30 | 1 | 23

Portuguese Journal of Gastroenterology

Highlights in this issue:

- Meta-Analysis: laparoscopic endoscopic cooperative surgery in upper GI lesions
- Treatment of anastomotic leaks following esophagectomy
- Prediction of liver decompensation prior to transarterial chemoembolization

OPEN ACCESS

Gastroenterology

RESEARCH

Sociedade Portuguesa de Gastrenterologia

A Partner Publication by

Karger

GE – Portuguese Journal of Gastroenterology

(Continued on next page)

Karger

Printed in Portugal by Printipo: printipo@printipo.com

GE – Portuguese Journal of Gastroenterology

(Continued)

(Continued on next page)

GE – Portuguese Journal of Gastroenterology

Karger

www.karger.com
karger@karger.com

GE – Portuguese Journal of Gastroenterology

Journal Information

Guidelines for Authors
We strongly encourage authors to read the Guidelines for Authors at www.karger.com/pjg _guidelines prior to submitting an article

Journal Contact
For questions or comments, please contact the persons responsible who can be found at http://www.karger.com/Journal/Contact/272027

Aims and Scope

The *GE Portuguese Journal of Gastroenterology* (formerly *Jornal Português de Gastrenterologia*), founded in 1994, is the official publication of Sociedade Portuguesa de Gastrenterologia (Portuguese Society of Gastroenterology), Sociedade Portuguesa de Endoscopia Digestiva (Portuguese Society of Digestive Endoscopy) and Associação Portuguesa para o Estudo do Fígado (Portuguese Association for the Study of the Liver).
The journal publishes clinical and basic research articles on Gastroenterology, Digestive Endoscopy, Hepatology and related topics. Review articles, clinical case studies, images, letters to the editor and other articles such as recommendations or papers on gastroenterology clinical practice are also considered. Only articles written in English are accepted.

Price per printed issue: Free of charge
Print run: 100
ERC-No.: 117866
Editor address: Rua Abranches Ferrão, nº 10–14º, PT–1600-001 Lisbon (Portugal)
Printed in: PT–2735-197 Cacém (Portugal)

ISSN Print Edition: 2341–4545
ISSN Online Edition: 2387–1954

Journal Homepage: www.karger.com/pjg
Bibliographic Indices: This journal is regularly listed in bibliographic services, including PMC, PubMed, Web of Science, SciELO Citation Index, Google Scholar, DOAJ, Scopus, and WorldCat.

Publication Data: *GE Port J Gastroenterol* is published 6 times a year. Volume 30 with 6 issues appears in 2023.

Karger

© 2023 S. Karger AG, Basel
www.karger.com
karger@karger.com

GE – Portuguese Journal of Gastroenterology

Vol. 30, No. 1, 2023

Contents

Cover illustration
Endoscopic image of a gastric melanoma metastasis, with a dark coloration area of 5mm in one of the edges. From Pinto et al., pp. 79-82.

Karger

GE – Portuguese Journal of Gastroenterology

Karger

GE – Portuguese Journal of Gastroenterology

Editorial

GE Port J Gastroenterol 2023;30:1–3
DOI: 10.1159/000527210

Received: August 14, 2022
Accepted: August 18, 2022
Published online: October 28, 2022

Metastatic Malignant Melanoma of the Gastrointestinal Tract: Too Dark to be Seen?

Jéssica Chaves[a] Diogo Libânio[a, b]

[a]Gastroenterology Department, Portuguese Institute of Oncology, Porto, Portugal; [b]MEDCIDS- Department of Community Medicine, Health Information and Decision, Faculty of Medicine, University of Porto, Porto, Portugal

Keywords
Melanoma · Metastatic · Gastrointestinal tract

Melanoma maligno metastático do trato gastrointestinal: demasiado escuro para ser visto?

Palavras Chave
Melanoma · Metastases · Gastrointestinal

Malignant melanoma (MM) is the most common cause of mortality due to skin cancer worldwide and its incidence is increasing [1]. The majority of MM are from cutaneous origin, and most gastrointestinal (GI) tract melanomas are a result of metastasis, although MM can, less frequently, arise primarily from GI origin [2].

Metastasis of MM in the GI tract is common (estimated in up to 60% of all patients with advanced disease), but in practice only a small proportion are clinically significant. Indeed, only about 1–5% are clinically diagnosed antemortem [2, 3]. In this issue of GE – Portuguese Journal of Gastroenterology, two case reports are published reporting interesting GI involvement of MM, highlighting the sometimes difficult task of diagnosing them.

Firstly, Soares-Santos et al. [4] described a case of an elderly woman with no previous history of melanoma who presents with a set of non-specific symptoms, including GI symptoms. The initial imaging study was negative for malignant disease and endoscopy with biopsies of dark-coloured polypoid lesions allowed the diagnosis of gastric metastasis from MM, which is a rare finding in metastatic MM. The prognosis, due to the patient's comorbidities which rendered her unfit for chemotherapy, was poor. This case highlights the role of endoscopy (the key to solve the mystery) in the diagnