive care, additional disutility	beta	0.27 (0.19)			[21]

AE, adverse event; CRT, chemoradiotherapy; CTC, Common Toxicity Criteria; CT, computed tomography; EGD, esophagogastroduodenoscopy; ESD, endoscopic submucosal dissection; HNN, head and neck neoplasia; NA, non-applicable; SD, standard deviation

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Notes:

We considered costs with diagnostic procedures (EGD, staging complementary diagnostic tests, consultations, and AE management), therapeutic interventions (ESD, surgery, CRT, palliative chemotherapy and AE management), transportation, and productivity losses due to work absenteeism. Transport expenses were based on a mean estimate of the distance between home and hospital for the patients from our center. Costs with productivity losses were calculated based on the human capital method, considering average wages per hour. Costs with presenteeism were not evaluated in the model.

Other: [†] - Detection of lesions in these patients occurred after EGD for other reasons, such as dysphagia, heartburn, dyspepsia or iron-deficiency anaemia; [‡] - The costs related with complications from procedures or treatments reflects the probability of these AEs occurring, i.e., the cost presented was cost of complication multiplied by the probability of the event. For all costs, a 10% deviation was assumed (5% below and 5% above the base case value) if no other information was available.

Supplementary Table 3

Modelling assumptions in the main analysis

Assumptions

- Patients without a diagnosis of EN were assigned a baseline utility of 0.70, considering previously published utility values in HNN survivors (Supplementary table 2). Given that no previous study had calculated the utilities associated with having an EN in HNN survivors, we assumed that these utilities were computed by subtracting (i) the disutility associated with each EN stage to (ii) the baseline utility of 0.70 considered for HNN survivors.
- We considered that the dropout rate of the screening arm was 0%.
- In the screening arm, we did not consider the possibility of identifying patients with a stage IV lesion.
- The model did not consider EN progression during treatment or EN recurrences in the follow-up after curative treatment.
- We did not consider the occurrence of additional SPTs (besides GEN).
- We assumed that patients under CRT completed all pre-determined treatment cycles.
- The probability of AEs following a diagnostic EGD was assumed as 0%.
- An estimation based on clinical experience was made in relation to the number of workdays lost with procedure-related AEs.

AEs, adverse events; CRT, chemoradiotherapy; EGD, esophagogastroduodenoscopy; EN, esophageal neoplasia; GEN, gastro-esophageal neoplasia; HNN, head and neck neoplasia; SPT, second primary tumor

Supplementary Table 4

Characteristics of patients with head and neck neoplasms and gastro-esophageal neoplasia, detected during screening.

ID	Sex/ Age (years)	Alcohol/ Smoking	HNN (location)	HNN (staging)	HNN Histology/ p16/ EBER	Time to EGD (months)	Location/ Paris Classification/ Size (mm)	Staging	Treatment/ Histology/ p16/ EBER	Outcomes in follow-up
1	Male/ 70	N/Ex	Larynx	T2N0M0	SCC/ negative/ negative	6	Stomach (Cardia)/ IIa+IIc/ 20	T1N0M0	ESD/ AC pT1b SM3 LP+ R1/ negative/ positive	HNN-Remission; GEN-Total Gastrectomy (no lesion in the surgical specimen)
2	Female/ 63	Y/N	Oral cavity	T1N0M0	SCC/ negative/ negative	5	Stomach (Antrum)/ IIa/ 10	NA	ESD/ LGD R0	HNN-Remission; GEN-Endoscopic Surveillance
3	Male/ 73	N/Ex	Hypopharynx	T2N0M0	SCC/ negative/ negative	1	Stomach (Cardia)/ Is/ 28	T1N0M0	ESD/ AC pT1b SM1 LP- R0/ negative/ negative	HNN- Remission; GEN- Endoscopic Surveillance
4	Male/ 71	N/Ex	Paranasal sinus	T4aN0M0	AC/ focal/ negative	0	Stomach (Cardia)/ Is/ 28	T1N0M0	ESD/ AC pT1b SM1, LP-, R0/ negative/ negative	Remission for both HNN and GEN
5	Male/ 64	N/Ex	Larynx	T4aN1M0	SCC/ negative/ negative	14	Stomach (Body)/ IIa+IIc/ 15	NA	ESD/ AC pTis/ focal/ negative	Remission for both HNN and GEN
6	Male/ 62	Y/Y	Larynx	T1N0M0	SCC/ negative/ negative	6	Esophagus/ IIa+IIb+IIc/ 30	T2N0M0	CRT/ SCC/ positive/ negative	Remission for both HNN and GEN
7	Male/ 72	Ex/Y	Larynx	T3N0M0	SCC/ negative/ negative	6	Esophagus/ IIb/ 12	NA	ESD/ LGD R0/ negative/ negative	Remission for both HNN and GEN
8	Female/ 62	Y/Ex	Larynx	NA	HGD/ focal/ negative	2	Esophagus/ IIb/ 30	T1N0M0	ESD/ pT1b SM1 LP- R1 focal/ negative	HNN- Remission; GEN- Esophagectomy (HGD in the surgical specimen)
9	Female/ 65	Y/Y	Oral cavity	T1N0M0	SCC/ negative/ negative	0	Esophagus/ IIb/ 12	NA	Surveillance due to advanced staging of HNN/ LGD/ negative/ negative	HNN- Metastatic progression
10	Female/ 55	Ex/Ex	Hypopharynx	T3N3bM0	SCC/ negative/ negative	0	Esophagus/ IIa+IIc/ 20	NA	ESD/ HGD, R0 negative/ negative	HNN-Metastatic progression; Died due to pneumonia; GEN- Additional radiotherapy due to non-curative ESD
							Esophagus/ IIa+IIc/ 8	NA	ESD/ SCC pT1b SM2 LP- R0 negative/ negative	

AC, Adenocarcinoma; CRT, Chemoradiotherapy; CT, Chemotherapy; EGD, Esophagogastroduodenoscopy; ESD, Endoscopic submucosal dissection; Ex, Ex- smoker/alcohol consumer; GEN, gastro-esophageal neoplasia; HGD; Head and Neck neoplasia; High-grade dysplasia; HNN, LGD, Low-grade dysplasia; LP, Lymphatic permeation; R, Resection; EBER, Epstein-Barr Virus encoding region; NA, Non-applicable; N, No; SCC, Squamous Cell Carcinoma; SM, Submucosa; Tis, carcinoma in situ; Y, Yes

Supplementary Table 5

Frequency of *H. pylori* infection and gastritis staging among patients with or without GEN

	Total (n=46)	GN (n=5)	No GN (n=41)	p value
Hp infection, n(%)				0.218
Yes	3 (17.6)	0 (0)	3 (25)	
No	14 (82.4)	5 (100)	9 (75)	
No data	29 (63)	0 (0)	29 (40.7)	
Gastric atrophy, n(%)				
Antrum				0.346
No	8 (57.1)	2 (66.7)	6 (54.5)	
Mild	0 (0)	0 (0)	0 (0)	
Moderate	4 (28.6)	0 (0)	4 (36.4)	
Severe	2 (14.3)	1 (33.3)	1 (9.1)	
No data	32 (69.6)	2 (40)	30 (73.2)	
Body				0.513
No	8 (66.6)	2 (66.7)	6 (66.7)	
Mild	0 (0)	0 (0)	0 (0)	
Moderate	2 (16.7)	0 (0)	2 (22.2)	
Severe	2 (16.7)	1 (33.3)	1 (11.1)	
No data	34 (73.9)	2 (40)	32 (78)	
Intestinal metaplasia, n(%)				
Antrum				0.306
No	7 (43.8)	2 (40)	5 (45.5)	
Mild	0 (0)	0 (0)	0 (0)	
Moderate	6 (37.5)	1 (20)	5 (45.5)	
Severe	3 (18.8)	2 (40)	1 (9.1)	
No data	30 (65.2)	0 (0)	30 (73.2)	
Body				0.276
No	7 (58.3)	2 (50)	5 (62.5)	
Mild	0 (0)	0 (0)	0 (0)	
Moderate	2 (16.7)	0 (0)	2 (25)	
Severe	3 (25.0)	2 (50)	1 (12.5)	
No data	34 (73.9)	1 (20)	33 (80.5)	

GN, gastric neoplasia; Hp, *Helicobacter pylori*

Supplementary figure legends

Supplementary Figure 1 – Decision tree diagram of the Markov model for comparison of endoscopic screening strategy *versus* no screening. The tree diagram represents all possible options for HNN patients if submitted to endoscopic screening versus no screening. In the model, every branch corresponds to an individual state of disease (circle), and Markov cycles start at the beginning of each branch for any of the defined strategies (circles with an M). On the far right are the terminal stages (triangles) for the Markov cycles and patients at these stages return to the beginning of the next cycle after a 1-year cycle, except for the Death state.

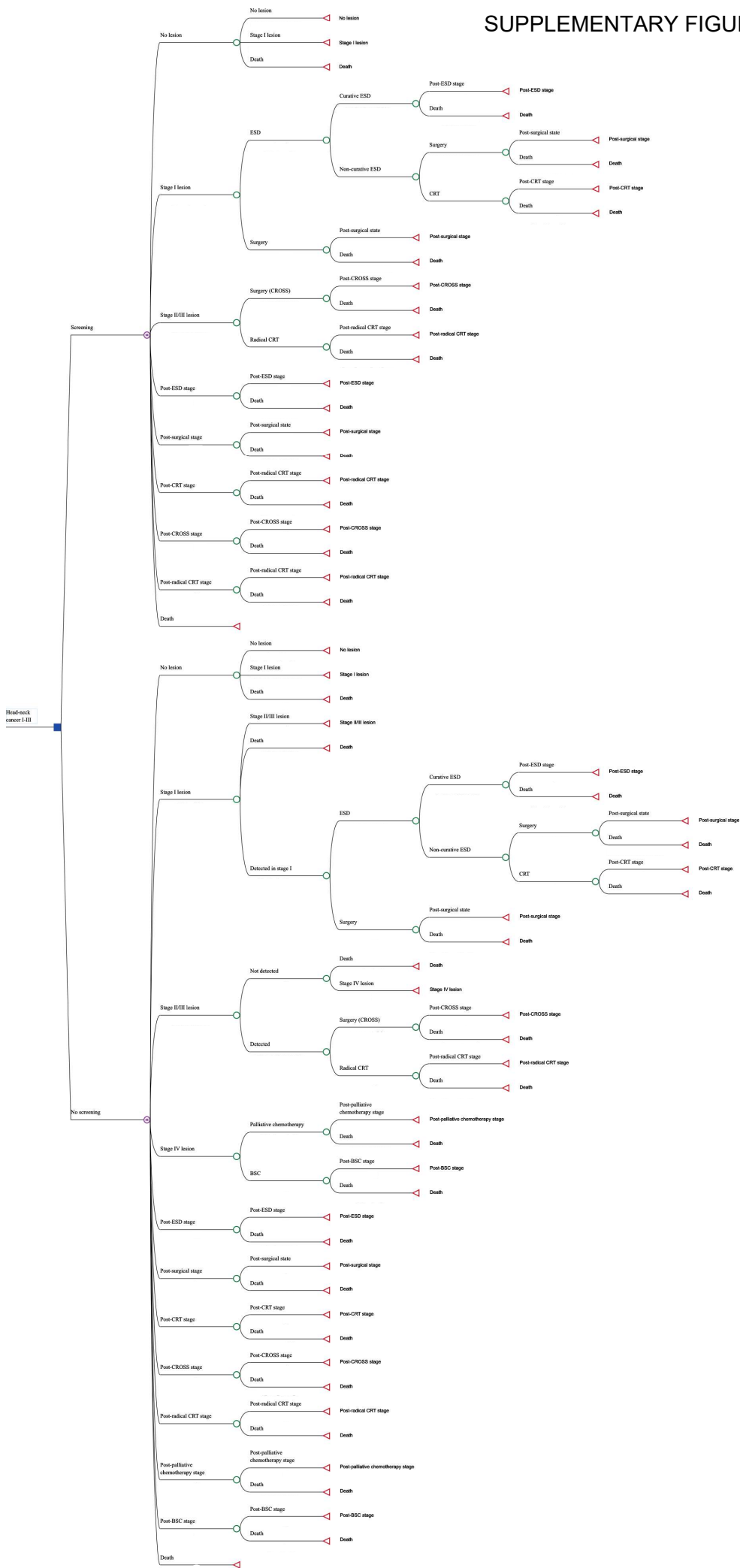
ESD, endoscopic submucosal dissection; CRT, chemoradiotherapy; CROSS, Chemoradiotherapy for Esophageal Cancer Followed by Surgery Study; BSC, best supportive care

Supplementary Figure 2 – A) Laryngeal squamous cell carcinoma (Haematoxylin and eosin, 40x original magnification) showing (B) no p16 expression (p16 immunohistochemistry, 100x original magnification). (C,D) Screening EGD revealed a 30mm lesion in the middle esophagus (Paris IIa+IIb+IIc). Endoscopic biopsies showed (E) squamous cell carcinoma (Haematoxylin and eosin, 100x original magnification). (F) By immunohistochemistry, the tumor showed diffuse, strong nuclear and cytoplasmic p16 expression (p16 immunohistochemistry, 100x original magnification). Patient underwent CRT, being in remission at the end of follow-up.

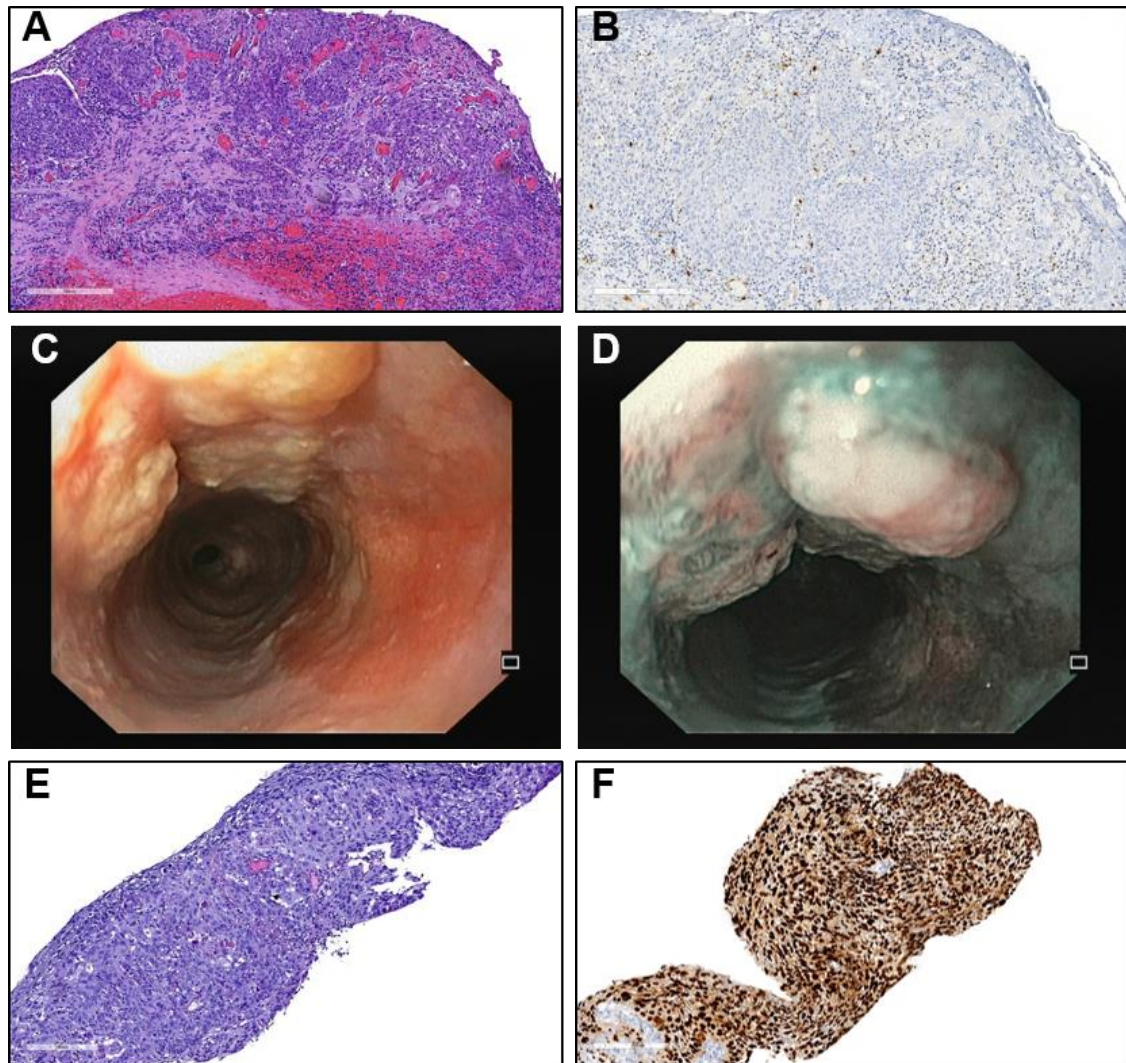
Supplementary Figure 3 - (A) Laryngeal squamous cell carcinoma with keratinization (Haematoxylin and eosin, 200x original magnification). (B) Screening EGD revealed a 20mm lesion in the cardia (Paris IIa+IIc) removed by ESD. (C) On histological examination, the tumor showed the morphologic characteristics of gastric carcinoma with lymphoid stroma (Haematoxylin and eosin, 100x original magnification) and (D) was associated to Epstein-Barr virus infection (EBER *In Situ* Hybridization, 40x original magnification). Due to evidence of lymphatic permeation, patient underwent total gastrectomy without evidence of residual lesion or lymph node metastasis.

Supplementary Figure 4 – Overall survival (A), cumulative QALYs (B) and cumulative costs (C) associated with the screening *versus* no screening strategy.

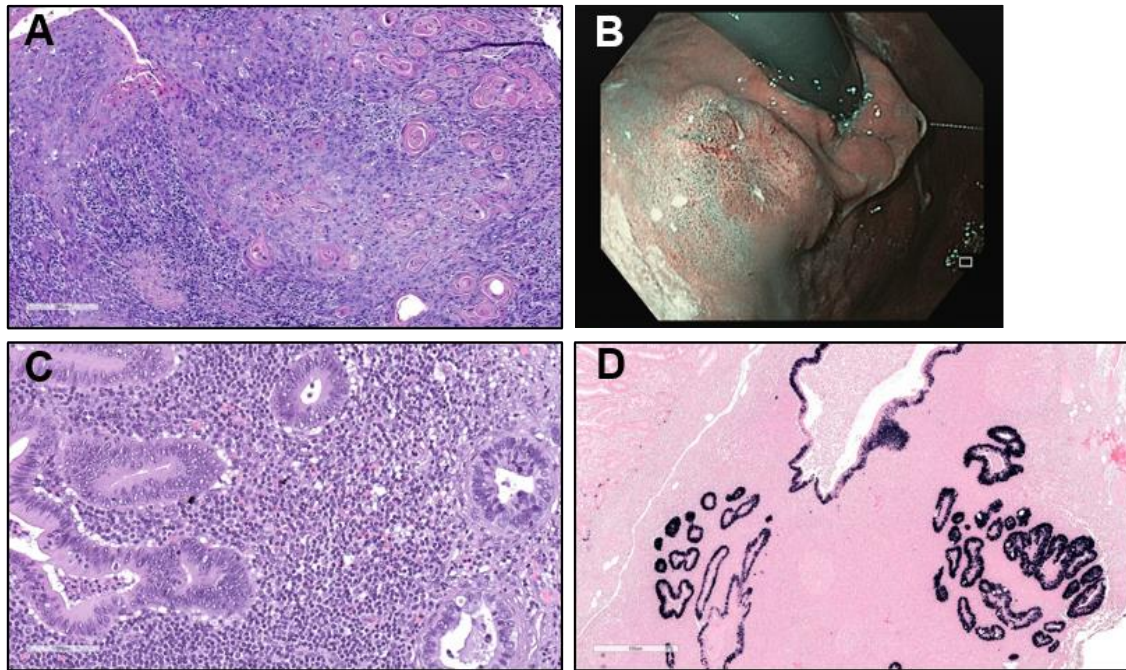
SUPPLEMENTARY FIGURE 1

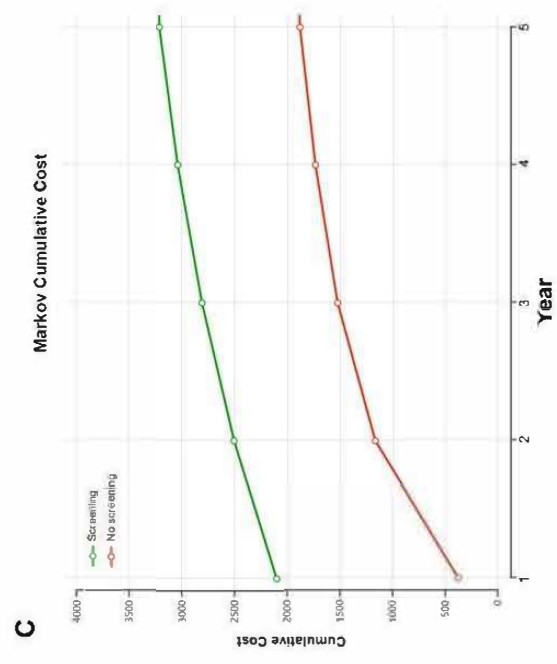
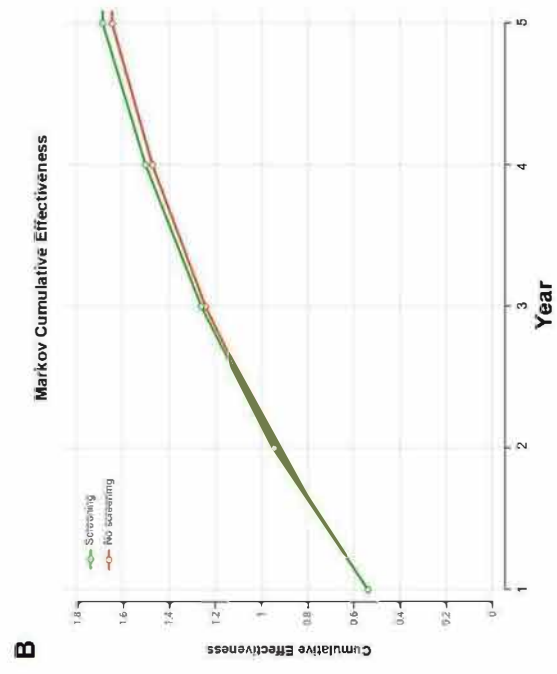
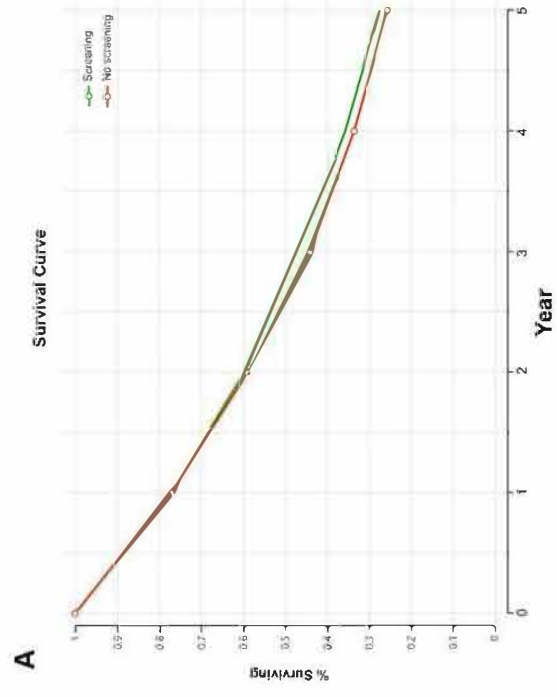


SUPPLEMENTARY FIGURE 2



SUPPLEMENTARY FIGURE 3





SUPPLEMENTARY
FIGURE 4

Supplementary references

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6.3.

Study 3

Underwater Endoscopic Mucosal Resection Vs Conventional Endoscopic Mucosal Resection for Superficial Nonampullary Duodenal Epithelial Tumors in the Western Setting

Morais R, Amorim J, Medas R, Sousa-Pinto B, Santos-Antunes J, Legros R, Albouys J, Moll F, Marques M, Vilas-Boas F, Rodrigues-Pinto E, Gullo I, Carneiro F, Soares EG, Amaro P, Mesquita P, Rodrigues J, Andrisani G, Sferrazza S, Archer S, Kuttner-Magalhães R, Manzano F, de Santiago ER, Rimondi A, Murino A, Despott E, Pioche M, Jacques J, Macedo G.

Clin Gastroenterol Hepatol. 2024 May 22:S1542-3565(24)00485-3

DOI: 10.1016/j.cgh.2024.05.011

Epub ahead of print

PMID: 38782173

Cited by 3 articles

(Google Scholar, 2025, April 24)

Impact factor 11.6

(Thomson-Reuters, 2023)

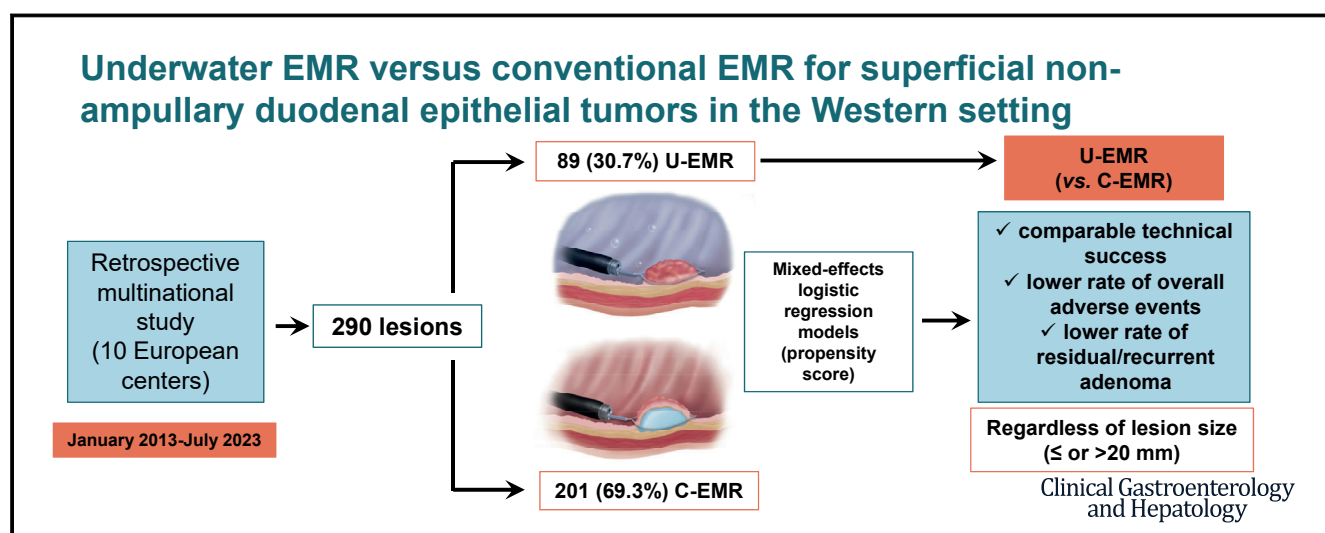
Rank 6 of 164 on Gastroenterology journals (Q1)

(Scimago Journal & Country Rank, 2023)

Underwater Endoscopic Mucosal Resection Vs Conventional Endoscopic Mucosal Resection for Superficial Nonampullary Duodenal Epithelial Tumors in the Western Setting

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Abbreviations used in this paper: AE, adverse event; C-EMR, conventional endoscopic mucosal resection; EMR, endoscopic mucosal resection; ER, endoscopic resection; IPB, intraprocedural bleeding; IQR, interquartile range; OR, odds ratio; PPB, postprocedural bleeding; PS, propensity score; RRA, residual/recurrent adenoma; SE1, first surveillance endoscopy; SE2, subsequent surveillance endoscopy;

SNADET, superficial nonampullary duodenal epithelial tumor; TMA, thermal margin ablation; U-EMR, underwater endoscopic mucosal resection.

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1542-3565/\$36.00

<https://doi.org/10.1016/j.cgh.2024.05.011>

BACKGROUND & AIMS:

Conventional endoscopic mucosal resection (C-EMR) is established as the primary treatment modality for superficial nonampullary duodenal epithelial tumors (SNADETs), but recently underwater endoscopic mucosal resection (U-EMR) has emerged as a potential alternative. The majority of previous studies focused on Asian populations and small lesions (≤ 20 mm). We aimed to compare the efficacy and outcomes of U-EMR vs C-EMR for SNADETs in a Western setting.

METHODS:

This was a retrospective multinational study from 10 European centers that performed both C-EMR and U-EMR between January 2013 and July 2023. The main outcomes were the technical success, procedure-related adverse events (AEs), and the residual/recurrent adenoma (RRA) rate, evaluated on a per-lesion basis. We assessed the association between the type of endoscopic mucosal resection and the occurrence of AEs or RRAs using mixed-effects logistic regression models (propensity scores). Sensitivity analyses were performed for lesions ≤ 20 mm or > 20 mm.

RESULTS:

A total of 290 SNADETs submitted to endoscopic resection during the study period met the inclusion criteria and were analyzed (C-EMR: $n = 201$, 69.3%; U-EMR: $n = 89$, 30.7%). The overall technical success rate was 95.5% and comparable between groups. In logistic regression models, compared with U-EMR, C-EMR was associated with a significantly higher frequency of overall delayed AEs (odds ratio [OR], 4.95; 95% CI, 2.87–8.53), postprocedural bleeding (OR, 7.92; 95% CI, 3.95–15.89), and RRAs (OR, 3.66; 95% CI, 2.49–5.37). Sensitivity analyses confirmed these results when solely considering either small (≤ 20 mm) or large (> 20 mm) lesions.

CONCLUSIONS:

Compared with C-EMR, U-EMR was associated with a lower rate of overall AEs and RRAs, regardless of lesion size. Our results confirm the possible role of U-EMR as an effective and safe technique in the management of SNADETs.

Keywords: Superficial Nonampullary Duodenal Epithelial Tumors; Underwater Endoscopic Mucosal Resection; Conventional Endoscopic Mucosal Resection; Endoscopic Resection.

Superficial nonampullary duodenal epithelial tumors (SNADETs) are rare, with an estimated prevalence of 0.3% to 4.6% in patients referred to esophagogastroduodenoscopy,¹ but the frequency of their diagnosis appears to be increasing.

Because 30% to 85% of duodenal adenomas may progress to malignancy, their surgical or endoscopic removal is mandatory.² Pancreaticoduodenectomy is the primary treatment for duodenal cancer but is associated with significant morbidity and is considered too invasive for SNADETs.³ Therefore, endoscopic resection (ER) has been established as the main treatment modality.¹

Although cold-snare polypectomy should be performed for small lesions (≤ 5 mm), conventional endoscopic mucosal resection (C-EMR) usually is recommended for lesions > 5 mm.¹ Performing C-EMR in the duodenum presents more significant technical challenges than its execution in the colon owing to various features (fibrous submucosal layer, rich vascularity, and thin muscularis propria layer), which increase the risk of adverse events (AEs).³ In particular, although perforation is relatively rare ($\approx 1\%$), postprocedural bleeding (PPB) occurs in up to 12%.^{3–5} In large SNADETs (> 20 mm), despite a lower rate of en bloc resection and consequentially higher risk of

recurrence, piecemeal C-EMR is an appropriate treatment.¹ Endoscopic submucosal dissection achieves higher rates of R0 resections but is associated with an increased risk of AEs (mostly perforation), even when performed in specialized centers.^{1,3} Recently, potentially effective alternatives to C-EMR have emerged, particularly underwater endoscopic mucosal resection (U-EMR) and cold-snare endoscopic mucosal resection (EMR).^{1,3}

As reported by Binmoeller et al⁶ in 2013, duodenal U-EMR implies an antigravity floating effect of the mucosa and submucosa as a result of saline/water immersion after air/CO₂ suctioning, with a reduced risk of muscular propria entrapment within the snare and thermal injury.³ A systematic review did not show differences in recurrence rates between U-EMR and C-EMR,⁷ despite a higher en bloc resection rate and shorter procedure time for lesions ≤ 20 mm in the former.⁸ Nonetheless, most studies focused on Asian populations and described only U-EMR outcomes for SNADETs ≤ 20 mm.^{8–14} Hence, the potential benefits and drawbacks of U-EMR for both Western populations and lesions > 20 mm are yet to be elucidated.

We aimed to compare the technical success, frequency of AEs, and the RRA rate of U-EMR vs C-EMR for SNADETs in a Western setting.

Methods

Study Design, Patient Selection, and Data Extraction

We conducted a retrospective analysis from 10 European centers in Portugal, Spain, France, the United Kingdom, and Italy that performed both C-EMR and U-EMR for SNADET treatment. Patients consecutively undergoing ER of SNADETs during a 10-year period (January 2013–July 2023) were screened for eligibility. Inclusion criteria were as follows: age ≥ 18 years and SNADETs ≥ 10 mm removed by U-EMR or C-EMR. Exclusion criteria were as follows: (1) major or minor papilla involvement; (2) hybrid EMR procedures (combination of different techniques); and (3) histopathologic analysis revealing nondysplastic lesions after ER.

Retrospectively collected data were obtained from electronic medical records.

Written informed consent was obtained before EMR. The study was approved by the Ethics Committee from the coordinating center (Centro Hospitalar Universitário de São João, Porto, Portugal; reference 239/2023). The study followed Strengthening the Reporting of Observational Studies in Epidemiology guidelines.¹⁵

Endoscopic Mucosal Resection Technique and Histopathologic Analysis

All procedures were performed by senior endoscopists trained in duodenal EMR (all with >30 procedures at the time of data collection and with a range of 10 to 15 procedures per year on average)/advanced trainees (Supplementary Figure 1 and Supplementary Video).

Technical details of the EMR procedures/histopathologic analysis are described in Supplementary Table 1.

The first surveillance endoscopy (SE1) was performed within 3 to 12 months after ER according to local center protocol. Subsequent endoscopic surveillance (SE2) was tailored to the presence of residual/recurrent adenoma (RRA) at SE1, as well as the patient's baseline characteristics and comorbidities.

Study Outcomes

The main outcome was the RRA rate, evaluated on a per-lesion basis. Additional outcomes included technical success and procedure-related AEs.

Overall RRA was defined as the presence of adenomatous tissue in the EMR scar at SE1 and/or SE2, confirmed by histologic evaluation of endoscopic biopsy specimens. Lesions with endoscopic evidence of recurrence but without further histopathologic confirmation after endoscopic resection were considered as nonrecurrent.

What You Need to Know

Background

Superficial nonampullary duodenal epithelial tumors (SNADETs) are rare, but endoscopic resection is challenging. This study compared underwater endoscopic mucosal resection (U-EMR) vs conventional endoscopic mucosal resection (C-EMR) for the management of SNADETs in the Western setting.

Findings

Compared with C-EMR, U-EMR was associated with comparable technical success but a lower rate of overall adverse events and residual/recurrent adenomas, regardless of lesion size.

Implications for patient care

Our study confirms the role of U-EMR as a safe and effective alternative to C-EMR in the management of SNADETs (including large lesions >20 mm).

Technical success was defined as the complete removal of all macroscopically visible tissue during the index EMR.

Intraprocedural bleeding (IPB) was defined as persistent bleeding requiring endoscopic hemostasis. Delayed AEs were eligible if they occurred within 30 days after the index EMR. PPB was defined as clinically significant bleeding (hematemesis, melena, or hemoglobin decrease >2 g/dL) resulting in an emergency department visit, admission, or intervention (endoscopy, angioembolization, surgery).¹⁶ Overall AEs included the occurrence of periprocedural and/or delayed AEs.

Statistical Analysis

Categorical variables were described as absolute and relative frequencies. Continuous variables were described using means and SDs or median and interquartile range (IQR). Continuous variables were compared using the Student *t* or Mann–Whitney tests, whereas chi-square or Fisher exact tests were used for categorical variables. For variables with missing data, no imputation methods were applied.

We assessed the association between the type of EMR and the occurrence of RRA or AEs using mixed-effects logistic regression models. In particular, we built logistic regression models (1) having either AEs (overall, delayed AEs, IPB, PPB), defect closure or RRA as the dependent variable, (2) considering the type of EMR as the independent variable, and (3) considering the center in which EMR was performed as a random effect. For each dependent variable, we built unadjusted and adjusted regression models. In adjusted models, the inverse probability of treatment weighting using the propensity score (PS) was applied to balance exposure groups for baseline characteristics (ie, to account for a set of

potential confounders). For models for which the dependent variable consisted of AEs or defect closure, PSs were built for the independent variable using multivariable logistic regression models and including—as covariates—sex, age, use of antiplatelet agents, use of anticoagulant agents, lesion size, lesion site, and whether the lesion was naïve. For models having the presence of RRA as the dependent variable, covariates for the PS models included the histopathology results, the lesion site and size, whether there was a hereditary gastrointestinal cancer syndrome, and whether the lesion was naïve. Sensitivity analyses were performed for lesions ≤ 20 mm or >20 mm. An additional analysis in both models was performed, including the year of the procedure as a covariate when building the PSs.

A mediation analysis was performed to assess whether an eventual association between the type of EMR and the occurrence of AEs could be explained in part by differences in the occurrence of defect closure. For this mediator, we calculated the average causal mediation effects (indirect effect of the type of EMR on the outcome variable that is mediated through the mediator), and the proportion of the effect of the type of EMR on the outcome variable that goes through the mediator. A quasi-Bayesian approximation was applied for CIs, with obtention of 1000 simulations.

Overall recurrence-free survival was estimated using the Kaplan–Meier method, and the differences among U-EMR and C-EMR were assessed using the log-rank test.

A *P* value less than .05 was set as the threshold for statistical significance. Statistical analysis was conducted with the support of IBM SPSS Statistics version 29 and R (version 4.3.1).

Results

Between January 2013 and July 2023, 331 SNADETs underwent ER in 10 European centers; 290 (87.6%) met the inclusion criteria and were analyzed further (Figure 1). U-EMR was performed in 89 (30.7%) patients and 201 (69.3%) underwent C-EMR.

Patient and Lesion Baseline Characteristics

Patient and lesion baseline characteristics are described in Table 1. The median age was 68 years (IQR, 55–73 y) and 61% were male. There were no significant differences between groups regarding the use of antithrombotic agents. Hereditary gastrointestinal cancer syndrome was present in 29.3%, and was more frequent in the C-EMR group (33.3% vs 20.2%; *P* < .001). Most lesions (*n* = 280; 96.6%; 96.6% U-EMR vs 96.5% C-EMR; *P* = .962) were naïve and similar between groups regarding size, location, and morphology. The median lesion size was 20 mm (IQR, 13–30 mm) and 42.4% (*n* = 123) of lesions were >20 mm (39.3% U-EMR vs 43.8% C-EMR; *P* = .521).

Histopathologic Results

Most of the lesions showed low-grade dysplasia (*n* = 197; 67.9%). There was a significant difference in the distribution of histopathologic results, with 9 cases of adenocarcinoma diagnosed in the C-EMR group vs no cases in the U-EMR group (Supplementary Table 2).

Endoscopic Mucosal Resection Procedure

En bloc resection was achieved in 37.9% (41.6% U-EMR vs 36.3% C-EMR; *P* = .432). Most lesions >20 mm were removed by piecemeal resection (92.7%).

The overall technical success rate was 95.5% and comparable between groups (97.8% U-EMR vs 94.5% C-EMR; *P* = .221) (Table 2). Partial submucosal injection U-EMR was used in 13 U-EMR cases (14.6%). Thermal margin ablation (TMA) was performed in 99 patients (34.1%; 28.1% U-EMR vs 36.8% C-EMR; *P* = .179). Complete or partial defect closure was performed in 70% (76.4% U-EMR vs 67.2% C-EMR; *P* = .221).

Procedure-Related Adverse Events and Clinical Outcomes in the Follow-Up Evaluation

Procedure-related AEs and clinical outcomes in the follow-up evaluation are described in Tables 3 and 4, respectively. Logistic regression analysis for evaluation of the association between the ER technique and outcomes (AEs and RRA), without or with adjustment for the year of the procedure, are described in Table 5 and Supplementary Table 3, respectively.

Adverse events. The overall AE rate was 21.0%, and was higher in the C-EMR group (25.4% vs 11.2%; *P* = .007), which persisted in the logistic regression models (odds ratio [OR], 5.04; 95% CI, 3.37–7.53).

The rate of periprocedural AEs was not statistically different between groups (C-EMR, 13.9%; U-EMR, 6.7%; *P* = .112). A total of 6 immediate perforations (2.1%) were reported (*n* = 5, 2.5% C-EMR; *n* = 1, 1.1% U-EMR; *P* = .452). After adjustment for potential confounders, C-EMR was associated with a significantly higher frequency of IPB (OR, 4.40; 95% CI, 2.51–7.71) and a lower frequency of defect closure (OR, 0.45; 95% CI, 0.31–0.64).

The frequency of overall delayed AEs was higher in the C-EMR group (13.9% vs 4.5%; *P* = .024), including a significantly higher rate of PPB (10.9% vs 2.2%; *P* = .011), although without significant differences regarding the rate of delayed perforations (3.0% C-EMR vs 1.1% U-EMR; *P* = .341) or the need for inpatient admission. In logistic regression models, C-EMR was associated with a significantly higher frequency of overall delayed AEs (OR, 4.95; 95% CI, 2.87–8.53) and PPB (OR, 7.92; 95% CI, 3.95–15.89).

The results of logistic regression models with adjustment for the year of the procedure were consistent

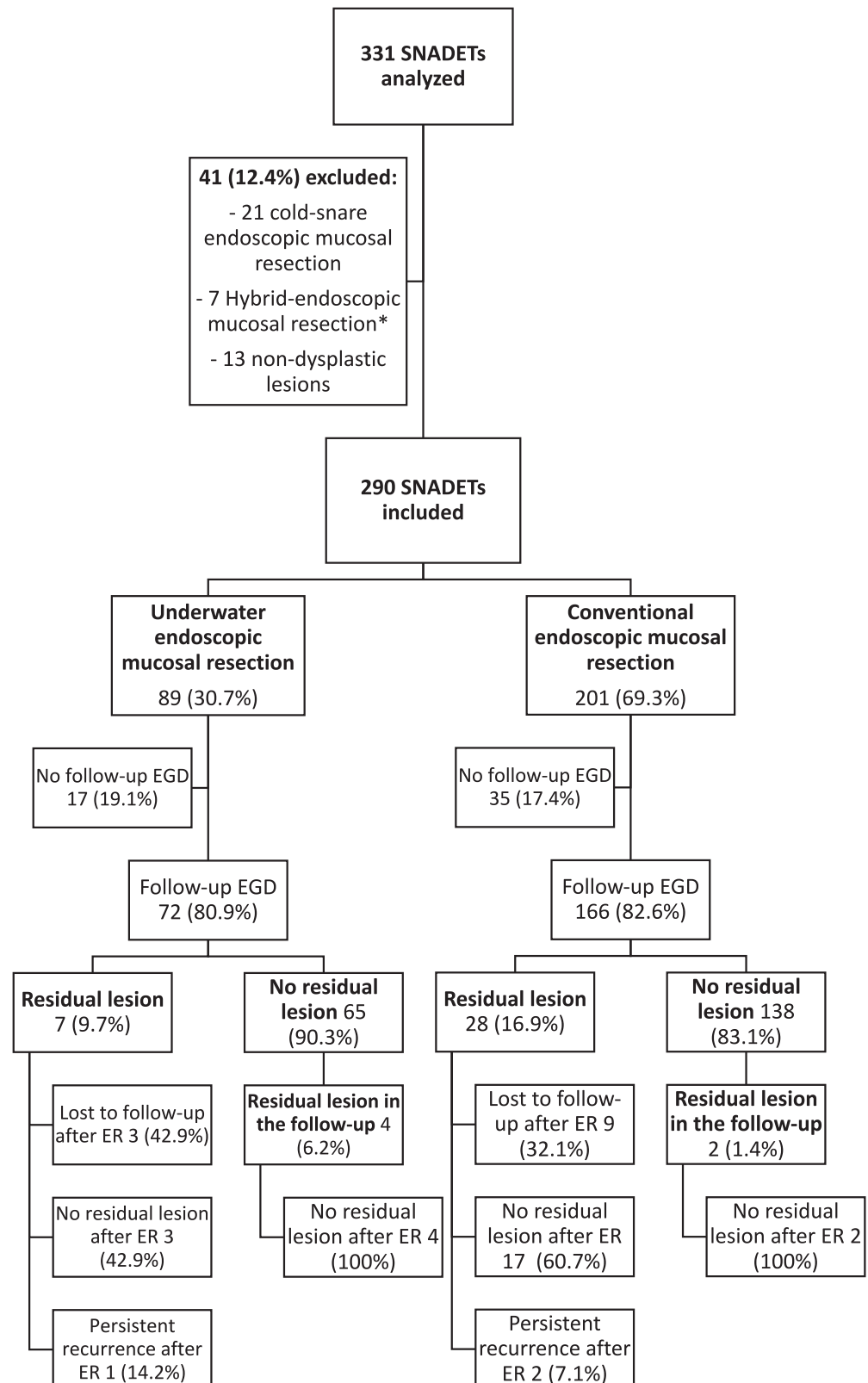


Figure 1. Study flowchart. EGD, esophagogastroduodenoscopy; ER, endoscopic resection; SNADET, superficial nonampullary duodenal epithelial tumor. *Underwater-conventional-endoscopic mucosal resection n = 4; Underwater-cold snare-endoscopic mucosal resection n = 2; Underwater-conventional-cold snare-endoscopic mucosal resection: n = 1.

with those reported previously, albeit with a lower estimate precision.

In the mediation analysis, no significant association was observed for the possibility that, in the U-EMR group, the lower frequency of AEs could be mediated in part by a higher frequency of defect closure (average

causal mediation effects, -0.01; proportion of mediated effects, -2%; $P = .21$).

During follow-up evaluation, 1 patient died of a procedure-related AE (delayed perforation after C-EMR) and 1 patient died of oncological progression of the resected lesion (adenocarcinoma pT1b R0 with vascular invasion).

Table 1. Baseline Patient and Lesion Characteristics

	Total (n = 290)	Underwater endoscopic mucosal resection (n = 89)	Conventional endoscopic mucosal resection (n = 201)	P value
Patient characteristics				
Sex, n (%)				.297
Female	113 (39.0)	39 (43.8)	74 (36.8)	
Male	177 (61.0)	50 (56.2)	127 (63.2)	
Age, median (IQR), y	68 (55–73)	70 (60–74)	67 (53–73)	.025
Antiplatelet drug, n (%)	44 (15.2)	15 (16.9)	29 (14.4)	.598
Anticoagulant drug, n (%)	29 (10.0)	9 (10.1)	20 (10.0)	.966
Hereditary gastrointestinal cancer syndrome, n (%)				<.001
No	205 (70.7)	71 (79.8)	134 (66.7)	
FAP	79 (27.3)	13 (14.6)	66 (32.8)	
Lynch syndrome	3 (1.0)	3 (3.4)	0 (0)	
Other	3 (1.0)	2 (2.2)	1 (0.5)	
Lesion characteristics				
Previous resection attempt, n (%)				.962
No	280 (96.6)	86 (96.6)	194 (96.5)	
Yes	10 (3.4)	3 (3.4)	7 (3.5)	
Lesion size, median (IQR), minimum–maximum, mm	20.0 (13.0 – 30.0), 10–80	17.0 (12.0 – 30.0), 10–70	20.0 (14.0 – 30.0), 10–80	.662
Lesion size >20 mm, n (%)	123 (42.4)	35 (39.3)	88 (43.8)	.521
Lesion location, n (%)				.189
Duodenal bulb	28 (9.7)	8 (9.0)	20 (10.0)	
Bulb-DII transition	20 (6.9)	2 (2.2)	18 (9.0)	
DII (proximal to the papilla)	134 (46.2)	41 (46.1)	93 (46.2)	
DII (distal to the papilla)	102 (35.2)	37 (41.6)	65 (32.3)	
DIII	6 (2.0)	1 (1.1)	5 (2.5)	
Laterally spreading tumor classification, n (%) ^a				.617
Granular	77 (44.3)	21 (40.4)	56 (45.9)	
Non-granular	97 (55.7)	31 (59.6)	66 (54.1)	
Paris classification, n (%) ^b				.318
Is	50 (22.0)	13 (18.6)	37 (23.5)	
IIa	135 (59.5)	38 (54.2)	97 (61.8)	
IIb	4 (1.8)	3 (4.3)	1 (0.6)	
IIa+IIb	6 (2.6)	3 (4.3)	3 (1.9)	
IIa+IIc	22 (9.7)	9 (12.9)	13 (8.3)	
IIa+Is	6 (2.6)	3 (4.3)	3 (1.9)	
Is+IIa+IIc	4 (1.8)	1 (1.4)	3 (1.9)	
Histopathologic results, n (%)				.037
Low-grade dysplasia	197 (67.9)	68 (76.4)	129 (64.2)	
High-grade dysplasia	84 (29.0)	21 (23.6)	63 (31.3)	
Adenocarcinoma	9 (3.1)	0 (0)	9 (4.5)	

NOTE. Bold entire relate to a P value that is statistical significant.

DII, second part of the duodenum; DIII, third part of the duodenum; FAP, familial adenomatous polyposis; IQR, interquartile range.

^aMissing data for 116 patients (40.0%).

^bMissing data for 63 patients (21.7%).

Residual/recurrent adenomas. Approximately 80% of lesions from both groups had proper endoscopic follow-up evaluation (U-EMR 80.9% vs C-EMR 82.6%; $P = .742$; biopsy specimens from the resection site: U-EMR 19.4% vs C-EMR 20.5%; $P = .855$) (median, 25 mo [IQR, 10–46 mo]; U-EMR, 12 mo [IQR, 8–27 mo] vs C-EMR 33 mo [IQR, 14–50 mo]; $P < .001$). In the unadjusted analysis, the RRA rate in the SE1 was 14.7%, with no significant differences between the C-EMR and U-EMR groups (16.9% vs 9.7%; $P = .169$). In 6 patients (2.5%) ($n = 2$, C-EMR 1.2%; $n = 4$, U-EMR 5.6%; $P = .070$), there was

evidence of recurrence after an initially negative SE1. At the end of the follow-up evaluation, the overall RRA rate was 17.2%, with no significant differences between groups ($P = .710$).

There were no significant differences between the 2 techniques regarding recurrence-free survival (U-EMR 59 ± 4 mo vs C-EMR 93 ± 4 mo; $P = .970$) (Supplementary Figure 2).

In logistic regression models, C-EMR was found to be associated with an increased frequency of RRA compared with U-EMR (OR, 3.66; 95% CI, 2.49–5.37). These results

Table 2. Procedure-Related Data and Technical Success

	Total (n = 290)	Underwater endoscopic mucosal resection (n = 89)	Conventional endoscopic mucosal resection (n = 201)	P value
Removal, n (%)				.432
En bloc	110 (37.9)	37 (41.6)	73 (36.3)	
Piecemeal	180 (62.1)	52 (58.4)	128 (63.7)	
Thermal margin ablation, n (%)	99 (34.1)	25 (28.1)	74 (36.8)	.179
Snare tip soft coagulation	87 (30.0)	24 (27.0)	63 (31.3)	
Argon plasma coagulation	12 (4.1)	1 (1.1)	11 (5.5)	
Technical success, n (%)	277 (95.5)	87 (97.8)	190 (94.5)	.221
Defect closure, n (%)				.221
No	87 (30.0)	21 (23.6)	66 (32.8)	
Yes (total)	186 (64.1)	61 (68.5)	125 (62.2)	
Yes (partial)	17 (5.9)	7 (7.9)	10 (5.0)	
Closure technique, n (%)				.884
Through-the-scope clips	198 (97.5)	66 (97.0)	132 (97.8)	
Band + clips	3 (1.5)	1 (1.5)	2 (1.5)	
Over-the-scope clip	2 (1.0)	1 (1.5)	1 (0.7)	

also were observed in models adjusting for the year of the procedure.

Sensitivity Analyses of Lesions by 20-mm Cut-Off Value

In lesions >20 mm, no differences were found regarding the rate of technical success (97.1% U-EMR vs 89.8% C-EMR; $P = .177$), but TMA was performed more frequently in the C-EMR group (56.8% vs 37.1% U-EMR; $P = .049$) ([Supplementary Table 4](#)). In logistic regression analysis, C-EMR was associated with a higher rate of overall AEs (OR, 2.48; 95% CI, 1.55–3.95), IPB (OR, 2.98; 95% CI, 1.76–5.04), and

RRAs (OR, 1.37; 95% CI, 1.04–1.81), as well as with a lower frequency of defect closures (OR, 0.12; 95% CI, 0.04–0.35).

In logistic regression analysis concerning lesions ≤ 20 mm, C-EMR was associated with a higher rate of overall AEs (OR, 10.03; 95% CI, 5.92–16.98) and RRAs (OR, 16.59; 95% CI, 4.85–56.78), but a lower frequency of defect closures (OR, 0.28; 95% CI, 0.17–0.45).

Management of Residual/Recurrent Adenomas

The management and outcomes after diagnosis of the first RRA are described in [Supplementary Table 5](#). At the

Table 3. Procedure-Related Adverse Events

	Total (n = 290)	Underwater endoscopic mucosal resection (n = 89)	Conventional endoscopic mucosal resection (n = 201)	P value
Overall adverse events, n (%)	61 (21.0)	10 (11.2)	51 (25.4)	.007
Periprocedural adverse events, n (%)	34 (11.7)	6 (6.7)	28 (13.9)	.112
Intraprocedural bleeding	30 (10.3)	6 (6.7)	24 (11.9)	.214
Perforation	6 (2.1)	1 (1.1)	5 (2.5)	.452
Anesthesia complications ^a	0 (0)	0 (0)	0 (0)	–
Delayed adverse events, n (%)	32 (11.0)	4 (4.5)	28 (13.9)	.024
Postprocedural bleeding	24 (8.3)	2 (2.2)	22 (10.9)	.011
Perforation	7 (2.4)	1 (1.1)	6 (3.0)	.341
Postpolypectomy coagulation syndrome	3 (1.0)	0 (0)	3 (1.5)	.247
Stricture ^b	2 (0.7)	1 (1.1)	1 (0.5)	.552
Admission to ward, n (%)				.331
No	241 (83.1)	70 (78.7)	171 (85.1)	
Programmed	42 (14.5)	17 (19.1)	25 (12.4)	
Urgent	7 (2.4)	2 (2.2)	5 (2.5)	

NOTE. Bold entire relate to a P value that are statistical significant (<.05).

^aIncludes aspiration pneumonia.

^bMild (resistance to successful passage of the gastroscop), n = 2.

Table 4. Clinical Outcomes in the Follow-Up Evaluation

	Total (n = 238)	Underwater endoscopic mucosal resection (n = 72)	Conventional endoscopic mucosal resection (n = 166)	P value
Residual/recurrent adenoma in SE1, n (%)	35 (14.7)	7 (9.7)	28 (16.9)	.169
Residual/recurrent adenoma in the follow-up evaluation, n (%)	6 (2.5)	4 (5.6)	2 (1.2)	.070
Overall RRA, n (%)	41 (17.2)	11 (15.3)	30 (18.1)	.710

RRA, residual/recurrent adenoma; SE1, first surveillance endoscopy.

end of the follow-up evaluation, 3 patients (1 from the U-EMR group, 2 from the C-EMR group) had persistent RRA. One patient was referred for surgical resection, and the remaining patients underwent surveillance because of age/comorbidities.

Table 5. Logistic Regression Analysis for Evaluation of the Association Between the Endoscopic Resection Technique and Outcomes (Adverse Events and Residual Lesion in the Follow-Up Period)

	OR (95% CI) ^a	P value
All lesions		
Adverse events		
Overall adverse events	5.04 (3.37–7.53)	<.001
Intraprocedural bleeding	4.40 (2.51–7.71)	<.001
Defect closure	0.45 (0.31–0.64)	<.001
Delayed complications	4.95 (2.87–8.53)	<.001
Postprocedural bleeding	7.92 (3.95–15.89)	<.001
Residual/recurrent adenoma		
Overall residual/recurrent adenoma	3.66 (2.49–5.37)	<.001
Lesions ≤20 mm		
Adverse events		
Overall adverse events	10.03 (5.92–16.98)	<.001
Intraprocedural bleeding ^b	–	–
Defect closure	0.28 (0.17–0.45)	<.001
Delayed complications ^b	–	–
Postprocedural bleeding ^b	–	–
Residual/recurrent adenoma		
Overall residual/recurrent adenoma	16.59 (4.85–56.78)	<.001
Lesions >20 mm		
Adverse events		
Overall adverse events	2.48 (1.55–3.95)	<.001
Intraprocedural bleeding	2.98 (1.76–5.04)	<.001
Defect closure	0.12 (0.04–0.35)	<.001
Delayed complications	2.06 (0.45–9.38)	.349
Postprocedural bleeding ^b	–	–
Residual/recurrent adenoma		
Overall RRA	1.37 (1.04–1.81)	.026

NOTE. Sensitivity analyses according to lesion size (≤20 mm and >20 mm) were performed. Bold entire relate to a P value that are statistical significant (<.05).

OR, odds ratio; RRA, residual/recurrent adenoma.

^aThe results translate C-EMR vs U-EMR.

^bThere was an insufficient number of events per group and therefore it was not possible to be computed.

Discussion

This study aimed to compare the clinical outcomes of U-EMR vs C-EMR in patients with SNADET within a large multinational Western cohort. Our results showed no significant differences regarding technical success but a significantly lower rate of AEs and RRA with U-EMR, after adjustment for potential confounders.

Three meta-analyses, including patients from Asian centers, found no significant differences in recurrence rate between U-EMR and C-EMR.^{7,8,17} However, Lv et al⁸ hypothesized that these results might be attributable to the low number of studies and recurrent cases. In our study, we tried to follow similar selection criteria to previous Asian studies, namely by excluding nondysplastic lesions, but we ultimately decided to include lesions in patients with hereditary gastrointestinal cancer syndromes (ensuring adequate weighing between groups with the PS) and lesions with previous resection attempts, to enhance the clinical generalizability in the Western setting. This may explain the differences found between U-EMR and C-EMR in our study. This study showed a lower RRA rate for U-EMR compared with C-EMR in the duodenum. It is important to note that the overall RRA in our study was higher than those from Asian studies (17.2% vs 2.18%–2.78%).^{7,17} Moreover, as previously observed, most published literature has focused on lesions ≤20 mm. The inclusion of larger lesions also may explain, to some extent, our results. Nevertheless, a sensitivity analysis found that the RRA rate remained significantly higher with C-EMR compared with U-EMR for lesions either ≤20 mm or >20 mm.

Most lesions >20 mm had piecemeal resection, previously identified as an independent risk factor for local recurrence or residual disease.¹⁸ Therefore, an Australian study proposed TMA after C-EMR and showed a significant reduction in the recurrence rate with similar AEs.¹⁹ Although it could be argued that, in our study, TMA after C-EMR was not performed in a large number of patients and that may pose relevant bias, it is important to highlight that for lesions >20 mm, TMA was performed less frequently in the U-EMR group.

A recent study proposed using partial submucosal injection U-EMR to achieve a higher en bloc resection rate compared with standard U-EMR.²⁰ Our study only

used it in 14.6% of the cases. This technique, together with TMA, should be addressed in future studies because it may contribute to even lower rates of RRA.

Previous meta-analyses showed no differences between U-EMR and C-EMR regarding AEs.^{7,8} However, in our study, the U-EMR group had a significantly lower rate of overall AEs, IPB, and delayed complications (particularly PPB) when compared with C-EMR. These differences were maintained after adjustment for potential confounders. Bleeding has been reported as the most common AE of C-EMR.²¹ The differences between U-EMR and C-EMR were most pronounced for PPB; although the rate of PPB in the U-EMR group was comparable with previously reported results from Asian studies (2.2% vs 0%–8.5%),⁷ it was higher than expected in the C-EMR group. Once again, the inclusion of lesions >20 mm partially may explain these differences because they are associated with a higher rate of AEs, even when preventive endoscopic measures are used.²² A meta-analysis including 438 patients reported that patients who had undergone defect closure were 86% less likely to develop PPB.²³ Indeed, after adjusting for cofounders, U-EMR was associated more frequently with defect closure even in lesions >20 mm, which may explain the lower rate of PPB in the U-EMR group (even though results were not significant in mediation analysis; this may be in relation to the small number of events). By ensuring greater stability of the muscle layer, U-EMR may facilitate defect closure. This also may be associated with a lower risk of delayed perforation, although we did not observe differences regarding this AE.

Most of the literature only describes the use of U-EMR for adenomas ≤20 mm.^{8–14} In our study, U-EMR was performed in 35 lesions >20 mm. Besides the lower rate of overall AEs and RRA, no significant differences regarding technical success were observed when compared with C-EMR. Although more studies are necessary to establish the role of U-EMR in the management of large SNADETs, our results show that it may be a promising, effective, and safe alternative to C-EMR, as initially suggested by Binmoeller et al.⁶

Our study had some limitations that were inherent to the study design. First, indication biases should be noted, resulting from the fact that the decision to perform U-EMR or C-EMR was left to the subjective decision of each endoscopist. Therefore, relevant confounders may be distributed unequally between groups. To ensure an adequate comparison regarding study outcomes (namely, rates of AEs and RRA), we used regression models based on PS, adjusting for potential cofounders such as participant center, histopathology grading, and lesion characteristics. We also conducted a sensitivity analysis adjusting for the year of the procedure (to avoid time period bias), with the results being comparable with those without adjustment for this variable. However, we cannot exclude the possibility of relevant residual confounding by unmeasured variables. Despite being one of the largest series on this topic, another limitation was the

reduced sample size in some subgroups (eg, >20 mm), leading to lower precision estimates or the impossibility of performing some analyses. Finally, some patients had a short follow-up time or were lost before SE1. In the recurrence analysis, we only included lesions with a histopathologically proven RRA. Scars without endoscopic evidence of RRA did not undergo a biopsy universally, which could have led to an underestimation of the actual rate of histologic RRA and partially may explain the relevant number of cases that had evidence of RRA at SE2, after an apparently negative SE1.

Nevertheless, our study had strengths that should be highlighted. This study compared U-EMR and C-EMR for the management of SNADETs in the Western setting, with well-defined inclusion and exclusion criteria. On the other hand, when considering the available data, it is one of the few studies that addresses the possible role of U-EMR as an effective and safe technique in the management of large SNADETs.

In conclusion, C-EMR and U-EMR had similar technical success, but U-EMR was associated with a lower rate of overall AEs and RRA, regardless of lesion size. With the advent of other techniques, such as endoscopic submucosal dissection and cold-snare EMR, further studies should be conducted to define the role of U-EMR and other ER techniques more precisely in the tailored management of SNADETs.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <https://doi.org/10.1016/j.cgh.2024.05.011>.

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Acknowledgments

Constance Grunewald, Beatriz Peñas García, and Sofia Parejo Carbonell.

CRediT Authorship Contributions

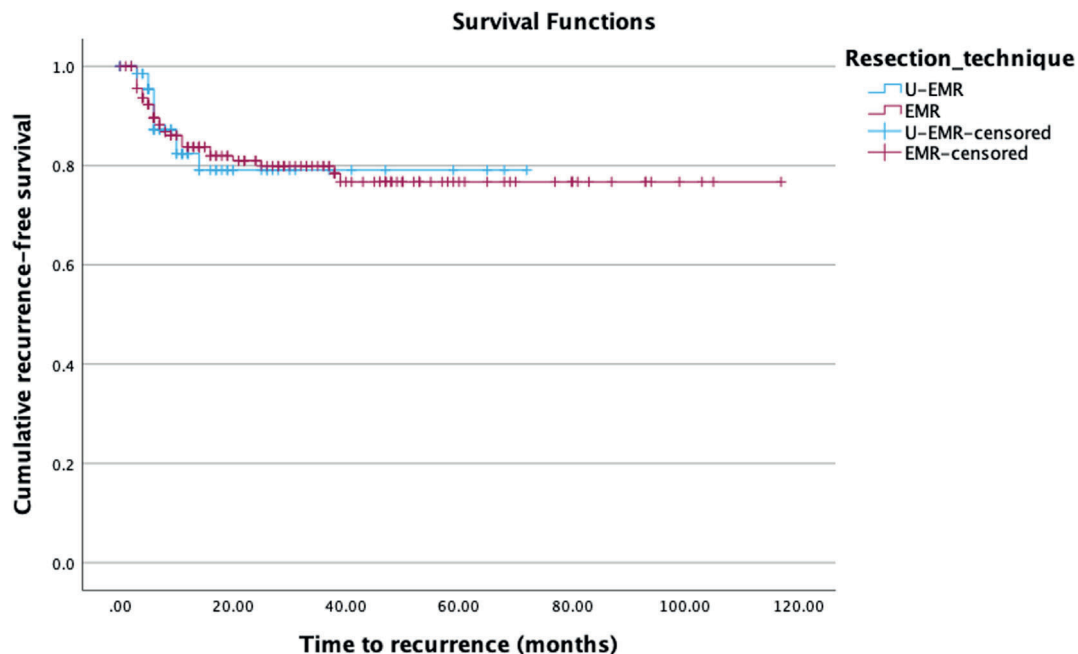
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Data Availability

Study materials will be made available to other researchers upon request.

Conflicts of interest

This author discloses the following: Enrique Rodríguez de Santiago has performed educational and advisory roles for Olympus, educational activities for Apollo Endosurgery, advisory roles for Adacety Therapeutics, and received congress fee support from Norgine and Casen Recordati. The remaining authors disclose no conflicts.



Supplementary Figure 2. Recurrence-free survival in the follow-up period according to the performed technique. C-EMR, conventional endoscopic mucosal resection; U-EMR, underwater endoscopic mucosal resection.

Supplementary Table 1. Technical Details of the EMR Procedures and Histopathologic Analysis

	U-EMR	C-EMR
Antithrombotic agents	Were withheld in accordance with established ESGE guidelines at the index procedure. ^{1,2}	
Sedation	In patients without significant comorbidities (ASA I–II) and no complex lesions, the procedure was performed under deep sedation with propofol, without endotracheal intubation. In patients with significant comorbidities (ASA III–IV) and/or complex lesions (with an expected longer duration), especially in whom U-EMR was programmed, the procedures were performed under general anesthesia with endotracheal intubation.	
Endoscopes	Gastrosopes, pediatric colonoscopes, or duodenoscopes were used, according to the endoscopist's preference.	
Lesion evaluation	All lesions were evaluated systematically with high-definition endoscopes using white-light and virtual chromoendoscopy. When available, electronic magnification was performed.	
Caps	Transparent caps were used systematically.	
Submucosal injection	Partial submucosal injection was performed as an adjunctive technique at the endoscopist's discretion.	Submucosal injection was saline, methylene blue, and diluted epinephrine in most cases.
Snare	All procedures (conventional or underwater EMR) were performed with a braided or monofilament snare using electrocautery energy.	
Thermal margin ablation	Thermal margin ablation, either by argon plasma coagulation or snare-tip soft coagulation, was performed at the endoscopist's discretion.	
Histopathologic analysis	Resected specimens were retrieved and evaluated by a board-certified pathologist. Whenever incomplete or incongruent pathologic data were noticed in the report, the center was contacted, and a re-evaluation of the histologic specimen was performed.	

ASA, American Society of Anesthesiologists; C-EMR, conventional endoscopic mucosal resection; ESGE, European Society of Gastrointestinal Endoscopy; U-EMR, underwater endoscopic mucosal resection.

Supplementary Table 2. Subanalysis of Adenocarcinoma Cases

	n = 9
Procedure-related adverse events ^a	
Overall adverse events	4 (44.4)
Periprocedural adverse events, n (%)	1 (11.1)
Intraprocedural bleeding	0 (0)
Perforation	1 (11.1)
Anesthesia complications ^b	0 (0)
Delayed adverse events, n (%)	3 (33.3)
Postprocedural bleeding	3 (33.3)
Perforation	0 (0)
Postpolypectomy coagulation syndrome	0 (0)
Stricture	0 (0)
Histopathologic analysis	
Staging, T, n (%)	
Tis	5 (55.6)
pT1a	2 (22.2)
pT1b	2 (22.2)
Staging, N, n (%)	
N0	0 (0)
Staging, M, n (%)	
M0	0 (0)
Lymphatic invasion, n (%)	0 (0)
Venous invasion, n (%)	1 (11.1)
Perineural invasion, n (%)	0 (0)
Vertical margin, n (%)	
Negative	9 (100)
Positive	0 (0)
Horizontal margin, n (%)	
Negative	5 (55.6)
Positive	4 (44.4)
R0 resection, n (%)	
Yes	4 (44.4)
Piecemeal resection	5 (55.6)
Outcomes in the follow-up period	
Decision after EMR, n (%)	
Watchful waiting	9 (100)
Recurrence in the follow-up period, n (%)	
No	7 (77.8)
Yes ^c	2 (22.2)

EMR, endoscopic mucosal resection.

^aLesions with adenocarcinoma were not associated significantly with a higher incidence of overall adverse events (44.4% vs 20.3% lesions without adenocarcinoma; $P = .080$) but were associated significantly with a higher incidence of postprocedural bleeding (33.3% vs 7.5%; $P = .006$).

^bIncludes aspiration pneumonia.

^cOne patient died of oncological progression of a duodenal adenocarcinoma. One patient had evidence of recurrence that was submitted to conventional endoscopic mucosal resection with curative resection, with no evidence of oncological progression in the follow-up period.

Supplementary Table 3. Logistic Regression Analysis (Adjusted for the Year of the Procedure) for Evaluation of the Association Between the Endoscopic Resection Technique and Outcomes (Complications and Residual Lesion in the Follow-Up Period)

	OR (95% CI) ^a	P value
All lesions		
Adverse events		
Overall AEs	9.16 (5.42–15.49)	<.001
Intraprocedural bleeding	9.41 (4.44–19.93)	<.001
Defect closure	0.34 (0.21–0.54)	<.001
Delayed complications	9.09 (4.30–19.23)	<.001
Postprocedural bleeding	13.00 (5.22–32.37)	<.001
Residual/recurrent adenoma		
Overall RRA	23.95 (20.46–28.03)	<.001
Lesions ≤20 mm		
Adverse events		
Overall AEs	7.15 (3.09–16.53)	<.001
Intraprocedural bleeding ^b	–	–
Defect closure	0.04 (0.02–0.10)	<.001
Delayed complications ^b	–	–
Postprocedural bleeding ^b	–	–
Residual/recurrent adenoma		
Overall RRA	16.38 (4.45–60.27)	<.001
Lesions >20 mm		
Adverse events		
Overall AEs	3.75 (2.41–5.84)	<.001
Intraprocedural bleeding	4.68 (2.85–7.67)	<.001
Defect closure	0.12 (0.09–0.17)	<.001
Delayed complications ^b	–	–
Postprocedural bleeding ^b	–	–
Residual/recurrent adenoma		
Overall RRA	1.37 (1.16–1.63)	<.001

NOTE. Sensitivity analyses according to lesion size (≤20 mm and >20 mm) were performed. Bold entire relate to a P value that are statistical significant (<.05).

AE, adverse event; OR, odds ratio; RRA, residual/recurrent adenoma.

^aThe results translate C-EMR vs U-EMR.

^bThere was an insufficient number of events per group and therefore it was not possible to be computed.

Supplementary Table 4. EMR Procedure and Main Outcomes in Lesions >20 mm

	Total (n = 123)	U-EMR (n = 35)	C-EMR (n = 88)	P value
EMR procedure				
Removal, n (%)				.736
En bloc	9 (7.3)	3 (8.6)	6 (6.8)	
Piecemeal	114 (92.7)	32 (91.4)	82 (93.2)	
Thermal margin ablation, n (%)	63 (51.2)	13 (37.1)	50 (56.8)	.049
Technical success, n (%)	113 (91.9)	34 (97.1)	79 (89.8)	.177
Defect closure, n (%) ^a	88 (71.5)	25 (71.4)	63 (71.6)	.986
Adverse events				
Overall AEs, n (%)	40 (32.5)	8 (22.9)	32 (36.4)	.201
Periprocedural AEs, n (%)	22 (17.9)	5 (14.3)	17 (19.3)	.609
Intraprocedural bleeding	19 (15.4)	5 (14.3)	14 (15.9)	.822
Perforation	3 (2.4)	0 (0)	3 (3.4)	.269
Delayed AEs, n (%)	23 (18.7)	3 (8.6)	20 (22.7)	.078
Postprocedural bleeding	17 (13.8)	1 (2.9)	16 (18.2)	.026
Perforation	5 (4.1)	1 (2.9)	4 (4.5)	.669
PPCS	3 (2.4)	0 (0)	3 (3.4)	.269
Stricture	1 (0.8)	1 (2.9)	0 (0)	.111
Residual/recurrent adenoma				
	Total (n = 100)	U-EMR (n = 29)	C-EMR (n = 71)	
RRA in SE1, n (%)	23 (23.0)	5 (17.2)	18 (25.4)	.443
RRA in the follow-up period, n (%)	5 (5.0)	4 (13.8)	1 (1.4)	.010
Overall RRA, n (%)	28 (28)	9 (31.0)	19 (26.8)	.806

NOTE. Bold entire relate to a P value that are statistical significant (<.05).

AE, adverse event; C-EMR, conventional endoscopic mucosal resection; PPCS, post-polypectomy coagulation syndrome; RRA, residual/recurrent adenoma; SE1, first surveillance endoscopy; U-EMR, underwater endoscopic mucosal resection.

^aTotal or partial.**Supplementary Table 5.** Management and Outcomes After Diagnosis of First Recurrence

	Total (n = 41)	U-EMR (n = 11)	C-EMR (n = 30)	P value
Size of residual lesion, median (IQR), mm	10 (5–20)	10 (5–12)	12 (5–20)	.444
Endoscopic technique, n (%)				
U-EMR	6 (14.6)	5 (45.4)	1 (3.3)	.009
C-EMR	16 (39.0)	3 (27.3)	13 (43.3)	
CS-EMR	10 (24.3)	3 (27.3)	7 (23.3)	
APC	8 (19.5)	0 (0)	8 (26.8)	
EFTR	1 (2.4)	0 (0)	1 (3.3)	
Overall AEs, n (%)	5 (12.5)	2 (18.2)	3 (10.0)	.478
Histopathologic results, n (%)				
LGD	25 (61.0)	11 (100.0)	14 (46.7)	.022
HGD	6 (14.6)	0 (0)	6 (20.0)	
Adenocarcinoma	1 (2.4)	0 (0)	1 (3.3)	
NA/specimen not recovered	9 (30.0)	0 (0)	9 (30.0)	
Outcomes in the follow-up period, n (%)^a				
No residual lesion after ER	26 (63.4)	7 (63.6)	19 (63.3)	.958
Persistent recurrence	3 (7.3)	1 (9.1)	2 (6.7)	
Loss of follow-up evaluation	12 (29.3)	3 (27.3)	9 (30.0)	

NOTE. Bold entire relate to a P value that are statistical significant (<.05).

AE, adverse event; APC, argon plasma coagulation; C-EMR, conventional endoscopic mucosal resection; CS-EMR, cold-snare endoscopic mucosal resection; EFTR, endoscopic full-thickness resection; ER, endoscopic resection; HGD, high-grade dysplasia; IQR, interquartile range; LGD, low-grade dysplasia; NA, nonapplicable; U-EMR, underwater endoscopic mucosal resection.

^aMore than 1 ER procedure was performed in 10 patients.

Supplementary References

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6.4.

Study 4

Predicting residual neoplasia after a non-curative gastric ESD: validation and modification of the eCura system in the Western setting: the W-eCura score

Morais R, Libanio D, Dinis Ribeiro M, Ferreira A, Barreiro P, Bourke MJ, Gupta S, Amaro P, Küttner Magalhães R, Cecinato P, Boal Carvalho P, Pinho R, Rodríguez de Santiago E, Sferrazza S, Lemmers A, Figueiredo M, Pioche M, Gallego F, Albéniz E, Ramos Zabala F, Uchima H, Berr F, Wagner A, Marques M, Pimentel-Nunes P, Gonçalves M, Mascarenhas A, Soares EG, Xavier S, Faria-Ramos I, Sousa-Pinto B, Gullo I, Carneiro F, Macedo G, Santos-Antunes J

Gut. 2023 Dec 7;73(1):105-117
DOI: 10.1136/gutjnl-2023-330804
PMID: 37666656

Cited by 20 articles
(Google Scholar, 2025, April 24)

Impact factor 24.5
(Thomson-Reuters, 2023)

Rank 3 of 164 on Gastroenterology journals (Q1)
(Scimago Journal & Country Rank, 2023)

Original research

Predicting residual neoplasia after a non-curative gastric ESD: validation and modification of the eCura system in the Western setting: the W-eCura score

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► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/gutjnl-2023-330804>).

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Received 30 July 2023
Accepted 25 August 2023
Published Online First
4 September 2023



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To cite: Morais R, Libanio D, Dinis Ribeiro M, et al. *Gut* 2024;**73**:105–117.

ABSTRACT

Objective To evaluate the risk factors for lymph node metastasis (LNM) after a non-curative (NC) gastric endoscopic submucosal dissection (ESD) and to validate and eventually refine the eCura scoring system in the Western setting. Also, to assess the rate and risk factors for parietal residual disease.

Design Retrospective multicentre multinational study of prospectively collected registries from 19 Western centres. Patients who had been submitted to surgery or had at least one follow-up endoscopy were included. The eCura system was applied to assess its accuracy in the Western setting, and a modified version was created according to the results (W-eCura score). The discriminative capacities of the eCura and W-eCura scores to predict LNM were assessed and compared.

Results A total of 314 NC gastric ESDs were analysed (72% high-risk resection (HRR); 28% local-risk resection). Among HRR patients submitted to surgery, 25% had parietal disease and 15% had LNM in the surgical specimen. The risk of LNM was significantly different across the eCura groups (areas under the receiver operating characteristic curve (AUC-ROC) of 0.900 (95% CI 0.852 to 0.949)). The AUC-ROC of the W-eCura for LNM (0.916, 95% CI 0.870 to 0.961; $p=0.012$) was significantly higher compared with the original eCura. Positive vertical margin, lymphatic invasion and younger age were associated with a higher risk of parietal residual lesion in the surgical specimen.

Conclusion The eCura scoring system may be applied in Western countries to stratify the risk of LNM after a gastric HRR. A new score is proposed that may further decrease the number of unnecessary surgeries.

INTRODUCTION

Gastric cancer is the fifth most common cancer and the third cause of cancer-related deaths.¹ In the last

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies assessed the risk factors for lymph node metastasis (LNM) after a non-curative (NC) gastric endoscopic submucosal dissection (ESD). The eCura score system was created in Japan to aid in decision-making by stratifying patients into low, intermediate and high risk for LNM.

WHAT THIS STUDY ADDS

⇒ No previous studies assessed the adequacy of eCura score in the Western setting. This study represents the largest Western cohort on NC gastric ESD and it is the first to validate the eCura system in the West. Furthermore, we propose a modification of this score (the Western-eCura score), according to the analysis obtained in this cohort.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The W-eCura showed a higher accuracy than the original eCura system. With this new score, unnecessary surgeries may be avoided, while maintaining a very high sensitivity. This could be particularly helpful in high-risk surgical patients.

two decades, endoscopic submucosal dissection (ESD) emerged as the first-line treatment for early gastric neoplasms with a low risk of lymph node metastasis (LNM).^{2,3} Compared with gastrectomy with lymphadenectomy, ESD is associated with similar long-term outcomes but with lower procedural time, risk of adverse events and costs and better health-related quality of life.^{3–8}

Table 1 Demographic, ESD and histopathological analysis-related data in the cohort (n=314)

Demographics	
Gender, n (%)	
Female	113 (36.0%)
Male	201 (64.0%)
Age, median (IQR), minimum–maximum, years	72 (65–79), 42–93
Lesion characteristics	
Location, n (%)	
Antrum	91 (29.0%)
Incisura	89 (28.4%)
Body	110 (35.1%)
Fundus	3 (1.0%)
Cardia	20 (6.4%)
Surgical anastomosis	1 (0.3%)
Morphology n (%)	
Polypoid	53 (16.9%)
Non-polypoid, non-depressed	89 (28.3%)
Depressed	172 (54.8%)
Lesion size, median (IQR), mm	26 (19–35)
Previous resection attempt, n (%)	3 (1.0%)
ESD procedure	
Duration, median (IQR), minutes	90 (60–150)
Complementary techniques, n (%)	49 (15.6%)
Hybrid ESD	31 (9.9%)
Traction clip-line	16 (5.1%)
Pocket creation method	2 (0.6%)
En bloc resection, n (%)	
Yes	241 (76.8%)
Piecemeal	73 (23.2%)
Histopathological analysis	
Resection-risk classification, n (%)	
Local-risk resection	89 (28.3%)
High risk resection	225 (71.7%)
Histology, n (%)	
Low-grade dysplasia	16 (5.1%)
High-grade dysplasia	38 (12.1%)
Adenocarcinoma	260 (82.8%)
Resection, n (%)	
R0	134 (42.7%)
R1	125 (39.8%)
Rx	55 (17.5%)
Horizontal margins, n (%)*	
HM0	169 (70.1%)
HM1	67 (27.8%)
HMx	5 (2.1%)
Histopathological analysis in adenocarcinoma cases†	
Vertical margins, n (%)	
VM0	203 (78.1%)
VM1	44 (16.9%)
VMx	13 (5.0%)
Adenocarcinoma staging, n (%)	
pT1a	83 (26.4%)
pT1b(SM1/>SM1)	177 (56.4%)(39 (22.0%)/138 (78.0%))
Exact extension of SM invasion, median (IQR), mm	1.0 (0.7–2.0)
Missing data, n (%)	50/177 (28.2%); >SM1 35/138 (25.4%)
Lesion size with SM invasion, median (IQR), mm	6.5 (2.0–12.0)

Continued

Table 1 Continued

Demographics	
Missing data, n (%)	74/177 (41.8%); >SM1 81/138 (58.7%)
Lymphatic invasion, n (%)	91 (35.0%)
Venous invasion, n (%)	39 (15.0%)
Perineural invasion, n (%)	9 (3.5%)
Ulceration, n (%)	61 (23.5%)
Missing data, n (%)	1 (0.4%)
Differentiation, n (%)	
Poor	78 (30.0%)
Well/moderate	182 (70.0%)
Signet ring cells, n (%)	52 (20.0%)
Papillary component, n (%)	36 (13.8%)
Missing data, n (%)	1 (0.4%)
Mucinous adenocarcinoma, n (%)	10 (3.8%)
Missing data, n (%)	1 (0.4%)

*Horizontal margins were evaluated in en-bloc removed lesions (n=241).
†n=260 cases.
ESD, endoscopic submucosal dissection.

The selection of patients for ESD is based on the size, morphology, presence of ulceration and histology of the lesion.^{2,3} Although endoscopic evaluation is the most accurate method to predict curability, 15%–20% of ESDs are considered non-curative (NC) after the evaluation of the resected specimen.^{3,9,10}

When facing the undesired outcome of NC resection, physicians and patients must decide whether further treatment (surgery with lymphadenectomy) is required. For adequate decision-making, an accurate estimation of the risk of parietal recurrence and LNM, according to the adverse prognostic factors, is paramount and needs to be balanced with surgical risk, patient's physical status and preference. Indeed, in some patients (eg, advanced age and severe comorbidities), the recurrence risk may be lower than the surgical risk and surveillance may be an option, with similar disease-specific survival between surveillance and surgery.^{11–14}

Some studies assessed the risk factors for LNM and gastric cancer mortality in patients with NC resection. The eCura score system was created in Japan and it stratifies patients into low, intermediate and high LNM risk.¹⁵ This score was validated in Asia and it showed significantly higher recurrence and LNM rates in the high-risk category.^{16,17} However, no previous studies assessed the adequacy of this score in the Western setting, and it is unclear whether there are additional prognostic variables that could be helpful in the estimation of recurrence and LNM risk, which can further aid in the decision-making process.

Thus, this study aimed to identify risk factors for LNM in a large cohort and to validate and eventually refine the eCura scoring system in the Western setting. Moreover, the rate and predictive factors for parietal lesion after a gastric NC-ESD were also addressed.

MATERIAL AND METHODS

Study design and patient selection

Retrospective analysis of prospectively collected registries from 19 centres (Portugal, Spain, France, Belgium, Italy, Austria and Australia). All the endoscopists had performed at least 100 ESDs at the time of data collection; nevertheless, in some centres, this series represents all the procedures that were performed since the beginning of the practice of ESD, early on their learning

Table 2 Characterisation of the criteria for curativeness of resection

n=89*	Local-risk resection, n (%)
Lesion histology	
Dysplasia	54 (60.7)
LGD	16 (18.0)
HGD	38 (42.7)
Adenocarcinoma	35 (39.3)
pT1a	32 (36.0)
pT1b SM1	3 (3.3)
Piecemeal resection	37 (41.6)
Horizontal margins (among <i>en-bloc</i> resections)	
HM1	48 (53.9)
HMx	4 (4.5)
n=225*	High-risk resection, n (%)
Lesion histology	
Adenocarcinoma	
pT1a	51 (22.7)
pT1b SM1	36 (16.0)
pT1b>SM1	138 (61.3)
Size>3 cm	
Intramucosal ulcerated lesions	5 (2.2)
pT1b SM1 differentiated lesions	15 (6.7)
Vertical margins	
VM1	44 (19.6)
VMx	12 (5.3)
Lymphovascular invasion	101 (44.9)
Lymphatic invasion	91 (40.4)
Venous invasion	39 (17.3)
Poorly differentiated lesions	
Ulceration	25 (11.1)
Size>2 cm	48 (21.3)

*There are patients with more than one criteria.
HGD, high-grade dysplasia; LGD, low-grade dysplasia.

curves. The pathological records of the ESD specimens and, whenever patients underwent surgery due to a NC-ESD, of the surgical specimens, were collected from each institution.

Consecutive patients submitted to gastric ESD between November 2007 and June 2022 were screened for eligibility. Indication for ESD was the presence of a gastric neoplastic lesion without endoscopic features of deep invasive (>SM1) adenocarcinoma, based on the endoscopic evaluation. NC resection criteria included local-risk resection (LocRR) and high-risk resection (HRR), defined by the 2022 European Society of Gastrointestinal Endoscopy (ESGE) ESD guidelines.³ These guidelines recommend that patients with LocRR may be submitted to endoscopic surveillance and retreated with ESD (preferable) or surgery whenever necessary. In contrast, patients with HRR are recommended to undergo further surgical treatment (gastrectomy with lymphadenectomy) unless there are significant comorbidities (high-surgical risk) or patient refusal. In the case of endoscopic surveillance, patients were submitted to an upper endoscopy at 3–6 months and staging CT, if deemed necessary, after multidisciplinary discussion.

Exclusion criteria were loss to follow-up (absence of surgical specimen in case of a decision to proceed to gastrectomy or absence of at least one follow-up endoscopy in the surveillance arm) and incomplete ESD pathological specimen data.

Patients gave their written informed consent before ESD and inclusion in the prospective ESD registries.

ESD procedure and pathological evaluation

En-bloc resection was considered if the target lesion was retrieved in a single specimen or *piecemeal* if it was removed in more than one fragment. R0 resection was considered whenever pathological evaluation showed free horizontal and vertical margins (VM and HM), in an *en-bloc* resected specimen. For the purpose of statistical analysis, patients with HMx and VMx resections (due to artefacts that precluded a definite margin evaluation) were considered HM1 and VM1, respectively. HM status was only considered in *en-bloc* resections. SM1 adenocarcinomas were those T1b lesions in which the submucosal invasion depth was not higher than 0.5 mm, measured perpendicularly from the *muscularis mucosa*.

Although the histological report could not be standardised and centrally analysed due to the retrospective design of the study, a systematic approach was followed in each centre to document an accurate histopathological diagnosis, agreed on by expert pathologists, according to international standards (with specimen examination by at least two expert pathologists).¹⁸ Whenever incomplete or incongruent pathological data were evident in the report, the centre was contacted and the histological specimen was re-evaluated for a complete and accurate data collection.

Residual disease was defined as the presence of neoplastic tissue in the ESD scar, confirmed by pathological evaluation in the follow-up endoscopy or surgery (parietal residual lesion), and/or as the detection of LNM in the surgical specimen.

Classifications

Recent guidelines suggest a new classification for ESD outcomes. ESGE recommends the use of the terminology ‘very-low risk resection’ and ‘low-risk resection’ for those considered ‘curative’. Among NC-ESDs, LocRR are those with a higher risk of having parietal residual lesion (in the ESD site), such as those piecemeal-resected or with positive (benign) HM, without other risk factors for LNM. HRR includes those with high-risk features of having LNM warranting complementary treatment, such as lymphatic permeation, positive vertical margins, large (>3 cm) submucosal (SM) or ulcerated intramucosal adenocarcinomas, large (>2 cm) undifferentiated carcinomas or lesions with deep (>SM1) SM invasion.³

The eCura system evaluates five risk factors for the development of LNM and weighs them according to the relative risk: 3 points for lymphatic permeation and 1 point each for lesion size above 30 mm, positive vertical margins, venous invasion and SM invasion equal or above 0.5 mm. In our study, patients were categorised in three groups as originally proposed: low-risk group (0–1 point, 2.5% risk of LNM), intermediate-risk group (2–4 points, 6.7% risk) and high-risk group (5–7 points, 22.7% risk).¹⁵

Evaluated outcomes

The two main outcomes were the rate of LNM observed in the surgical specimen in patients submitted to surgery and the rate of parietal residual lesion observed either in the follow-up endoscopy (confirmed by pathological analysis) or in the surgical specimen, after an NC-ESD. The rate of LNM in patients referred to surveillance who underwent CT evaluation in the follow-up was also reported.

Risk factors for parietal residual lesion (considering the entire cohort) and for LNM or for the combined endpoint of residual disease (in HRR patients submitted to surgery) were analysed.

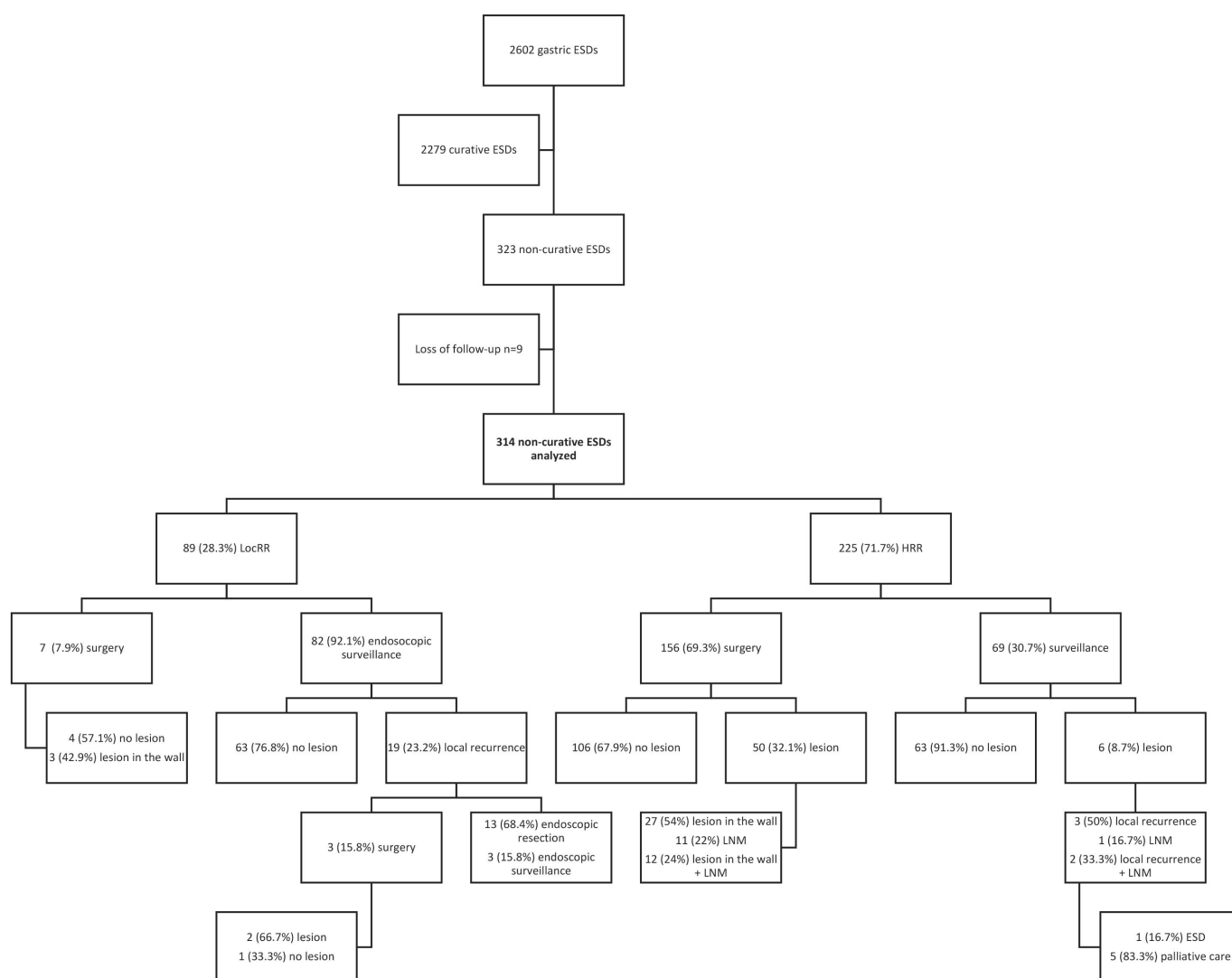


Figure 1 Flowchart of study design. ESD, endoscopic submucosal dissection; LNM, lymph node metastasis.

Among patients with adenocarcinoma submitted to surgery, we applied the eCura system in order to assess its accuracy in predicting LNM in the Western setting. Furthermore, considering the analysis of our Western cohort, a modification to this system was proposed by changing the cut-off of the ‘SM invasion’ variable (see the section Data collection and statistical analysis)—the Western e-Cura (W-eCura) score. The W-eCura was applied and evaluated as previously described for the eCura system. LNM rate, mortality and overall survival (OS) after ESD in each risk category were evaluated and compared using both scores.

Data collection and statistical analysis

Participant centres were asked to fill out a database that included the variables of interest.

Categorical variables were described as absolute (n) and relative frequencies (%). Continuous variables were described using means and SD or medians and IQRs, as appropriate. Continuous variables were compared using the Student’s t-test or the Mann-Whitney test, while the χ^2 test or the Fisher’s exact test were used for categorical variables, as appropriate. For variables with missing data, available cases analysis was performed.

We built univariable logistic regression models to identify potential predictors for LNM, parietal residual lesion and

residual disease (dependent variables). Tested independent variables included those related to demographic and clinical characteristics of the patients. Variables having $p < 0.100$ on univariable analysis were incorporated into stepwise multivariable logistic regression models (one per dependent variable). In the stepwise analysis, a $p < 0.05$ was used to keep the variables in the model.

Receiver operating characteristic (ROC) analysis was performed to define the optimal cut-point value for the variable ‘SM invasion’, by choosing a cut-off with best sensitivity and acceptable specificity for the prediction of LNM in the surgical specimen. The sensitivity and specificity of the identified cut-point and of the original eCura SM invasion cut-point (0.5 mm) were assessed. Furthermore, we projected the expected positive predictive value (PPV) and negative predictive value (NPV) for both cut-points based on their sensitivity and specificity and considering an LNM prevalence range of 0%–100%. A cut-off of 1 mm was identified. SM invasion depth ≥ 1 mm independent association with LNM in the surgical specimen in the multivariate analysis was confirmed. The W-eCura was then calculated, taking into consideration this change in the ‘SM invasion’ variable.

We assessed and compared the discriminative capacities of the eCura and W-eCura scores to predict LNM, computing the respective areas under the ROC curve (AUC-ROC), and

Table 3 Risk of LNM among HRR operated patients (n=156)

	LNM		Unadjusted OR (95%CI), P
	Yes	No	
Demographics			
Gender, n (%)			
Female	12 (52.2%)	41 (30.8%)	Ref.
Male	11 (47.8%)	92 (69.2%)	0.409 (0.167 to 1.002), 0.050
Age, median (IQR), years	70 (68–77)	68 (61–74)	1.069 (1.006 to 1.136), 0.030
Lesion characteristics			
Morphology, n (%)			
Polypoid	6 (26.1%)	15 (11.3%)	Ref.
Non-polypoid, non-depressed	4 (17.4%)	37 (27.8%)	0.270 (0.067 to 1.096), 0.067
Depressed	13 (56.5%)	81 (60.9%)	0.401 (0.132 to 1.221), 0.108
Lesion size, median (IQR), mm	22 (16–30)	25 (20–35)	0.965 (0.924 to 1.007), 0.101
ESD procedure			
Complementary techniques, n (%)			
Yes	4 (17.4%)	12 (9.0%)	2.123 (0.620 to 7.267), 0.231
No	19 (82.6%)	121 (91.0%)	Ref.
En bloc resection, n (%)			
Yes	21 (91.3%)	109 (82.0%)	Ref.
Piecemeal	2 (8.7%)	24 (18.0%)	0.433 (0.095 to 1.970), 0.279
Histopathological analysis			
Horizontal margins, n (%)*			
HM1	1 (4.8%)	7 (6.4%)	0.729 (0.085 to 6.251), 0.773
HM0	20 (95.2%)	102 (93.6%)	Ref.
Vertical margins, n (%)			
VM1	7 (30.4%)	32 (24.1%)	1.381 (0.522 to 3.654), 0.516
VM0	16 (69.6%)	101 (75.9%)	Ref.
Carcinoma staging, n (%)			
pT1a	4 (17.4%)	30 (22.6%)	Ref.
pT1b	19 (82.6%)	103 (77.4%)	1.383 (0.437 to 4.380), 0.581
SM invasion depth, n (%)			
SM1	1 (5.3%)	21 (20.4%)	Ref.
>SM1	18 (94.7%)	82 (79.6%)	4.610 (0.582 to 36.529), 0.148
Extension of SM invasion, median (IQR), mm	2.5 (2–3)	1 (0.7–1.8)	3.007 (1.500 to 6.027), 0.002
SM invasion depth≥1 mm			
Present	11 (91.7%)	42 (51.2%)	10.476 (1.293 to 84.904), 0.028
Absent	1 (8.3%)	40 (48.8%)	Ref.
Lesion size with SM invasion, median (IQR), mm	9 (6–14)	7 (3–12)	1.026 (0.905 to 1.164), 0.683
Lymphatic invasion, n (%)			
Present	23 (100%)	41 (30.8%)	†
Absent	0 (0%)	92 (69.2%)	
Venous invasion, n (%)			
Present	13 (56.5%)	18 (13.5%)	8.306 (3.172 to 21.747), <0.001
Absent	10 (43.5%)	115 (86.5%)	Ref.
Perineural invasion, n (%)			
Present	1 (4.3%)	6 (4.5%)	0.962 (0.110 to 8.383), 0.972
Absent	22 (95.7%)	127 (95.5%)	Ref.
Ulceration, n (%)			
Present	5 (21.7%)	38 (28.6%)	0.553 (0.212 to 1.440), 0.500
Absent	18 (78.3%)	95 (71.4%)	Ref.

Continued

Table 3 Continued

	LNM		Unadjusted OR (95%CI), P
	Yes	No	
Differentiation, n (%)			
Poor	6 (26.1%)	47 (35.3%)	0.646 (0.238 to 1.749), 0.390
Well/moderate	17 (73.9%)	86 (64.7%)	Ref.
Signet ring cells, n (%)			
Present	5 (21.7%)	33 (24.8%)	0.842 (0.290 to 2.444), 0.751
Absent	18 (78.3%)	100 (75.2%)	Ref.
Papillary component, n (%)			
Present	7 (30.4%)	21 (15.8%)	2.333 (0.856 to 6.362), 0.098
Absent	16 (69.6%)	112 (84.2%)	Ref.
Mucinous carcinoma, n (%)			
Present	1 (4.3%)	7 (5.3%)	0.818 (0.096 to 6.980), 0.854
Absent	22 (95.7%)	126 (94.7%)	Ref.

*Horizontal margins were evaluated in lesions removed *en-bloc* (n=130).

†Since in patients with LNM all cases had lymphatic permeation, univariate logistic regression and subsequently multivariate logistic regression analysis were not performed.

ESD, endoscopic submucosal dissection; HGD, high-grade dysplasia; HRR, high-risk resection; LGD, low-grade dysplasia; LNM, lymph node metastasis.

estimating the continuous Net Reclassification Improvement (NRI) index and the Integrated Discrimination Index. Finally, we assessed the calibration of the eCura and the W-eCura scores by obtaining the respective calibration plots. We performed an internal validation with bootstrap resampling (with 2000 bootstrap replicates)—summary AUC-ROC and *p* values for the Hosmer-Lemeshow test were obtained for both the eCura and the W-eCura scores in relation to LNM.

OS was estimated using the Kaplan-Meier method, and the differences among the three risk groups in eCura and W-eCura were assessed using the log-rank test.

Statistical analysis was conducted with the support of IBM SPSS Statistics Version 29 and R.

RESULTS

Sample description

Of the 2602 gastric ESDs from the 19 centres, 323 (12%) were identified as NC. From them, 314 (97%) had proper follow-up and were further analysed (median follow-up=16 months, IQR=6–36).

Table 1 describes the assessed participants' demographic, ESD and histopathological analysis-related data. Most of the NC-ESDs corresponded to adenocarcinoma (n=260, 83%) or high-grade dysplastic lesions (n=38, 12%), with the remaining being low-grade dysplasia.

Of the 314 analysed NC-ESDs, 225 (72%) were classified as HRR and 89 (28%) as LocRR. The characterisation of the criteria for the curativeness of the resection is detailed in table 2.

Figure 1 depicts the outcomes of assessed patients according to the classification of the resection. Most (n=156, 69%) patients with HRR were submitted to surgery; in the LocRR group, the majority (n=82, 92%) was referred for endoscopic surveillance. In patients submitted to surgery (n=163), the overall rate of residual disease was 33% (LocRR: n=3, 43%; HRR: n=50, 32%). The overall recurrence rate in non-operated patients (n=151) was 8% (LocRR n=19, 23%; HRR n=6, 9%), after a median time of 11 months (IQR=4–14). The mortality rate was 13% (n=41). The cause of death was, in most cases, unrelated to the lesion that motivated ESD (n=29). Five patients died due

Endoscopy

Table 4 Risk factors for parietal residual lesion in the ESD site among HRR patients (n=225)

	Parietal residual lesion		Unadjusted OR (95% CI), P	Covariate adjusted OR (95% CI), P
	Yes	No		
Demographics				
Gender, n (%)				
Female	19 (43.2%)	59 (32.6%)	Ref.	
Male	25 (56.8%)	122 (67.4%)	0.409 (0.167 to 1.247), 0.188	
Age, median (IQR), years	70 (63–75)	72 (65–79)	0.971 (0.939 to 1.003), 0.073	0.943 (0.895 to 0.994), 0.029
Lesion characteristics				
Morphology, n (%)				
Polypoid	5 (11.4%)	35 (19.3%)	Ref.	
Non-polypoid, non-depressed	9 (20.5%)	43 (23.8%)	1.465 (0.450 to 4.772), 0.526	
Depressed	30 (68.2%)	103 (56.9%)	2.039 (0.734 to 5.662), 0.172	
Lesion size, median (IQR), mm	27 (20–30)	26 (20–38)	0.984 (0.959 to 1.010), 0.220	
ESD procedure				
Complementary techniques, n (%)				
Yes	5 (11.4%)	20 (11.0%)	1.032 (0.365 to 2.921), 0.953	
No	39 (88.6%)	161 (89.0%)	Ref.	
En bloc resection, n (%)				
Yes	31 (70.5%)	158 (87.3%)	Ref.	Ref.
Piecemeal	13 (29.5%)	23 (12.7%)	2.881 (1.319 to 6.294), 0.008	2.620 (0.860 to 7.984), 0.090
Histopathological analysis				
Horizontal margins, n (%)*				
HM1	4 (12.9%)	16 (10.1%)	1.315 (0.408 to 4.238), 0.647	
HM0	27 (87.1%)	142 (89.9%)	Ref.	
Vertical margins, n (%)				
VM1	20 (45.5%)	36 (19.9%)	3.356 (1.672 to 6.737), <0.001	5.323 (1.968 to 14.398), <0.001
VM0	25 (54.5%)	145 (80.1%)	Ref.	Ref.
Adenocarcinoma staging, n (%)				
pT1a	8 (18.2%)	43 (23.8%)	Ref.	
pT1b	36 (81.8%)	138 (76.2%)	1.402 (0.606 to 3.245), 0.430	
SM invasion depth, n (%)				
SM1	7 (19.4%)	29 (21.0%)	Ref.	
>SM1	29 (80.6%)	109 (79.0%)	1.102 (0.439 to 2.770), 0.836	
Exact extension of SM invasion, median (IQR), mm	2 (0.8–2.2)	1 (0.7–1.6)	1.518 (0.980 to 2.350), 0.061	
Lesion size with SM invasion, median (IQR), mm	7 (3–11)	7 (2–12)	1.039 (0.952 to 1.134), 0.392	
Lymphatic invasion, n (%)				
Present	23 (52.3%)	68 (37.6%)	1.820 (0.937 to 3.534), 0.077	3.407 (1.203 to 9.651), 0.021
Absent	21 (47.7%)	113 (62.4%)	Ref.	Ref.
Venous invasion, n (%)				
Present	11 (25.0%)	28 (15.5%)	1.821 (0.825 to 4.023), 0.138	
Absent	33 (75.0%)	153 (84.5%)	Ref.	
Perineural invasion, n (%)				
Present	5 (11.4%)	4 (2.2%)	5.673 (1.456 to 22.097), 0.012	
Absent	39 (88.6%)	177 (97.8%)	Ref.	
Ulceration, n (%)				
Present	14 (31.8%)	45 (25.0%)	1.400 (0.682 to 2.872), 0.359	
Absent	30 (68.2%)	135 (75.0%)	Ref.	
Differentiation, n (%)				
Poor	16 (36.4%)	60 (33.1%)	1.152 (0.579 to 2.292), 0.686	
Well/moderate	28 (63.6%)	121 (66.9%)	Ref.	
Signet ring cells, n (%)				
Present	10 (22.7%)	40 (22.1%)	1.037 (0.472 to 2.279), 0.928	
Absent	34 (77.3%)	141 (77.9%)	Ref.	
Papillary component, n (%)				
Present	8 (18.2%)	27 (15.0%)	1.259 (0.528 (3.001), 0.603	
Absent	36 (81.8%)	153 (85.0%)	Ref.	
Mucinous carcinoma, n (%)				

Continued

Table 4 Continued

	Parietal residual lesion		Unadjusted OR (95% CI), P	Covariate adjusted OR (95% CI), P
	Yes	No		
Present	2 (4.5%)	7 (3.9%)	1.177 (0.236 to 5.871), 0.843	
Absent	42 (95.5%)	173 (96.1%)	Ref.	

*Horizontal margins were evaluated in lesions removed *en-bloc* (n=189).

ESD, endoscopic submucosal dissection; HGD, high-grade dysplasia; HRR, high-risk resection; LGD, low-grade dysplasia.

to gastric cancer progression and seven due to surgery-related complications.

Local-risk resection

The reasons for classifying the resection as LocRR (n=89) were piecemeal resection (n=37, 42%) and HM1/HMx (n=52, 58%).

Within this group, 7 (8%) were referred to surgery considering multidisciplinary discussion and patient's preference (6 pT1a adenocarcinoma and 1 high-grade dysplasia (HGD)), with 3 showing residual lesion in the wall (2 pT1a adenocarcinoma and 1 HGD).

Eighty-two patients (92%) were surveilled by endoscopy (median 17 months, IQR 12–35), with a parietal recurrence rate of 23% (n=19). The median time to recurrence was 8 months (IQR 4–12), with most of the cases (n=14, 74%) being diagnosed in the first follow-up endoscopy.

Patients with recurrence after LocRR were successfully treated with re-ESD (68%) or surgery (16%), with the remaining (16%) being referred for surveillance due to comorbidities. Of the three patients who underwent subsequent surgery, this approach was decided due to impossibility of endoscopic resection in two and concomitant mass in the head of the pancreas in one patient. In two patients, surgical specimen analysis revealed parietal residual (pT1a) adenocarcinoma. There were no cases of gastric lesion-related mortality during the follow-up.

Risk factors for parietal residual lesion

Risk factors for parietal residual lesion among LocRR patients are described in online supplemental table 1.

High-risk resection

Regarding the lesions classified as HRR, 45% had lymphovascular invasion (40% lymphatic invasion; 17% venous invasion), 61% had deep SM invasion, 25% had VM1/VMx, 32% were poorly differentiated and larger than 20 mm or ulcerated and 9% were bigger than 30 mm with ulceration or with superficial submucosal invasion.

Of the 225 patients classified as HRR, 156 (69%) underwent surgery, while the remainder were followed up due to high surgical risk (n=53) or patient refusal (n=16).

Among the 156 patients undergoing surgery, 50 (32%) had parietal lesion and/or LNM: 23 (15%) had LNM and 39 (n=25%) lesion in the gastric wall (adenocarcinoma n=44, HGD n=3, LGD n=2). No lesion (T0N0) was identified in 106 patients (68%) undergoing surgery.

From the 69 patients submitted to follow-up, only 6 (9%) (median follow-up=16 months, IQR=7–31), presented disease recurrence (two patients with parietal recurrence only, one with LNM and two with parietal recurrence plus LNM (LNM presence based on radiological criteria in this group)). One patient underwent re-ESD and the remainder were referred for palliative care. The follow-up cohort's gastric cancer-related death was 4% (n=3).

Risk factors for LNM in operated patients

In univariable logistic regression models, venous invasion (OR=8.306, 95% CI 3.172–21.747), extension of SM invasion (OR=3.007, 95% CI=1.500 to 6.027) and SM invasion depth ≥ 1 mm (OR 10.476, 95% CI 1.293 to 84.904) were significantly associated with the risk of LNM (table 3). All patients with LNM had lymphatic invasion in the ESD specimen. Only one patient with LNM in the surgical specimen had an SM invasion < 1 mm (pT1b SM1 adenocarcinoma with lymphovascular invasion).

Risk factors for parietal residual lesion

In the multivariable logistic regression analysis, positive VM (OR=5.323, 95% CI 1.968 to 14.398) and lymphatic invasion (OR=3.407, 95% CI 1.203 to 9.651) were independently associated with a higher risk of parietal residual lesion in the ESD site, while age was related with a lower risk (OR=0.943, 95% CI 0.895 to 0.994) (table 4).

Risk factors for residual disease

In the multivariable logistic regression analysis, piecemeal resection (OR=5.286, 95% CI 1.329 to 21.025), extension of SM invasion (OR=1.970, 95% CI 1.158 to 3.351) and lymphatic invasion (OR=5.070, 95% CI 1.781 to 14.427) were independently associated with the risk of residual disease (parietal residual lesion and/or LNM) in the surgical specimen (table 5).

Validation of the eCura score

From the 156 patients with HRR that underwent surgery, 59 were classified as low-risk (38%), 65 as intermediate-risk (42%) and 32 as high-risk (20%) resections according to the eCura score (table 6).

The risk of LNM was significantly different across the eCura groups (low-risk 0% (95% CI 0% to 6.1%), intermediate-risk 9.2% (95% CI 3.5 to 19.0%), high-risk 53.1% (95% CI 34.7% to 70.9%), $p<0.001$). The AUROC of the eCura system for LNM was 0.900 (95% CI 0.852 to 0.949). There were no significant differences between groups regarding mortality and OS; however, cancer-related mortality was significantly different across groups.

Modified eCura score (W-eCura)

Considering the analysis for the risk of LNM among operated HRR patients, a cut-point of SM invasion ≥ 1 mm was identified, with a sensitivity of 92% and specificity of 51% for the presence of LNM using ROC analysis (online supplemental figure 1). By comparison, the sensitivity of the cut-point of SM invasion ≥ 0.5 mm was of 91.7% and the specificity of 48.8% (for most possible prevalence values of LNM, the SM ≥ 1 mm displayed a higher PPV and NPV—figure 2).

Therefore, a modification in the original eCura system was performed in which the SM invasion cut-off was changed from ≥ 0.5 mm to ≥ 1 mm. This modification implied a shift from

Endoscopy

Table 5 Risk of residual disease (parietal residual lesion and/or LNM) among HRR operated patients (n=156)

	Residual disease		Unadjusted OR (95% CI), P	Covariate adjusted OR (95% CI), P
	Yes	No		
Demographics				
Gender, n (%)				
Female	22 (44.0%)	31 (29.2%)	Ref.	
Male	28 (56.0%)	75 (70.8%)	0.526 (0.262 to 1.057), 0.071	
Age (IQR), years	70 (64–75)	68 (62–74)	1.017 (0.977 to 1.058), 0.410	
Lesion characteristics				
Morphology, n (%)				
Polypoid	9 (18.0%)	12 (11.3%)	Ref.	
Non-polypoid, non-depressed	11 (22.0%)	30 (28.3%)	0.489 (0.162 to 1.478), 0.205	
Depressed	30 (60.0%)	64 (60.4%)	0.625 (0.238 to 1.644), 0.341	
Lesion size (IQR), mm	25 (20–30)	25 (18–35)	0.983 (0.957 to 1.010), 0.217	
ESD procedure				
Complementary techniques, n (%)				
Yes	7 (14.0%)	9 (8.5%)	1.755 (0.613 to 5.019), 0.294	
No	43 (86.0%)	97 (91.5%)	Ref.	
En bloc resection, n (%)				
Yes	36 (72.0%)	94 (88.7%)	Ref.	Ref.
Piecemeal	14 (28.0%)	12 (11.3%)	3.046 (1.287 to 7.209), 0.011	5.286 (1.329 to 21.025), 0.018
Histopathological analysis				
Horizontal margins, n (%)*				
HM1	3 (8.3%)	5 (5.3%)	1.618 (0.366 to 7.152), 0.526	
HM0	33 (91.7%)	89 (94.7%)	Ref.	
Vertical margins, n (%)				
VM1	19 (38.0%)	20 (18.9%)	2.635 (1.245 to 5.581), 0.011	
VM0	31 (62.0%)	86 (81.1%)	Ref.	
Adenocarcinoma staging, n (%)				
pT1a	9 (18.0%)	25 (23.6%)	Ref.	
pT1b	41 (82.0%)	81 (76.4%)	1.406 (0.601 to 3.288), 0.432	
SM invasion depth, n (%)				
SM1	5 (12.2%)	17 (21.0%)	Ref.	
>SM1	36 (87.8%)	64 (79.0%)	1.912 (0.651 to 5.618), 0.238	
Exact extension of SM invasion (IQR), mm	2 (0.9–2.3)	1 (0.7–1.6)	1.675 (1.037 to 2.708), 0.035	1.970 (1.158 to 3.351), 0.012
SM invasion depth ≥1 mm, n (%)				
Present	20 (64.5%)	33 (52.4%)	1.653 (0.681 to 4.011), 0.267	
Absent	11 (35.5%)	30 (47.6%)	Ref.	
Lesion size with SM invasion (IQR), mm	7 (4–12)	8 (3–13)	1.026 (0.938 to 1.123), 0.572	
Lymphatic invasion, n (%)				
Present	32 (64.0%)	32 (30.2%)	4.111 (2.019 to 8.370), <0.001	5.070 (1.781 to 14.427), 0.002
Absent	18 (36.0%)	74 (69.8%)	Ref.	Ref.
Venous invasion, n (%)				
Present	15 (30.0%)	16 (15.1%)	2.411 (1.077 to 5.394), 0.032	
Absent	35 (70.0%)	90 (84.9%)	Ref.	
Perineural invasion, n (%)				
Present	4 (8.0%)	3 (2.8%)	2.986 (0.642 to 13.881), 0.163	
Absent	46 (92.0%)	103 (97.2%)	Ref.	
Ulceration, n (%)				
Present	14 (28.0%)	29 (27.4%)	1.033 (0.487 to 2.187), 0.933	
Absent	36 (72.0%)	77 (72.6%)	Ref.	
Differentiation, n (%)				
Poor	17 (34.0%)	36 (34.0%)	1.002 (0.493 to 2.037), 0.996	
Well/moderate	33 (66.0%)	70 (66.0%)	Ref.	
Signet ring cells, n (%)				
Present	12 (24.0%)	26 (24.5%)	0.972 (0.443 to 2.131), 0.943	
Absent	38 (76.0%)	80 (75.5%)	Ref.	
Papillary component, n (%)				

Continued

Table 5 Continued

	Residual disease		Unadjusted OR (95% CI), P	Covariate adjusted OR (95% CI), P
	Yes	No		
Present	11 (22.0%)	17 (16.0%)	1.477 (0.633 to 3.443), 0.367	
Absent	39 (78.0%)	89 (84.0%)	Ref.	
Mucinous carcinoma, n (%)				
Present	2 (4.0%)	6 (5.7%)	0.694 (0.135 to 3.569), 0.662	
Absent	48 (96.0%)	100 (94.3%)	Ref.	

*Horizontal margins were evaluated in lesions removed *en-bloc* (n=130).

ESD, endoscopic submucosal dissection; HGD, high-grade dysplasia; HRR, high-risk resection; LGD, low-grade dysplasia; LNM, lymph node metastasis.

intermediate to low-risk group in four patients and high-risk to intermediate-risk in three patients. Of these seven downgraded patients, none had LNM: six had no evidence of residual disease in the surgical specimen (T0N0), and 1 (previous ESD with VM1 resection), had focal residual adenocarcinoma (T1N0) in the gastric wall.

The AUC-ROC of the W-eCura for LNM (0.916, 95% CI 0.870 to 0.961) was significantly higher compared with the original eCura (p value for the comparison between AUROCs=0.012); NRI index 0.681, 95% CI 0.309 to 1.053 (p<0.001); IDI 0.053 95% CI 0.026 to 0.081 (p<0.001)) (figure 3). The calibration plots of the eCura and W-eCura models are displayed in figure 4. Using a bootstrap strategy, the AUC-ROC for the eCura was of 0.900 (SE=0.025), while for the W-eCura, it was of 0.916 (SE=0.023), with a p value of 0.014 having been observed for the comparison between the AUC-ROCs. The p values for the Hosmer-Lemeshow test were of 0.206 for the eCura score and 0.237 for the W-eCura score, suggesting good calibration of the models.

There were no significant differences between groups regarding mortality, but cancer-related mortality and OS were significantly different among groups when the W-eCura was applied.

DISCUSSION

The NC-ESD project was created aiming to evaluate the risk factors for residual disease after an NC-ESD along the gastrointestinal tract,¹⁰ to better identify who would benefit from further treatment, due to the high rate of futile surgeries that is being observed in this group of patients. In this study, specifically analysing gastric NC-ESDs in a large multinational western cohort, we found that 68% of the patients who underwent surgery did not present residual lesion in the gastric wall or in the lymph nodes (T0N0). Also, we found that a new score (W-eCura), modified from the original eCura system, may potentially avoid some unnecessary surgeries.

Gastric ESD is well established as the first-line treatment for early gastric lesions with low risk of LNM, with curative resection rates between 80 and 90%.^{3 19 20} Patients with NC resection have higher risk of parietal residual lesion or LNM. Therefore, risk stratification would allow a better decision concerning surgery referral.

In recent years, studies from the East assessed risk factors for LNM and proposed a risk stratification tool (eCura) that was externally validated in the East.¹⁵ However, there is some debate regarding the different biological behaviour of Eastern and Western gastric cancers, and there are differences in pathological specimen handling and histopathological analysis between Eastern and Western pathologists.²¹⁻²³ This prompted the need to assess risk factors for LNM in Western populations and to validate the eCura scoring system in this setting.

We found that younger age, positive vertical margins (VM1) and lymphatic invasion were independently associated with parietal lesions, while SM invasion depth ≥ 1 mm, lymphatic invasion (presented in all cases of patients with LNM in the surgical specimen) and venous invasion were associated with LNM. The independent risk factors for the composite outcome of residual disease were piecemeal resection, SM invasion depth and lymphatic invasion. Our findings are in line with previous studies identifying similar risk factors for LNM/persistent disease.²⁴⁻²⁸

One of the goals of this study was to address the application of the eCura system in a Western population, with the inherent different baseline characteristics comparing to the cohort that was used to create the original score. We found that the eCura system is actually a valuable tool to stratify the risk of LNM in the West. Indeed, none of the patients in the low-risk eCura group had LNM, while this risk increased to 9% in the intermediate-risk group and to 53% in the high-risk group. This reinforces that this score can be used to stratify LNM risk and perform a more appropriate selection of patients for surgical treatment. The rates of LNM in our study were similar to the eCura studies in the low and intermediate-risk groups (0% vs 2.5% and 9.0%

Table 6 Rate of LNM, mortality and overall survival estimate according to the eCURA classification risk categories and the modified eCURA (W-eCura) in HRR operated patients (n=156)

	Low		Intermediate		High		P value	
	eCura (n=59)	W-eCura (n=63)	eCura (n=65)	W-eCura (n=64)	eCura (n=32)	W-eCura (n=29)	eCura	W-eCura
LNM, n (%)	0 (0)	0 (0)	6 (9.2)	6 (9.4)	17 (53.1)	17 (58.6%)	<0.001	<0.001
Mortality, n (%)	3 (5.1)	3 (4.8)	9 (13.8)	10 (15.6)	5 (15.6)	4 (13.8)	0.185	0.125
Cancer-related mortality	0 (0)	0 (0)	5 (7.7)	6 (9.4)	4 (12.5)	3 (10.3)	0.035	0.039
Overall survival estimate (mean $\pm$ SD), months	88 $\pm$ 3	88 $\pm$ 2	74 $\pm$ 5	73 $\pm$ 5	63 $\pm$ 7	61 $\pm$ 8	0.080	0.050

LNM, lymph node metastasis.

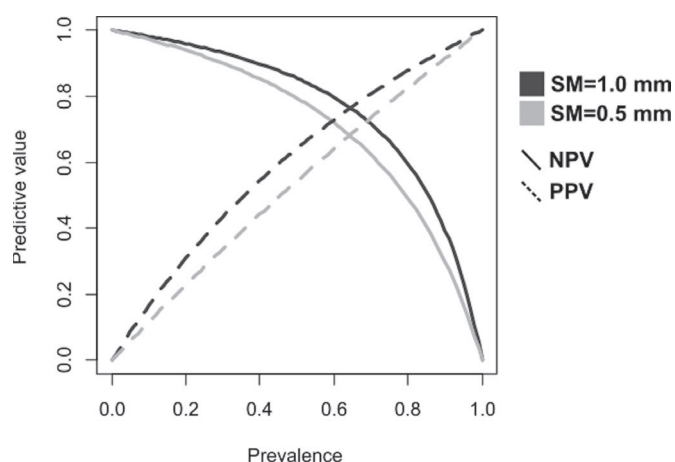


Figure 2 Comparison of the expected positive and negative predictive values (PPV and NPV) for the submucosal invasion cut-offs of 0.5 mm and 1 mm.

vs 6.7%), although we found an unexpectedly higher proportion of patients with LNM in the high-risk group (53.1% vs 22.7% in the eCura study). Adequate and timely lesion evaluation is mandatory before starting ESD.³ Western endoscopists' lesser experience in lesion assessment before ESD, as compared with Japanese endoscopists, in association with a later diagnosis of these lesions, may have led to an over-representation of higher risk patients among the high-risk group. A recently published multicentre study also suggested that Western practice involves more advanced lesions, with a quarter of patients being outside the new absolute indications for ESD.²⁹ Although this analysis was not performed in our study, this data support, to some extent, our findings. Differences in pathological specimen handling and histopathological analysis between Eastern and Western pathologists, as previously reported regarding the

higher rate of LNM for expanded criteria resections outside Japan,³⁰ may also explain these differences. Nevertheless, independently of the higher-than-expected rate of LNM in the high-risk group, our results validate and support the role of eCura in the multidisciplinary decision-making after a NC-ESD.

In our study, among HRR patients undergoing surgery, we identified an optimal cut-off of ≥ 1 mm for SM invasion depth (with a sensitivity of 92%, although with a specificity of 51%). In fact, among operated patients, only one patient with SM invasion depth < 1 mm had LNM in the surgical specimen (eCura high-risk lesion with lymphovascular invasion). Our results should be interpreted with caution, especially considering the short follow-up in our cohort and missing data regarding the exact extension of SM invasion in 28% of patients. Nevertheless, further investigation on which is the best cut-off point of SM invasion depth is mandatory to optimise risk stratification. Indeed, there is currently much debate in the colon regarding the prognostic significance of depth invasion in the absence of other adverse prognostic features and a recent meta-analysis found that invasion depth is not an independent risk factor for LNM.³¹ In gastric lesions, current evidence still advocates the cut-off of 0.5 mm as the one with prognostic value regarding the risk of LNM after an NC resection.³ However, considering our findings, we developed and analysed a modification of the eCura (W-eCura), using a cut-off of 1 mm for SM invasion. This implied a downstaging in the eCura group in seven patients (4.4% of the HRR-operated patients), and none of them presented LNM. More interesting, the W-eCura score displayed a higher accuracy than the original eCura. On the other hand, although a direct comparison was not performed, OS was significantly different among groups when the W-eCura was applied as opposed to eCura, in which no significant differences were observed between groups. Although prospective studies are necessary to validate these findings, our results suggest that in patients without other high-risk factors, the cut-off of SM invasion may be extended

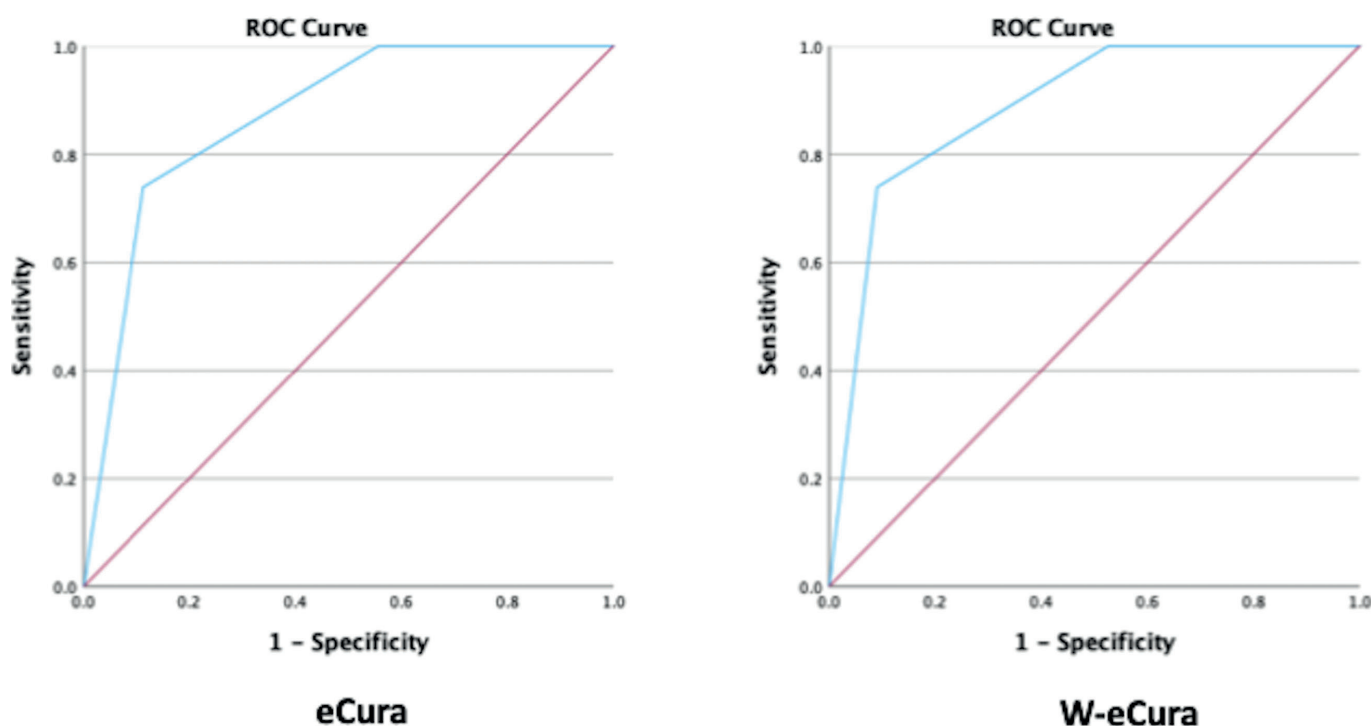


Figure 3 Comparison of AUC-ROC of eCura and W-eCura for LNM. AUC-ROC, areas under the receiver operating characteristic curve; LNM, lymph node metastasis.

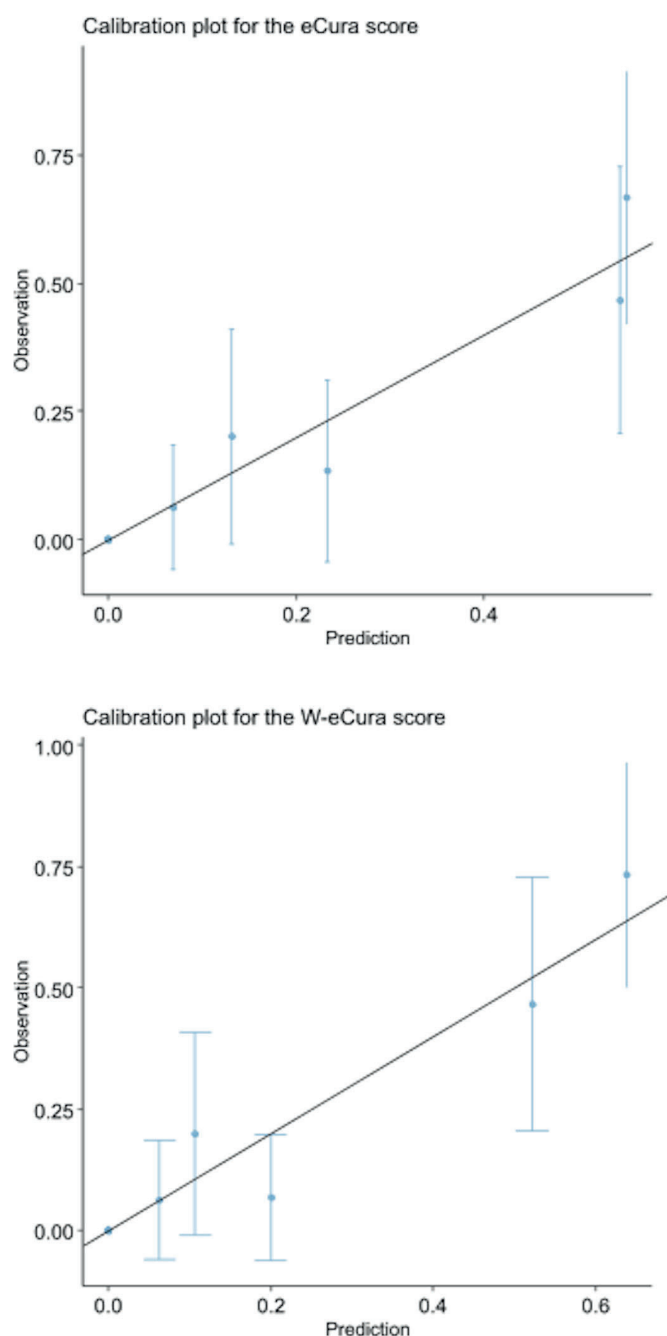


Figure 4 Calibration plots of the eCura and W-eCura models.

to 1 mm. This may have a positive impact, especially in high-risk surgical patients, by avoiding unnecessary surgeries (and maintaining a high sensitivity) and supporting the adoption of surveillance strategies in multidisciplinary discussions in a very difficult-to-treat and difficult-to-decide population.

Regarding patients with local risk resection, we found that most are adequately treated without surgery, with further resection in case of recurrence. The follow-up time of our study was adequate to evaluate this outcome, according to the literature.³²

Our study has some limitations. The retrospective design did not allow further analysis of some variables that may influence the risk of LNM, such as the width of SM invasion, due to the presence of missing data in a significant proportion of cases. Nevertheless, all included patients had information on the main prognostic variables given that participating centres

had a pathological standardised report with adequate margins, lymphatic invasion, vascular invasion and tumour size assessment. Furthermore, all participating centres had a prospective ESD registry minimising the risk of selection and information biases associated with retrospective studies. Nevertheless, it is important to address the potential selection bias, especially regarding undifferentiated early-gastric lesions. Undifferentiated early-gastric cancer accounts for 35%–40% of early-gastric cancer,^{33–34} and it is reported to lead to a higher incidence of LNM. In our study, the prevalence of undifferentiated cancers was lower than that reported in the literature. These lesions may also be underestimated by the eCura system: in the development and validation cohort of the original eCura only few undifferentiated early-gastric cancer cases were observed (13.6% and 16.1%, respectively).¹⁵ Other studies suggested that the validity of the eCura system must be confirmed or a new scoring system for undifferentiated early-gastric cancer must be developed.^{16–35}

Similarly, that is also a limitation in our study, and our new system should also be mainly applied to differentiated cancers. Also, although the number of included patients is high for a Western setting, our sample size is smaller than that used in the development and validation cohort of the eCura scoring system. This impaired the de novo derivation of a new scoring system (independent of the eCura) assessing the prognosis of Western patients with LNM. However, our results strongly suggest that the eCura scoring system is also applicable in the West, with higher accuracy by changing one of the criteria, and we present the CIs for the eCura validation. Finally, the relatively short follow-up time did not allow us to adequately validate the prognostic value of eCura regarding cancer-specific mortality (we also used overall mortality and OS as a surrogate due to the low number of cases) and cancer recurrence.

In conclusion, our study represents the largest Western series on NC gastric ESD. The eCura scoring system may also be applied in Western countries to stratify the risk of LNM, but we propose a variation, the W-eCura score, that should now be externally validated in prospective studies. Also, we found positive VM, lymphatic invasion and age independently associated with parietal lesion in HRR patients, which may also be important factors in the selection of patients to gastrectomy.

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Acknowledgements Authors would like to thank Beatriz Peñas García, Sofia Parejo and Sofia Pedrosa.

Contributors RM and DL wrote the first draft of the manuscript and performed data collection and statistical analysis. MDR, MB, AL, PP-N, FB, IG, FC and GM performed interpretation of data and revised for intellectual content. AF, PB, SG, PA, RKM, PC, PB-C, RP, SS, MF, MP, FG, EA, FR-Z, HU, AW, MM, MG, AM, EGS, SX, IF-R performed data acquisition and revised for intellectual content. ERdS performed data acquisition, statistical analysis and revised for intellectual content. BS-P performed statistical analysis and revised for intellectual content. JS-A created, designed and coordinated the study, performed data collection and wrote the final manuscript, being the guarantor of the study. All authors contributed to the writing and approved the final version of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The Ethics Board from the coordinating centre (Centro Hospitalar Universitário São João, Porto, Portugal) approved the study (reference number 255/2020), with clinicaltrials.gov identifier NCT04484311.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. Gathered data from all the participating centers are available upon reasonable request by contacting the corresponding author.

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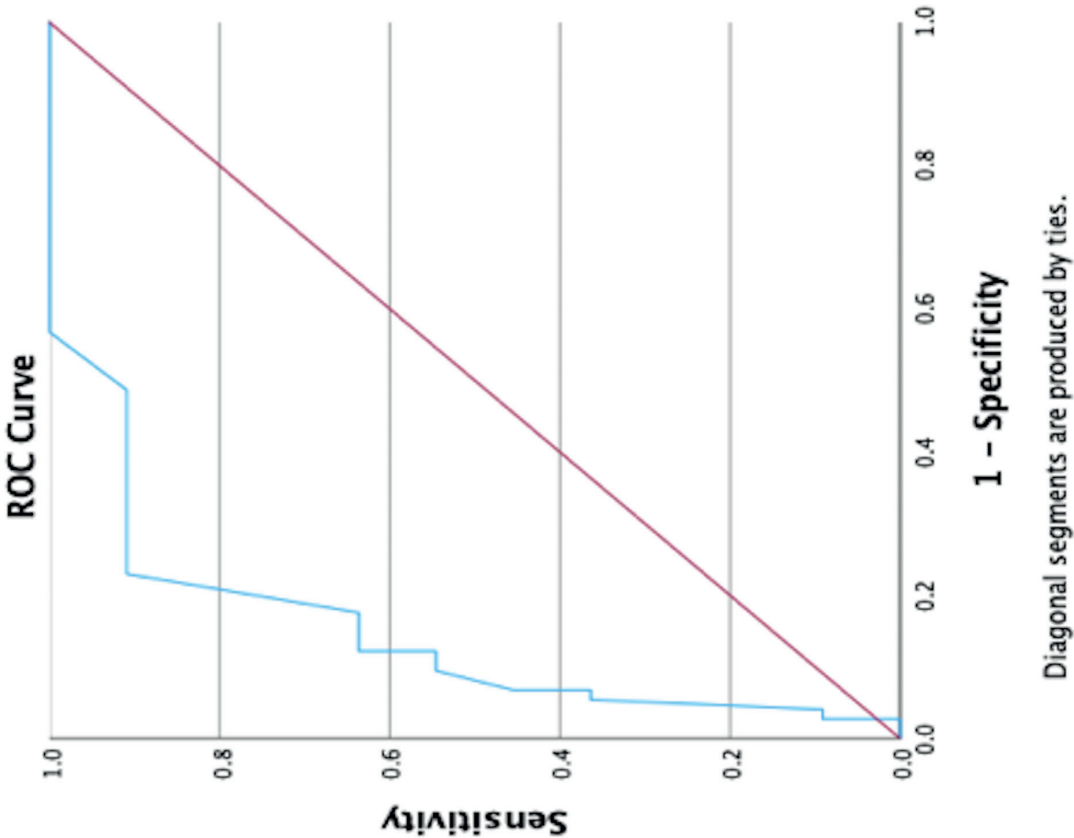
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Supplementary table 1. Risk factors for parietal residual lesion in the ESD site among LocRR patients (n=89)

	Parietal residual lesion		
	Yes	No	Unadjusted OR (95% CI), p*
	Demographics		
Gender, n (%)			
Female	6 (27.3%)	29 (43.3%)	Ref.
Male	16 (72.7%)	38 (56.7%)	2.035 (0.708-5.847), 0.187
Age, median (IQR), years	78 (68-81)	74 (70-82)	1.004 (0.953-1.057), 0.878
	Lesion characteristics		
Paris Classification, n (%)			
Polypoid	1 (4.5%)	12 (17.9%)	Ref.
Non-polypoid, non-depressed	11 (50.0%)	26 (38.8%)	5.077 (0.586-43.951), 0.140
Depressed	10 (45.5%)	29 (43.3%)	4.138 (0.476-35.985), 0.198
Lesion size, median (IQR), mm	30 (10-40)	22 (15-33)	1.016 (0.986-1.047), 0.292
	ESD procedure/Histopathological analysis		
Complementary techniques, n (%)			
Yes	5 (22.7%)	19 (28.4%)	0.743 (0.240-2.300), 0.606
No	17 (77.3%)	48 (71.6%)	Ref.
LocRR criteria, n (%)			
En-bloc HM1 resection*	15 (68.2%)	37 (55.2%)	1.737 (0.628-4.810), 0.288
Piecemeal	7 (31.8%)	30 (44.8%)	Ref.

LocRR: local-risk resection, IQR: interquartile range, ESD: endoscopic submucosal dissection, LGD: low-grade dysplasia, HGD: high-grade dysplasia, HM: horizontal margin

* Since in patients with residual lesion no cases of HM0 were observed in the “Horizontal margins” variable, univariate logistic regression and subsequently multivariate logistic regression analysis were not performed

* Horizontal margins were evaluated in lesions removed en-bloc (n=52)

7. Discussion

A detailed discussion of each study is provided within the manuscript documents, in the Results section. An integrated discussion of the main findings of the studies performed is presented below, along with a summary of their limitations, strengths and future perspectives regarding clinical applicability and impact in the current practice.

7.1. Improving screening of upper GI neoplasia

The applicability and cost-effectiveness of endoscopic screening strategies for upper GI neoplasia in Western settings is still an open field for research. This could be explained by the relatively low incidence of ESCC and GC in most Western countries, with most of the studies focusing on endoscopic surveillance of BE (4). Interestingly, a cost-utility study from 2011 by Neil G *et al* showed that, in the Western world, extending the screening for ESCC to Barrett's-associated EAC and GC (by performing a single EGD at the time of screening colonoscopy) might be a cost-effective method to screen for multiple cancers simultaneously, with an incremental cost-effectiveness ratio comparing favorably with commonly performed screening strategies for other cancers (268). Nevertheless, what we see in our current clinical practice, specifically in Europe, is distant from what is recommended in the guidelines. Starting with ESCC, most of the European countries have not routinely implemented endoscopic screening programs in high-risk populations such as patients with HNN or achalasia. In addition, the cost-effectiveness of these approaches remains to be evaluated. Regarding GC, both ESGE guidelines and the Council of the European Union have recommended the implementation of GC screening programs in countries or regions with intermediate-high incidence (4, 269). Nevertheless, no organized GC screening programs have been launched in the European Union yet (65). Several pilot studies are currently ongoing, such as the TOGAS project (Towards Gastric Cancer Screening Implementation in the European Union), designed to evaluate the effectiveness of various strategies for reducing GC mortality in European Union countries; this study will potentially provide policymakers with evidence to incorporate GC screening into

healthcare priorities, considering not only effectiveness, but also feasibility, acceptability and potential long-term consequences (65). In Portugal, although the cost-effectiveness of performing GC screening concurrently with CRC screening colonoscopy has been established (162), its nationwide implementation remains pending. Moreover, in contrast to colonoscopy, EGD with sedation is not yet reimbursed by the Portuguese Government.

Therefore, there is still a long road ahead for global implementation of endoscopic screening strategies in the Western countries and, more particularly, in Portugal. Thus, one of the main objectives of this thesis was to readily identify subgroups of patients that would conceptually benefit from “opportunistic” screening strategies for upper GI neoplasia. Three subgroups were pointed out and analyzed, based on the current body of literature and clinical experience: i) asymptomatic patients proposed for EGD at the same time as screening colonoscopy for CRC; ii) patients with cACLD proposed for EGD for GOEV screening; iii) patients with newly diagnosed HNN. We focused specifically on the epidemiological setting of Portugal that, as previously discussed, presents unique characteristics compared to most European countries, namely the intermediate to high incidence of GC.

In Study 1, we evaluated the frequency of GN in all asymptomatic cACLD patients who underwent EGD for GOEV screening during a ten-year period (2008-2018) in a tertiary referral center in Porto, Portugal (270). These patients were compared with asymptomatic healthy individuals who underwent EGD for GC screening at the same time as of colonoscopy performed for CRC screening, during a one-year period (2017-2018) in a private hospital setting. We found a 4-times higher frequency of GN in patients with cACLD compared to those without this condition. This difference was observed even after adjustment to demographic (such as age, sex and family history of GC) and clinical variables (namely Hp status and gastritis staging). Interestingly, 36.8% of GN cases in the cACLD cohort were diagnosed in patients who, according to the Baveno VII criteria, would have not been submitted to EGD. Two other findings of our study were that (i) rare histopathological subtypes accounted for 28.7% of gastric carcinoma cases in the cACLD cohort, and that (ii) over half of the gastric adenocarcinoma cases were diagnosed in patients without ALD. This suggests that

other factors beyond the etiology of ACLD, such as liver cirrhosis-associated immune dysfunction, may contribute to an increased risk of GN in this population.

In the past years, a significant effort has been made with the Baveno VI and Baveno VII criteria to assess the risk of GOEV noninvasively, in order to avoid unnecessary EGDs (while maintaining a very high sensitivity). This is particularly relevant not only taking into consideration the planetary health impact of endoscopic practice (as previously highlighted in a study by Ribeiro T *et al*) (271), but also the associated costs: a recently published study by Pizzo *et al* demonstrated that the Baveno VI criteria compared to generalized EGD are cost-effective and should be considered for widespread implementation on the basis of safety, appropriateness and economic grounds (272). However, this analysis was performed from the UK National Health Service perspective and then repeated for Canada and Spain (all of them countries with low incidence of GC). This motivated a letter to the Editor by our group, alerting that some points should be addressed before a widespread implementation of the Baveno VI criteria, namely regarding the potential for opportunistic upper GI neoplasia detection with EGD (273). The authors from the original article briefly addressed this question, stating that the Baveno VI criteria can result in missing GEN detection, particularly in patients at higher risk, such as those with ALD.

In Study 1, despite being lower than in the cACLD cohort, the frequency of GC among asymptomatic healthy individuals was still considerable (1%). While the cost-effectiveness of a screening strategy by EGD at the same time as first screening colonoscopy has already been demonstrated in Portugal (162), to our knowledge no previous study evaluated its clinical impact in a real-life scenario. The results of our study support not only the benefits of screening EGD in the general population but also that continuing to perform EGD in patients with cACLD may be beneficial, at least in countries with intermediate-high incidence of GC such as Portugal. Patients with Child-Pugh A cirrhosis are the ones that will mostly benefit from an early detection of GC, considering the safety and efficacy of ER techniques (including EMR and ESD) in this population; previous studies reported similar rates of technical and clinical success, and of AEs, as compared to the general population (274-277).

In Study 2, we conducted a prospective single-center study that evaluated an endoscopic screening program for EN and GN in patients diagnosed with HNN, in a tertiary referral center. A collaboration protocol was established with the Otorhinolaryngology and Head and Neck Surgery Department in 2020 and all patients with newly diagnosed HNN were started to be referred to a Gastroenterology consultation, for evaluation for screening EGD.

Several Asian studies had previously evaluated the diagnosis and management of EN in this population, with a recent systematic review and meta-analysis showing a prevalence of EN of 15% among HNN patients submitted to screening EGD with chromoendoscopy (278). However, most European countries have not implemented routine endoscopic screening in patients with HNN. In fact, over the last ten years, only one study from the Netherlands described an organized endoscopic screening program in this population (36). Conceptually, endoscopic screening in patients with HNN can potentially lead to the detection of EN in early stages amenable to ER (279, 280). This is particularly relevant considering that, in the absence of screening strategies, secondary EN in patients with HNN are often diagnosed at advanced stages, potentially impacting patient survival even more significantly than the primary HNN (281-283). Therefore, the potential reasons for the lack of implementation of endoscopic screening programs in patients with HNN in the Western setting should be addressed. Such reasons included the uncertainty of the applicability of the results from Asian studies due to differences in the incidence of HNN and EN. Secondly, when considering the criteria of Wilson and Jungner to assess the appropriateness of population-based screening (284), it is questionable whether the criteria for acceptable treatment can be met in this population in the Western setting. It should not be forgotten that HNN are many times diagnosed at advanced stages and even when submitted to treatment with curative intent, the risk of mortality in the follow-up is significant (279, 285). This is a consequence not only of the baseline HNN but also of other risk factors, such as (i) the development of second primary tumors other than EN, (ii) the presence of significant comorbidities, or (iii) unfavorable social-economic conditions (which in fact was evident in our study, with many refusing to perform screening EGD or refusing to be enrolled in metachronous screening). While we were not able to address all these barriers, we evaluated the cost-effectiveness of such an

endoscopic screening in the Western setting. We defined strict inclusion and exclusion criteria (namely by only including patients after or proposed to treatment with curative intent) in order to account, to some extent, for the previously referred issues and difficulties. In the main analysis, we observed a large overall frequency of EN and GN (21.7%), with most cases being identified at early stages amenable to ER. While the frequency of EN was consistent with what has been reported in recent Western studies (10.9%) (286), the frequency of GN was unexpectedly high (10.9%). Most previous studies on this topic have focused exclusively on EN, and in the few that also addressed GN, reported frequency rates ranged only from 0.5 to 1.8% (36, 170, 287). Our findings suggest that, particularly in a country with intermediate-high incidence of GC such as Portugal, the clinical impact of EGD screening in patients with HNN may be increased by the simultaneous screening for two high-risk neoplasias (EN and GN). The health economic analysis confirmed that such endoscopic screening strategy is cost-effective in Portugal. Although many questions remain regarding the timing, frequency and logistical implementation of the endoscopic screening strategy, these results pave the way for its implementation in all reference centers in Portugal.

7.2. Improving therapeutic management of upper GI neoplasia

ESD is now established in the Western setting as the first-line therapy in the endoscopic management of early EN and GN due to its efficacy, safety and favorable oncological and quality of life-related outcomes (184).

Nevertheless, regarding SNADETs, many questions remain regarding the most appropriate ER technique. In fact, the potential benefits of ESD in the duodenum (namely higher rates of *en-bloc* resection and low rates of recurrence in the follow-up) are associated with significant drawbacks, namely a very high incidence of AEs, with perforation rates between 13-50% even in expert centers (117). Most of the older published series come from Asian centers (with *en-bloc* resection rates higher than 90%) (288) but there is also limited evidence on duodenal ESD from Europe. The largest series to date reported an *en-bloc* resection rate of 29.7% with a 14.7% recurrence rate (289). A recent systematic review and meta-analysis by the Royal Free Unit for

Endoscopy (London, UK) evaluated the efficacy and safety of ESD in the management of duodenal nonampullary lesions. Analysis of 54 studies including 3672 procedures showed an *en-bloc* resection rate of 98.1% (95% CI=96.2-99.1), R0 resection rate of 86.3% (95% CI=82.0-89.7), intraoperative perforation rate of 8.5% (95% CI=6.4-11.2) and delayed perforation rate of 2.0% (95% CI=1.3-3.1) (290). Low recurrence and mortality were observed. While these are promising results, it is important to note that most of the data comes from ultra-specialized expert centers in Asia, and the applicability of these results in the Western setting requires further evaluation. Therefore, other alternatives to ESD and C-EMR are being considered, as alternatives in the therapeutic armamentarium of SNADETs.

In Study 3, we conducted a retrospective multicenter study (10 European centers) that compared the efficacy and safety of U-EMR versus C-EMR in the management of SNADETs (291). This was the first study addressing this question in the Western setting. We found that, after adjustment for potential confounders, U-EMR was associated with a lower rate of AEs and recurrence. More interestingly, these results were confirmed in the sensitivity analysis for lesions >20 mm.

Recently, cold-snare endoscopic mucosal resection (CS-EMR) was proposed as an alternative in the management of these lesions. A retrospective study comparing CS-EMR versus C-EMR for large SNADETs showed a significantly lower rate of AEs (bleeding and perforation) in the CS-EMR group (including no cases of perforation), with comparable recurrence rate (292). These results were confirmed in a recently published meta-analysis (293). A subsequent multicenter study from the USA reported a recurrence rate of 31.5%, with AEs occurring in 3.9% of cases (294). These data show that CS-EMR is a safe technique, at the cost of a significant rate of recurrence. To date, only a recent Japanese study compared CS-EMR versus U-EMR for the management of small (≤ 12 mm) SNADETs (295). Only immediate outcomes were analyzed, with U-EMR showing superior vertical resectability compared to CS-EMR. On the other hand, CS-EMR had shorter procedure time and fewer bleeding events. While further comparative studies are unquestionably necessary, particularly with CS-EMR for large lesions, our study has shown that U-EMR is a valid and effective technique in the endoscopic management of SNADETs.

7.3. Improving long-term management of upper GI neoplasia

As demonstrated in Study 1 and 2, accurate patient selection for endoscopic screening can lead to early detection of upper GI neoplasia, in a state still amenable to ER (270). The choice of endoscopic technique is also of paramount importance to optimize patient's outcomes. Nevertheless, even after an uneventful ESD it can be NC in a significant proportion of cases (up to 36% in EN and 20% in GN) (191, 220, 240, 243, 296). While these patients should be referred for additional treatment (namely surgical resection), many do not present residual lesion (either LNM or local residual lesion) in the surgical specimen (210). This emphasizes not only the need to improve clinical staging and patient selection for ER but also to refine the criteria determining the need for additional treatment in the event of a NC-ESD (237).

In Study 4, we conducted a multicenter retrospective study (19 Western centers) that aimed to validate, in the Western setting, the eCura criteria after a NC-gastric ESD, in an effort to avoid unnecessary surgeries (297). We confirmed that the eCura system can serve as a valuable tool to stratify the risk of LNM in our population, despite its baseline characteristics differing from those of the Asian cohort used to develop the original scoring system. Notably, the area under the curve (AUC) in our study was superior to the original eCura study (0.900 vs. 0.74) (191). Based on the analysis obtained in this cohort, we proposed a modification of the original eCura score: the W-eCura. The W-eCura showed a higher accuracy (albeit minimal) than the original eCura system, while maintaining a very high sensitivity. This highlights the potential benefit of this score, particularly in high-risk surgical patients in whom a careful and thoughtful decision should be taken. Our study motivated a letter to the Editor from the authors of original eCura score (298). In this letter, the need for further validation in an external cohort was underscored. As stated in our letter of response (299), a validation study with an external cohort is warranted to assess the real differences between the two systems, and which could fit better in Western and Asian cohorts. In an optimal setting, the study should involve either Western and Asian centers and include a centralized and standard evaluation of the ESD specimens by expert pathologists. This would minimize the differences in specimen handling and

histopathological analysis (239) that may contribute to the significant differences observed in the discriminative ability of the scores in the two studies. On the other hand, a significant effort is needed for further refinement of risk stratification. This may involve a future use of liquid biopsy: recently, risk stratification consisting of transcriptomic panel and pathological factors for predicting LNM in T1 CRC has been developed, demonstrating an AUC of 0.90 (300). Some other tools have been developed, namely nomograms to predict not only the preprocedural risk of needing further gastrectomy, considering morphological, histological and imaging features of the ESD target lesion, but also postprocedural features, to predict the rate of LNM; the use of Artificial Intelligence (AI) systems has also been reported (301, 302). Other alternatives under investigation include: i) the combination of ESD with laparoscopic lymph node dissection to potentially avoid gastrectomy (303); ii) sentinel node biopsy (304-306).

Another important point that should be discussed, also highlighted in the letter to the Editor by the creators of eCura, is the growing evidence suggesting that high-risk resections with low-risk eCura category could be reclassified as very low or low-risk resections (curative), particularly in elderly patients and those with severe comorbidities. In our study, no LNM were detected in the low-risk category of both eCura and W-eCura, which supports these assumptions. Nevertheless, in our study, the number of patients in this subgroup was low and these results should be interpreted cautiously. Two recent studies (one from Australia and one from Japan) confirmed the safety and efficacy of ESD on elderly patients with EGC, even in those with only relative indication for ESD (307, 308). Our study highlights the growing role of ER in the management of EGC with expanded criteria and may help to avoid significant morbidity associated with unnecessary surgeries.

After a successful ESD, long-term follow-up with annual EGD is necessary not only due to the risk of local recurrence but particularly due to the risk of metachronous lesions (244, 247, 309). In this regard, a recent multicenter study is ongoing, with the objective to externally validate the FAMISH Score (unpublished data). Preliminary data showed that the FAMISH risk score achieved a fair diagnostic accuracy with an AUC of 0.618 at 3 years of follow-up and of 0.597 at five years of follow-up. This score may be

a useful tool to identify patients with low risk for metachronous lesions, possibly allowing to safely extend surveillance intervals and reduce the burden of care.

8. Limitations, strengths and clinical implications

This thesis has several limitations that should be acknowledged. First, three out of the four studies are retrospective, so that there was missing information for some key variables. This limitation restricted the scope of further analyses.

A selection bias was also evident in all studies, since, even in those that were multicenter, only tertiary referral centers were included. While this is a consequence of our current clinical practice, this may limit the generalizability of our results. It is important to note that particularly the studies that aimed to improve screening of upper GI neoplasia (Study 1 and 2) were performed in Portugal, a country with very specific epidemiological characteristics compared to most European countries, namely regarding the incidence of GC. This may limit the generalization of the results to other European countries. Nevertheless, an effort was made to increase the generalizability of our finding: for example, in Study 2, in the cost-utility analysis, a probabilistic sensitivity analysis using data on prevalence of EN among HNN patients in studies from 4 other Western countries (the Netherlands, Brazil, Germany and France) was performed.

This thesis has also several strengths. First, two of the studies were multicentric involving very important reference Western centers, which supports the clinical applicability of the findings. On the other hand, all the studies bring innovative and clinically relevant insights on significant gaps of knowledge in the current body of the literature:

- Study 1 was the first study to compare the frequency of GN in cACLD patients compared to healthy individuals.
- Study 2 was the first to analyze the cost-utility of endoscopic screening in HNN in the Western setting.
- Study 3 was the first Western study to compare U-EMR with C-EMR for the management of SNADETs. It is also one of the largest series on this topic.

- Study 4 was the first to assess the adequacy of eCura in the Western setting. It also represents the largest Western cohort in NC gastric ESD.

In all studies, the main endpoints were clinical. Nevertheless, whenever possible, a clinical-histopathological correlation was established. In fact, this collaboration is of paramount importance and may have significant clinical implications. In Study 1, a thorough histopathological characterization of the GN in cACLD patients was performed and gave us further insights into the unexpected high incidence of GN in this population. In Study 2, a detailed histopathological characterization of the detected GEN and matched HNN was performed, with evaluation of biomarkers of viral infections. The underlying results confirmed that viral infections play a limited role in the field cancerization phenomenon that initiate synchronous GEN. This could potentially influence patient selection for endoscopic screening. For example, in a patient with an HPV-associated HNN who is a non-smoker and does not consume alcohol, endoscopic screening is likely unwarranted. Finally, a recently published study that is related with this PhD thesis (see Appendix – other related outputs) is a primer example of the importance and potential impact of a close correlation between clinical and histopathological data (310). In this study, a complete characterization of gastric polyps in patients with FAP was performed in a series of Portuguese patients and showed a high prevalence of intestinal-type gastric adenomas, comparable to Asian cohorts, in probable relation to the high prevalence of Hp infection in the Portuguese population. These specific lesions were larger (>7 mm), occurred predominantly in the distal stomach and in patients with gastric IM and duodenal adenomas. These findings may have a significant clinical impact in patients with FAP in Portugal, tailoring the endoscopic follow-up and therapeutic management in these patients.

Even in the short-term, the works developed in this thesis can have significant clinical implications. Regarding screening of upper GI neoplasia, at least in Portugal and other European countries with intermediate-high incidence of GC, continuing to perform EGD in patients with cACLD should be considered, instead of a non-invasive approach for evaluation of GOEV. Our evidence also supports the implementation of a nationwide endoscopic screening program for EN in patients with HNN (with strict inclusion and exclusion criteria) in Portugal, with these recommendations probably being applicable to most middle-high income European countries. Regarding the

therapeutic management of SNADETs, U-EMR is an effective and safe alternative to C-EMR, and should be considered, particularly in expert centers with experience in the technique. Finally, eCura and W-eCura can be useful tools in the decision-making after a NC gastric ESD in the Western setting. Their utility may be more pronounced in older patients or those with significant comorbidities.

9. Future perspectives

After the work developed in this thesis, many open questions remain and should be addressed in the medium and long-term, highlighting the continuous effort from our team and Department to improve the diagnosis, management of upper GI neoplasia.

Regarding the screening of upper GI neoplasia, an accurate identification of which individuals of the asymptomatic individuals who may benefit from screening assumes a fundamental role. However, precise diagnostic risk stratification tools are still needed, possibly based on a combination of demographic features, family history and serology (63). For example, of great promise is the development of next-generation sequencing-based tests to risk stratify affected mucosa at highest risk for GC progression, as well as molecular risk stratification through genomic, epigenomic, or transcriptomic profiling (63, 311). The potential role of AI in this setting should not be underestimated, with recent studies using both machine learning and deep learning models having shown the potential of this technology in the identification of high-risk patients that could benefit from endoscopic screening and surveillance (312, 313). Nevertheless, these technologies require further validation and assessment of their effectiveness, so that they will probably not be readily available in daily clinical practice in the near future.

Regarding endoscopic screening of patients with cACLD, further studies should focus on the evaluation of the cost-effectiveness analysis of the Baveno criteria in European countries with intermediate-high risk of GC (such as Portugal, Lithuania, Romania, or Slovenia). A sensitivity analysis could take into consideration the significantly higher prevalence of GN in this population and the potential benefits of early detection. Identification of additional risk factors for GC in these patients (other than the etiology of cirrhosis) seems of paramount importance, as it may lead to a tailored selection of those who really benefit from an invasive and simultaneous screening for both GOEVs and upper GI neoplasia. Taking these factors into consideration, a new project from our team is ongoing that aims to perform a health economic analysis to evaluate the cost-utility of the Baveno VII criteria compared to screening EGD in European countries with intermediate-high risk of GC.

Regarding the therapeutic management of upper GI neoplasia, this thesis focused only on epithelial lesions. Nevertheless, many questions remain regarding the best therapeutic approach and long-term outcomes of gastroduodenal neuroendocrine tumors (314). In this context, we are conducting a multinational project (including at the end of data collection 445 patients from 24 Western centers) to characterize the endoscopic techniques used and outcomes after resection of gastroduodenal neuroendocrine tumors in the last ten years.

Currently, there is no evaluation system for NC esophageal ESD. With the NC-ESD project, we are now aiming to evaluate the frequency of residual disease and outcomes after a NC ESD for ESCC (226). If possible, drawing on the eCura and W-eCura models, it is our objective to design and validate a tool to evaluate the risk of LNM and residual disease after NC esophageal ESD, in order to better select patients who are more likely to benefit from salvage surgery or other additional treatments.

Current guidelines only take into consideration the lesion size or if it causes symptoms in the decision to resect a hyperplastic gastric polyp (315, 316). Another ongoing multicenter project (including 782 cases from 8 centers from Portugal) aims at evaluating the frequency and risk factors for malignant transformation of gastric hyperplastic polyps. With this study, we seek to identify novel risk factors that may contribute to the development of GN within the gastric hyperplastic polyp or as a metachronous lesion in the follow-up. This may improve ER technique selection and further surveillance in patients with these lesions.

The healing process of the post-ESD defect is still not well understood. The majority of patients that undergo curative *en-bloc* endoscopic resection of GN usually develop homogeneous and flat epithelized scar covered by a regular-appearing mucosa with correspondent fibrosis. However, not infrequently, certain patients can develop aberrant and protuberant polypoid nodules in the post-ESD scar (317). This may have direct clinical implications because it may render evaluation of post-ESD neoplastic recurrence difficult. In the original project of this thesis, an AI project was intended, with the objective of developing a convolutional neural network based on images of the scar to predict the presence of residual lesion after gastric ESD. Currently, images and video collection are being performed. The very low rate of local recurrence after

gastric ESD (318) in association with the need for a very high number of images/videos is the explanation behind the need for more time before an AI model can be designed. Nevertheless, if this model shows good accuracy, its impact may be significant not only for a clinical standpoint but also from an economic and environmental perspective (by obviating the need for biopsies of the scar or unnecessary ER procedures).

In the long-term, it is important to note that the endoscopic screening program in patients with HNN is still ongoing at our Department, and it is our objective to re-analyze the data in 5 years. Further studies could focus on optimizing patient selection, evaluating the long-term clinical impact of screening, and the cost-effectiveness of alternative strategies, such as metachronous or one-time screening.

Finally, in the future, it would be relevant to conduct a multicenter Western-Asian study with the objective to further validate the W-eCura, with centralized evaluation both by Western and Japanese pathologists. This would further support the generalized use of this score for patient selection for additional treatment after a NC gastric ESD.

The complete list of the ongoing projects I am currently participating as a main author/coordinator is present in Table 2.

Table 2. Future research

ONGOING PROJECTS	STUDY TYPE
Cost-utility of endoscopy versus the Baveno VII criteria for gastroesophageal varices screening in a country with intermediate-high incidence of gastric cancer	Health economic analysis
Endoscopic management of gastroduodenal neuroendocrine neoplasms – clinical outcomes and prognostic factors	Retrospective multicenter study (Europe and Australia)
Risk of residual neoplasia after a noncurative esophageal endoscopic submucosal dissection	Retrospective multicenter study (Europe and Australia)
Frequency and risk factors for malignant evolution of gastric hyperplastic polyps in a country with an intermediate-high risk for gastric cancer	Retrospective multicenter study (Portugal)
Role of artificial intelligence in the scar evaluation after endoscopic submucosal dissection of early gastric cancer	Prospective single-center study

10. Conclusions

This thesis aimed at improving the diagnosis, endoscopic management and long-term outcomes after ER of upper GI neoplasia. We demonstrated that:

- There is a large frequency of GN among healthy individuals who undergo colonoscopy in Portugal. We have found evidence supporting the adoption of concurrent EGD and colonoscopy in Portugal.
- In Portugal, EGD should continue to be the first-line screening method for GOEV in cACLD patients, due to the high frequency of GN in this population.
- Screening for EN in HNN patients is cost-effective in Portugal.
- U-EMR is a safe and effective alternative to C-EMR in the management of SNADETs.
- eCura is applicable in the Western setting for risk stratification after a NC gastric ESD. The W-eCura is a promising tool, potentially with higher accuracy than eCura. It can help in the decision making for risk stratification, particularly in elder patients or those with significant comorbidities.

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12. Appendices

12.1. Other PhD related outputs

12.1.1 Original research articles

Study 1

Gastric Polyps in Familial Adenomatous Polyposis Portuguese Patients: The First Western Cohort with Asian Features.

12.1.2 Letters to the editor

Study 2

Screening Endoscopy in Patients With Advanced Chronic Liver Disease - Is It All About Varices?

Study 3

NC-ESD Study Group. eCura and W-eCura: different scores, different populations, same goal

Study 1

Gastric Polyps in Familial Adenomatous Polyposis Portuguese Patients: The First Western Cohort with Asian Features

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Pathobiology. 2024;91(3):196-204

DOI: 10.1159/000534571

Epub 2023 Oct 18. PMID: 37852192

Cited by 2 articles

(Google Scholar, 2025, April 24)

Impact factor 3.5

(Thomson-Reuters, 2023)

Rank 27 of 206 on Pathology journals (Q2)

(Scimago Journal & Country Rank, 2023)

Gastric Polyps in Familial Adenomatous Polyposis Portuguese Patients: The First Western Cohort with Asian Features

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Keywords

Familial adenomatous polyposis · Gastric polyps · Gastric cancer · *Helicobacter pylori*

Abstract

Introduction: Chronic atrophic gastritis may contribute to gastric polyps (GP) phenotype in familial adenomatous polyposis (FAP). Considering the high prevalence of *Helicobacter pylori* (HP) infection in Portugal, we aim to characterize GP in a series of Portuguese patients. **Methods:** In a retrospectively selected series of 53 FAP patients, clinical data and histopathological features of GP and background gastric mucosa were studied. SPSS (27.0) was used for statistical analysis. **Results:** Thirteen patients (24.5%) developed fundic gland polyps (FGP), seven (13.2%) gastric adenomas (GA), and ten (18.9%) both FGP and GA. Out of 100 GP, four were hyperplastic polyps, 58 FGP (24 with dysplasia), 35 intestinal-type GA (intGA), and three foveolar-type GA (fovGA). IntGA were larger (60% >7 mm, $p = 0.03$), occurred predominantly in the distal stomach (66.7%, $p = 0.024$), in patients harboring gastric in-

testinal metaplasia (IM) (86.7%, $p < 0.001$), and duodenal adenomas (86.7%, $p < 0.001$). **Conclusion:** This is the first Western series showing high prevalence of intGA in FAP patients, comparable to Asian cohorts. HP infection and chronic atrophic gastritis/intestinal metaplasia are likely responsible for this difference, with risk of neoplastic transformation and management implications. Biopsy/excision of GP >7 mm in the distal stomach and in patients harboring gastric intestinal metaplasia/duodenal adenomas should be considered.

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Introduction

Familial adenomatous polyposis (FAP) is a rare autosomal dominant inherited syndrome associated with germline variants in the adenomatous polyposis coli (*APC*) gene, with the clinical phenotype of colorectal

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adenomatous polyps (CAP) in all patients [1]. This condition poses a high risk of progression to colorectal adenocarcinoma, ultimately leading to prophylactic colectomy as the standardized treatment option [2]. According to the clinicopathological phenotype, FAP patients can be classified into classic FAP, attenuated FAP, and profuse FAP, if presenting above 100 CAP, below 100 CAP, or above 5,000 CAP, respectively [3].

Duodenal adenomas (DA) are the most common extracolonic manifestation of this cancer predisposition syndrome, affecting up to 90% of FAP patients worldwide [4]. As these polyps may progress to duodenal carcinoma (5%) [5], endoscopic excision is recommended. According to the most recent clinical guidelines, the surveillance interval for upper GI endoscopy should be based on the duodenal phenotype, according to the Spigelman Classification [6].

Gastric polyps, also an important extracolonic manifestation, occur in 50–90% of patients [3], with gastric phenotype differing between the Western FAP population (WFP) and the Asian FAP population (AFP). Fundic gland polyps (FGPs) are small exophytic lesions usually located in the fundus. Histologically, they are characterized by the presence of dilated cystic glands lined by parietal cells, chief cells, and/or mucous foveolar cells [7]. These polyps occur more frequently in WFP (80%) than in AFP (50%) [8, 9], and although may develop dysplasia, mainly of foveolar type, only few documented cases evolved to high-grade dysplasia and eventually gastric carcinoma [10, 11]. Gastric adenomas (GA), occurring more infrequently in Western cohorts, include foveolar-type adenomas, pyloric gland adenoma, and rarely, intestinal-type adenomas [12].

Intestinal-type gastric adenomas (intGA), with a known risk of evolving to gastric cancer, are clonal neoplastic growths characterized by flat or polypoid dysplastic epithelium and commonly occur in gastric mucosa with atrophic gastritis and intestinal metaplasia [13]. In contrast to FGP, intGA are more prevalent in AFP (10% vs. 1–2%) [8, 9, 14].

The variability of the gastric phenotype between WFP and AFP can be attributed to the higher prevalence of *Helicobacter pylori* (HP) infection in AFP, which is a definite (class I) carcinogen of gastric cancer [8, 15, 16]. The different prevalence of HP infection may explain the higher overall risk of gastric cancer in AFP (2.6–13.6%) compared with WFP (0.6%) [8, 9].

Currently, there are no guidelines accounting for the risk of developing gastric neoplasia in FAP patients. In this context, the development of specific guidelines considering the higher risk of developing gastric cancer

in patients with HP infection is of pivotal importance. Portugal has one of the highest prevalence of HP among Western countries, and evidence from the literature suggests that the prevalence could be as high as 85% [17].

In this study, we hypothesized that a meticulous analysis of clinical and pathological features of gastric polyps in a well-characterized cohort of FAP patients from a country with high prevalence of HP infection could shed light on the association between HP infection and the development of gastric lesions in WFP. To this end, we aimed to characterize a series of Portuguese FAP patients with respect to the risk of development of gastric polyps. Specifically, we intended to analyze the gastric phenotype in FAP patients, namely, the presence or absence of gastric polyps and their histopathological characterization, as well as to correlate them with HP infection and the pathological steps of the Correa's cascade. Finally, we aimed to analyze possible associations between the gastric phenotype and the duodenal phenotype.

Materials and Methods

Patient Series

Fifty-three patients with genetic confirmation of a pathogenic or likely pathogenic germline variant in the *APC* gene were retrospectively selected from the clinical database of the High-Risk Consultation of Digestive Tumor at Centro Hospital Universitário São João (CHUSJ) between 1992 and 2022. Exclusion criteria were cases in which specimens from the stomach were not available. Ethical approval was obtained from the CHUSJ Ethics Committee (CES 113/2023).

The following clinicopathological data were collected from the clinical files and the reports from the Department of Pathology database: age and gender, HP infection status in any gastric specimen, presence/absence of gastric and duodenal polyps, as well as their number and size, degree of dysplasia of DA, colonic phenotype, and other extracolonic manifestations.

Histopathological Evaluation

In each patient, the initial gastric endoscopic biopsies were analyzed. In patients with chronic gastritis, the degree of inflammation, neutrophilic activity, and glandular atrophy were assessed both in antral and oxyntic mucosa using a three-tier system (mild, moderate, and severe). Moreover, the presence of intestinal metaplasia was recorded both in the antrum and body.

In patients harboring gastric polyps, gastric polyp morphology was evaluated according to the 5th edition of the WHO Classification of Tumors of the Digestive System [12] by a pathologist with experience in gastrointestinal pathology (I.G.). The following gastric polyp types were identified: FGP with or without dysplasia, foveolar-type gastric adenomas (fovGA), and adenomas with predominantly intestinal-type dysplasia (intGA). Dysplasia was

graded using a two-tier system (low grade and high grade). The location of each gastric polyp recorded in the endoscopic report was confirmed by histology.

More detailed morphological features of FGP were also assessed according to the criteria proposed by Fukuda et al. [18] and studied by Kóvári et al. [19]. Specifically, FGP were analyzed according to the presence of distorted, irregular, and tortuous glands, glandular buds, as well as stellate configurations. Also, the microcyst lining was assessed, distinguishing FGP with oxyntic-type, foveolar, or mixed foveolar/oxyntic-type cell lining. The superficial foveolar epithelium was also examined, looking for foveolar hyperplasia.

Study of Helicobacter pylori Infection Status by Immunohistochemistry

Modified Giemsa staining was performed in tissue sections obtained from formalin-fixed paraffin-embedded (FFPE) blocks of the initial gastric endoscopic biopsies for screening of HP infection. In HP-negative cases, immunohistochemistry (IHC) using primary monoclonal antibody against *Helicobacter pylori* (clone SP48) was performed (Ventana Medical Systems, AZ, USA). Samples were processed in the automatic Ventana Benchmark Ultra platform using the OptiView Universal DAB detection kit. Evaluation of HP infection by Giemsa staining and IHC was carried out blindly by two independent observers (D.B. and I.G.).

Statistical Analysis

Statistical analysis was performed using SPSS software (version 27.0, IBM, New York, NY, USA). Categorical variables were compared using χ^2 test. For multiple categorical variables, the post hoc Bonferroni correction was applied. The Kruskal-Wallis non-parametric test was used to compare quantitatively independent variables within different gastric phenotypes. Differences were considered statistically significant if $p < 0.05$.

Results

The series encompassed 53 FAP patients. The median age was 52 years, and 32/53 (60.4%) were males. Information about histopathological evaluation of colectomy specimens was available in 30/53 patients (56.6%). Of these, 26.7% ($n = 8/30$) were diagnosed with colorectal adenocarcinoma at the time of colectomy. The majority of patients (24/30, 80%) had more than 100 CAP, while 6 patients (6/30, 20%) had less than 100 CAP. Duodenal polyps were identified in 21/53 (39.6%). The series encompassed 46 DA with low-grade dysplasia and two DA with high-grade dysplasia. As only few endoscopic reports described the size of DA, this variable was not retrieved for statistical analysis. One patient (1/53; 1.9%) was diagnosed with ampullary carcinoma and another (1/53, 1.9%) with gastric cancer, which was diagnosed at another institution and was not available for histopathological evaluation. Moreover, 2 patients (2/53, 3.8%) were diagnosed with desmoid tumors. A detailed descrip-

tion of the series according to the gastric phenotype is shown in Figure 1. The majority of patients ($n = 30/53$, 56.6%) had FGP and/or GA. Thirteen (13/53, 24.5%) were diagnosed exclusively with FGP, 10/53 (18.9%) with FGP and GA, and 7/53 (13.2%) with GA. The series encompassed 100 gastric polyps, including four hyperplastic polyps, 34 FGP without dysplasia, 24 FGP with gastric type dysplasia, 35 intGA (Fig. 2), and three fovGA (online suppl. Fig. 1; for all online suppl. material, see <https://doi.org/10.1159/000534571>). High-grade dysplasia was diagnosed in 6/35 (17.1%) of intGA. The patient with a previous history of gastric adenocarcinoma belonged to the group of patients diagnosed with intGA with high-grade dysplasia.

Status of Background Gastric Mucosa Influences the Presence and Histopathological Type of Gastric Polyps

To evaluate if the presence and histopathological type of gastric polyps were associated with specific clinicopathological features, we divided our cohort of Portuguese FAP patients into four groups, according to the gastric phenotype: (a) absence of FGP and GA; (b) patients harboring only FGP without dysplasia; (c) patients harboring fovGA and/or FGP with foveolar-type dysplasia; (d) patients harboring intGA with or without FGP. Clinicopathological features are listed and detailed in Table 1.

The four cohorts showed distinct clinicopathological features. A total of twenty-three cases were positive for HP, with 19 detected using modified Giemsa stain and the remaining identified by IHC. HP infection was observed more frequently in the group with no gastric polyps (15/23, 65.2%) compared to patients with FGP and/or GA ($p = 0.014$). Moreover, when comparing both groups harboring dysplasia, HP infection was more frequent in group d (6/15, 40%) than in group b (0/15, 0%) and c (2/15, 13%) ($p = 0.014$). Patients harboring intGA showed more frequent intestinal metaplasia in the background mucosa (13/15, 86.7%) when compared to other groups ($p < 0.001$). As detailed in Table 1, a statistically significant difference was observed when intestinal metaplasia was evaluated in the antrum ($p = 0.012$) but not in the body/fundus ($p = 0.75$). No statistically significant differences were identified between the four groups regarding the presence and degree of chronic inflammation and neutrophilic activity.

Regarding the association between the histopathological subtype and the location and size of gastric polyps, we found an association between intGA (group d) and location in the distal stomach (10/15, 66.7%). By contrast, all patients harboring FGP and/or fovGA had polyps in the proximal stomach ($p = 0.024$). Moreover, intGA was

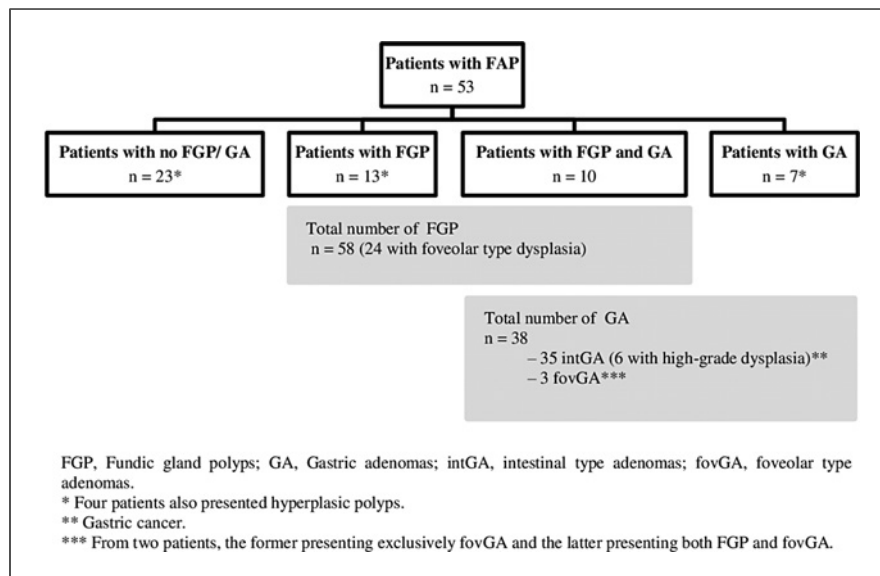


Fig. 1. Characterization of the cohort of FAP patients according to the gastric phenotype.

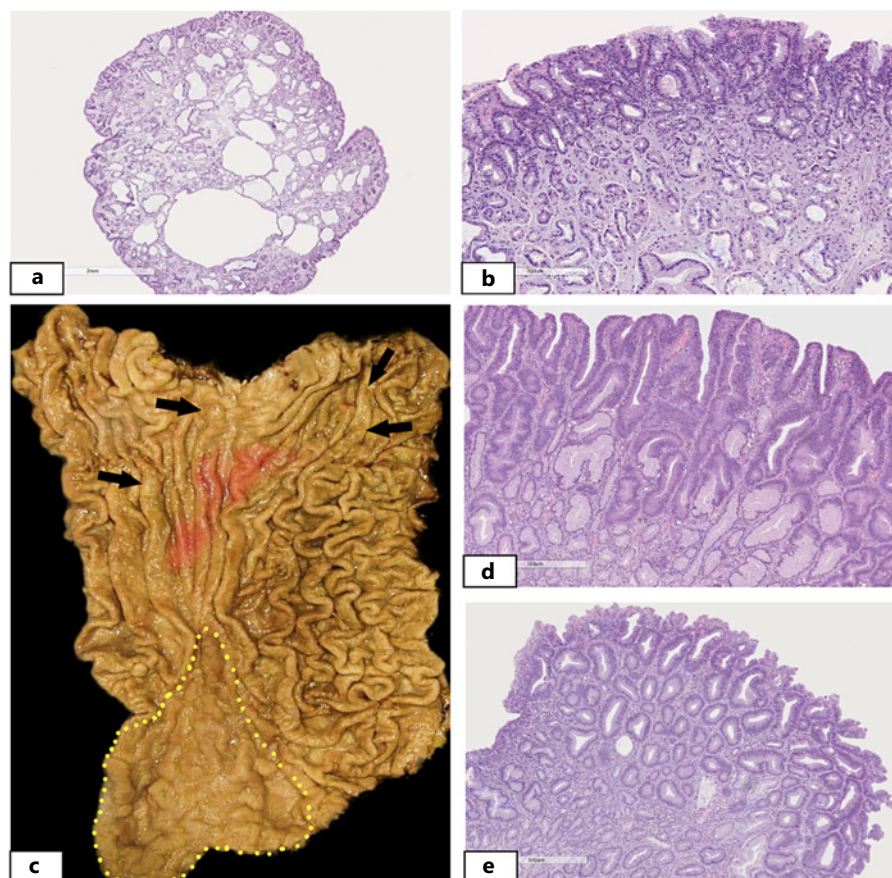


Fig. 2. Polyps and gastrectomy specimens from FAP patients, showing fundic gland polyp (FGP) without dysplasia (**a** $\times 40$ amplification) and FGP with dysplasia (**b** $\times 100$ amplification). The gastrectomy specimen (**c**) showed multiple FGP in the proximal stomach (the larger indicated by black arrows) and irregular, elevated, and depressed areas in the distal stomach (circled by yellow dotted line) corresponding to intestinal type gastric adenomas (intGA) (**d**). Patients with intGA presented more frequently with duodenal adenomas (**e**).

Table 1. Comparison of clinicopathological features between four different cohort groups: (a) absence of fundic gland polyps (FGP) and gastric adenomas (GA); (b) patients harboring only FGP without dysplasia; (c) patients harboring foveolar type GA (fovGA) or FGP with low-grade foveolar type dysplasia; (d) patients harboring intestinal type GA (intGA) with or without FGP

Clinicopathological feature	Category	(a), n = 23 (43.4%)	(b), n = 5 (9.4%)	(c), n = 10 (18.9%)	(d), n = 15 (28.3%)	Total, n = 53 (100%)	p value
Age, years, median (range)	–	52 (26–84)	57 (30–76)	31 (27–50)	55 (30–87)	52 (26–87)	0.198
Sex, n (%)	Male	15 (65.2)	3 (60)	6 (60)	8 (53.3)	32 (60.4)	0.911
	Female	8 (34.8)	2 (40)	4 (40)	7 (46.7)	21 (39.6)	
<i>Helicobacter pylori</i> , n (%)	Identified	15 (65.2)*	0	2 (20)	6 (40)	23 (43)	0.014
	Not identified	8 (34.8)*	5 (100)	8 (80)	9 (60)	30 (57)	
Inflammation antrum, n (%)	Absent/mild	10 (52.7)	1 (100)	3 (75)	7 (63.6)	21 (39.6)	0.837
	Moderate/severe	9 (47.3)	0	1 (25)	4 (36.4)	14 (26.4)	
Inflammation body, n (%)	Absent/mild	11 (91.7)	2 (100)	6 (85.7)	6 (100)	25 (47.2)	0.487
	Moderate/severe	1 (8.3)	0	1 (14.3)	0	2 (3.8)	
Activity antrum, n (%)	Absent/mild	16 (84.2)	1 (100)	4 (100)	10 (90.9)	31 (58.5)	0.849
	Moderate/severe	3 (15.8)	0	0	1 (9.1)	4 (7.5)	
Activity body, n (%)	Absent/mild	11 (91.7)	2 (100)	8 (100)	5 (100)	26 (49)	0.719
	Moderate/severe	1 (8.3)	0	0	0	1 (1.9)	
Intestinal metaplasia antrum, n (%)	Absent	12 (66.7)	1 (100)	4 (80)	2 (15.4)*	19 (35.8)	0.012
	Present	6 (33.3)	0	1 (20)	11 (84.6)*	18 (34)	
Intestinal metaplasia body, n (%)	Absent	11 (84.6)	2 (100)	7 (87.5)	5 (71.4)	25 (47.2)	0.746
	Present	2 (15.4)	0	1 (12.5)	2 (28.6)	5 (9.4)	
Intestinal metaplasia location, n (%)	Antrum only	5 (71.4)	NA	0	9 (81.8)	14 (26.4)	0.203
	Antrum and/or body	2 (28.6)	NA	1 (100)	2 (18.2)	5 (9.4)	
Atrophy antrum, n (%)	Absent/mild	11 (68.8)	1 (100)	3 (100)	7 (63.6)	22 (41.5)	0.232
	Moderate/severe	5 (71.2)	0	0	4 (36.4)	9 (17)	
Atrophy body, n (%)	Absent/mild	9 (90)	1 (100)	6 (85.7)	7 (100)	23 (43.4)	0.702
	Moderate/severe	1 (10)	0	1 (14.3)	0	2 (3.8)	
Number of gastric polyps, n (%)	Less than 3	NA	4 (80)	7 (77.8)	9 (60)	20 (37.7)	0.205
	More than or equal to 3	NA	1 (20)	2 (22.2)	6 (40)	9 (17)	
Location of polyps, n (%)	Proximal stomach	NA	5 (100)	9 (100)	5 (33.3)*	19 (35.8)	0.024
	Distal stomach	NA	0	0	10 (66.7)*	10 (18.9)	
Maximum gastric polyp size, mm, median (range)	–	NA	4 (0.5–8)	7 (4–9)	8 (2–25)	6.8 (0.5–25)	0.032

*Significant p value after Bonferroni post hoc correction. Statistically significant values are highlighted in bold.

larger (median size = 8 mm) when compared with polyps from group (b) (median size = 7 mm) and (c) (median size = 4 mm) ($p = 0.032$).

In summary, clinicopathological data from this series showed that HP infection and the steps of chronic inflammation culminating in intestinal metaplasia might influence the histopathological subtype of gastric polyps in the context of FAP. Particularly, the long-standing presence of intestinal metaplasia in the

background mucosa was associated with the development of intGA, which occurred predominantly in the distal stomach.

FGP in FAP Patients Showed Specific Histopathological Features

The presence of specific histopathological characteristics of FGP associated with FAP in a previous study [19] prompted us to analyze whether these

Table 2. Histological features of fundic gland polyps (FGP) in our cohort evaluated according to Kóvári et al. [19]

Histological feature	Category	FGP (n = 58)
Disordered glandular architecture, n (%)	Irregular tortuous glands	39 (67.2)
	Glandular buds	48 (82.6)
	Stellate configurations	35 (60.3)
Microcyst lining, n (%)	Fundic cells	2 (3.4)
	Mucin-secreting cells	0
	Mixed cells	56 (96.6)
Parietal cell hyperplasia, n (%)	Yes	8 (13.8)
	No	50 (86.2)
Hyperplasia of surface foveolar epithelium, n (%)	Yes	12 (20.7)
	No	46 (79.3)

characteristics could also be detected in our FGP series. The histopathological characteristics that were evaluated are listed in Table 2 (online suppl. Fig. 2). The majority of FGP showed irregular tortuous glands (39/58, 67.2%), glandular buds (48/58, 82.8%), and stellate configurations (35/58, 60.3%). Regarding the microcyst lining, almost the totality showed mixed cell (foveolar and oxyntic) lining (56/58, 96.6%). Pure foveolartype lining was not observed and only two cases (2/58, 3.4%) showed exclusively oxyntic-type cells. Only a minority of FPG showed parietal cell hyperplasia (8/58, 13.8%) and foveolar hyperplasia of the surface foveolar epithelium (12/58, 20.7%).

Characteristics of Duodenal Adenoma Are Related to Gastric Polyp Phenotype

As DA are the most frequent extracolonic manifestation in FAP patients and their characteristics define upper endoscopic surveillance, we considered that the evaluation of the relationship between DA characteristics and the gastric polyp phenotype was of paramount importance. As shown in Table 3, a significant association was observed between the presence of DA and the gastric phenotype, with DA developing more frequently in the group of patients harboring intGA (13/15, 86.7%) when compared to the other groups, assuming this finding a greater significance when patients from group (a) (1/23, 4.3%) were considered ($p < 0.001$). Two DA with high-grade dysplasia were excised in 2 different patients, the former in group (b) and the latter in group (d). The patient with history of ampullary carcinoma also belonged to group (d).

Discussion and Conclusion

Within the different types of gastric polyps in FAP patients, intGA are of particular interest because of their increased risk for gastric cancer development. Evidence from the literature suggests that the incidence of intGA is variable, ranging from 1.3% to 15.4% in several Western FAP cohorts [2, 20–29] and from 14.2% to 66.7% in Asian FAP cohorts [8, 9, 15, 30–34]. The distinct gastric phenotype in WFP and AFP can be explained by geographic differences, heterogeneity of patient cohorts, and, most importantly, by the higher prevalence of HP infection in AFP.

In our series, we observed that individuals harboring intGA accounted for 28% of FAP patients, which is higher than previously described WFP cohorts. This finding prompted us to investigate a possible correlation between HP infection and the gastric phenotype in Portuguese FAP patients, a population of particular interest, since a high prevalence (~85%) of HP infection has been described in recent studies [17]. Due to the heterogeneity of prevalence of HP infection and a general lack of research on the correlation between HP infection and gastric polyp development in FAP, we hypothesized that a thorough clinicopathological characterization of gastric polyps could suggest a correlation between HP infection and the gastric phenotype in FAP patients in Western series.

The Correa's cascade is the histological model of progression from the normal gastric mucosa to gastric cancer, with the main precipitating factor being HP infection. We observed that intestinal metaplasia was significantly associated with a gastric phenotype characterized by intGA. Particularly, the majority

Table 3. Presence of duodenal adenomas, number and pathological features comparison between four different cohort groups: (a) absence of fundic gland polyps (FGP) and gastric adenomas (GA); (b) patients harboring only FGP without dysplasia; (c) patients harboring foveolar type GA (fovGA) or FGP with low-grade foveolar type dysplasia; (d) patients harboring intGA (with or without FGP)

Clinicopathological feature	Category	(a), <i>n</i> = 23 (43.4%)	(b), <i>n</i> = 5 (9.4%)	(c), <i>n</i> = 10 (18.9%)	(d), <i>n</i> = 15 (28.3%)	Total, <i>n</i> = 53 (100%)	<i>p</i> value
Duodenal adenoma, <i>n</i> (%)	Absent	22 (95.7)*	4 (80)	5 (50)	2 (13.3)*	33 (62.3)	<0.001
	Present	1 (4.3)*	1 (20) ^a	5 (50)	13 (86.7)*,b	20 (37.7)	
Number of duodenal polyps, <i>n</i> (%)	Less than 3	2 (100)	1 (100)	1 (20)	5 (38.5)	9 (17)	0.106
	More than or equal to 3	0	0	4 (80)	8 (61.5)	12 (22.6)	

^aHigh-grade dysplasia. ^bOne with high-grade dysplasia. *Significant *p* value after Bonferroni post hoc correction. Statistically significant values are highlighted in bold.

(86.7%) of Portuguese FAP patients with intGA harbored intestinal metaplasia in the background mucosa, particularly in the antrum. These findings suggest that the status of background gastric mucosa, besides the well-known genotype-phenotype correlation described in FAP [35], could influence and determine the gastric phenotype in FAP patients, highlighting the pivotal role of environmental factors for the phenotypic expression of genetic syndromes.

In our study, HP infection was more frequently observed in patients without gastric polyps. Putative interpretations for these findings include the inhibitory effect of HP infection on the development of FGP [36] and in patients with intGA, the spontaneous disappearance of HP as a result of severe atrophy and intestinal metaplasia, i.e., previous HP infection-induced atrophic gastritis [37, 38].

Our findings could have important clinical consequences for the management of FAP patients. Currently, the surveillance interval of upper gastrointestinal endoscopy is based on the duodenal phenotype on the basis of Spiegelman classification. In this study, we stressed the importance of the gastric phenotype for more accurate and personalized follow-up strategies, based on the risk of developing gastric neoplasia. Although this statement needs validation in further studies involving both Western and Asian FAP populations, we showed that FAP patients harboring intestinal metaplasia are more prone to develop intGA and could represent optimal candidates for shorter follow-up periods and personalized strategies, given the higher risk of intGA of malignant transformation in comparison to FGP with dysplasia and fovGA. As proof of concept, in our series, the only patient with gastric adenocarcinoma belonged to the group of patients harboring intGA.

Regarding the location of the polyps, the majority of intGA (66.7%) were located at the distal stomach, possibly related to the fact that the intestinal metaplasia was predominantly restricted to the antral region, while all FGP were located in the proximal stomach, given their primary origin in oxyntic glands. Moreover, intGA presented a greater size (median 8 mm) compared to other types of gastric polyps and was associated with the presence of duodenal adenomas (86.7%). Accordingly, gastroenterologists should be aware of the higher risk of development of intGA in patients harboring gastric polyps with concerning features, including size greater than 7–8 mm, distal location, and, as described in previous studies, reddish, depressed, sessile, or subtle lesions [22, 30].

A secondary objective of the present study was to describe specific histopathological patterns of FGP which could correlate to different etiologies, according to Kóvári et al. [19]. According to this study, FAP-associated gastric polyps demonstrated small microcysts predominantly lined by fundic epithelium, with limited parietal cell hyperplasia or foveolar hyperplasia (pattern B). Although in our series some characteristics belonged to the FAP-associated pattern (only 14% and 21% of FGP showed parietal cell hyperplasia and foveolar hyperplasia, respectively), other characteristics corresponded to those associated with non-syndromic FGP typically described in proton-pump inhibitors (PPI) therapy (pattern A), namely, the distorted glandular architecture in the form of irregular tortuous glands and glandular buds (up to 91%) and mixed cell lining (97%). A limitation of this study is that no information about PPI therapy is available on the clinical records of our patients. Thus, we cannot exclude that some of these non-syndromic features could be associated with concomitant PPI therapy in FAP patients.

In conclusion, to our knowledge, this is the first Western series of FAP patients to show a higher incidence of gastric dysplasia of predominantly intestinal phenotype, as previously described in Asian studies. This study showed that atrophic gastritis with intestinal metaplasia and/or previous history of HP infection is likely responsible for this difference, with oncogenic potential and surveillance implications. Closer follow-up by gastro-duodenoscopy should be recommended in FAP patients with previous HP infection, intestinal metaplasia, and/or duodenal adenomas on previous endoscopic biopsies. Biopsy or excision of gastric polyps with concerning features (i.e., >7 mm and/or reddish, flat, or depressed lesions) located in the distal stomach and developing in patients with gastric intestinal metaplasia and duodenal adenomas should be considered.

Acknowledgments

This study was distinguished with the Pathobiology Award (34th European Congress of Pathology held in Basel, Switzerland). We thank Lúcia Pinho for her technical support provided during this study.

Statement of Ethics

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Centro Hospitalar Universitário de São João (CES 113/2023) for studies involving humans. Written informed consent was obtained from all subjects involved in the study.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Funding Sources

This project has received funding from (1) European Reference Network on Genetic Tumor Risk Syndromes (ERN GENTURIS)–Project ID No. 739547. ERN GENTURIS is partly cofounded by the European Union within the framework of the Third Health Program “ERN-2016–Framework Partnership Agreement 2017–2021; (2) solve-RD project has received funding from the European Union’s Horizon 2020 research and innovation program under grant agreement no. 779257; (3) European Union’s Horizon Europe Coordination and Support action under the Grant Agreement No. 101095483 (PREVENTABLE).”

This study was also funded by the European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the Health and Digital Executive Agency (HaDEA). Neither the European Union nor the granting authority can be held responsible for them.

Author Contributions

Manuscript writing: Diana Baptista, Marco Fernandes, and Irene Gullo; critical manuscript review: Mónica Garrido, Irene Gullo, and Fátima Carneiro; study concept: Irene Gullo and Mónica Garrido; study design and planning: Irene Gullo, Diana Baptista, Mónica Garrido, Fabiana Sousa, and Manuela Baptista; case selection: Diana Baptista, Marco Fernandes, Mónica Garrido, Fabiana Sousa, Rui Morais, Roberto Silva, Manuela Baptista, and José Barbosa; data analysis: Diana Baptista, Marco Fernandes, Mónica Garrido, Jose Pelaez, Roberto Silva, and José Barbosa; histopathological evaluation: Diana Baptista, Irene Gullo, Roberto Silva, and Fátima Carneiro; immunohistochemistry assays: Dina Leitão. All authors revised the manuscript and approved the final version to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Study 2

Screening Endoscopy in Patients With Advanced Chronic Liver Disease - Is It All About Varices?

Morais R, Liberal R, Macedo G.

Clin Gastroenterol Hepatol. 2024 Jun 11:S1542-3565(24)00511-1

DOI: 10.1016/j.cgh.2024.05.036

Epub ahead of print

PMID: 38871153

Cited by 0 articles

(Google Scholar, 2025, April 24)

Impact factor 11.6

(Thomson-Reuters, 2023)

Rank 6 of 164 on Gastroenterology journals (Q1)

(Scimago Journal & Country Rank, 2023)

LETTERS TO THE EDITOR

Readers are encouraged to write letters to the editor concerning articles that have been published in *Clinical Gastroenterology and Hepatology*. Short, general comments are also considered, but use of the Letters to the Editor section for publication of original data in preliminary form is not encouraged. Letters should be typewritten and submitted electronically to <http://www.editorialmanager.com/cgh>.

Screening Endoscopy in Patients With Advanced Chronic Liver Disease – Is It All About Varices?

Dear Editor:

We read with great interest the article by Pizzo et al¹ regarding the cost-effectiveness of the Baveno VI criteria compared with endoscopy for high-risk varices in patients with Child Pugh A cirrhosis. Previous studies have validated the Baveno VI criteria regarding the prediction of gastroesophageal varices (GOEVs),²⁻⁵ but this is the first study to demonstrate the cost-effectiveness of this approach in the United Kingdom, Canada, and Spain. Although we congratulate the authors for their findings, some points should be addressed before a widespread implementation of the Baveno VI criteria for GOEV screening should be considered, namely regarding the potential for opportunistic upper gastrointestinal neoplasia detection with the performance of esophagogastroduodenoscopy (EGD). The authors briefly address this question, stating that the Baveno VI criteria can result in missing gastro-esophageal cancer detection, particularly in patients at higher risk, such as those with alcoholic liver disease.

Our group recently aimed to evaluate the frequency of gastric neoplasia in patients with compensated advanced chronic liver disease (cACLD) who underwent EGD screening for GOEVs, in a Western country with intermediate-high risk of gastric cancer (Portugal).⁶ We found a significantly higher frequency of gastric neoplasia in patients with cACLD compared with a healthy population (4.0% vs 1.0%). More interestingly, 36.8% of gastric neoplasia cases were diagnosed on patients who, according to the Baveno VII criteria, would not have been submitted to EGD. Finally, 2 interesting findings were that rare histopathological subtypes (World Health Organization classification) accounted for 28.7% of gastric carcinoma cases in the cACLD cohort, and more than one-half the cases of gastric adenocarcinoma were diagnosed in patients without alcoholic liver disease, suggesting that other factors beside the etiology of ACLD may be associated with an increased risk of gastric neoplasia in this population (namely liver cirrhosis-associated immune dysfunction). Recent evidence has shown that in countries with intermediate to

high risk of gastric cancer, screening with EGD appears to be cost-effective in the healthy population when performed at the same time as screening colonoscopy.⁷ Our results support that continuing to perform EGD in patients with cACLD may be beneficial. Patients with Child Pugh A cirrhosis are the ones that will mostly benefit from an early detection of gastric neoplasia, considering the safety and efficacy of endoscopic resection techniques in this population.⁸

Further studies should focus on the evaluation of the cost-effectiveness analysis of the Baveno criteria in countries with intermediate-high risk of gastric cancer (such as Portugal, Lithuania, Romania, or Slovenia). A sensitivity analysis could take into consideration the significantly higher prevalence of gastric neoplasia in this population and the potential benefits of early detection. Identification of additional risk factors for gastric cancer in these patients (other than the etiology of cirrhosis) seems of paramount importance, because that, in the future, may lead to a tailored selection of those who really benefit from an invasive and simultaneous screening for both GOEVs and upper gastrointestinal neoplasia.

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Conflicts of interest

The authors disclose no conflicts.

<https://doi.org/10.1016/j.cgh.2024.05.036>

Study 3

NC-ESD Study Group. eCura and W-eCura: different scores, different populations, same goal

Morais R, Libanio D, Santos-Antunes J.

Gut. 2024 Oct 7;73(11):e29

DOI: 10.1136/gutjnl-2024-331924

PMID: 38286588

Cited by 2 articles

(Google Scholar, 2025, April 24)

Impact factor 24.5

(Thomson-Reuters, 2023)

Rank 3 of 164 on Gastroenterology journals (Q1)

(Scimago Journal & Country Rank, 2023)

eCura and W-eCura: different scores, different populations, same goal

We read with great interest the letter by Hatta *et al*¹ and thank the authors for their valuable insight on the management of patients after a high-risk resection (HRR) gastric endoscopic submucosal dissection (ESD).

Our primary objective was to validate eCura in a Western cohort that, as mentioned, showed a remarkable discriminative ability, and support that it may be applied in Western countries to stratify the risk of lymph node metastasis (LNM) after a gastric HRR. With W-eCura, we proposed a slight modification of the original system, increasing the cut-off of the submucosal invasion to 1 mm, which showed a small, although statistically significant, higher accuracy, while maintaining a very high sensitivity.² We agree that besides the internal validation that was already performed, a validation study with an external cohort is warranted to assess the real differences between the two systems, and which could fit better in Western and Eastern cohorts. In an optimal setting, the study should involve either Western and Eastern centres and include a centralised and standard evaluation of the ESD specimens by expert pathologists. This would minimise the differences in specimen handling and histopathological analysis³ that could contribute to the significant differences observed in the discriminative ability of the scores in the two studies.

The initial eCura study⁴ was the first step in this long road that ultimately aims to avoid unnecessary surgeries, while maintaining a comparable survival rate.⁵ As the authors stated, despite the low number of cases, there is now growing evidence that in HRR patients scoring in the eCura/W-eCura low-risk category the benefit of further gastrectomy may be lower than its morbidity and mortality.

Further refinement of both eCura and W-eCura may be necessary. Some tools have been developed, namely nomograms to predict not only the preprocedural risk of needing further gastrectomy, considering morphological, histological and imagiological features of the ESD target lesion,⁶ but also postprocedural, to predict the rate of LNM, some of them using artificial intelligence systems.^{7–9}

Therefore, despite the need for additional data and validation, we consider

that we are all on the right track for improving the management after an HRR gastric ESD, which could be particularly important in high-risk surgical patients.

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Contributors All authors and collaborators have read, commented and agreed with the submission.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; internally peer reviewed.

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To cite Morais R, Libanio D, Santos-Antunes J, *et al*. Gut 2024;**73**:e29.

Received 8 January 2024

Accepted 17 January 2024

Published Online First 29 January 2024

Gut 2024;**73**:e29. doi:10.1136/gutjnl-2024-331924

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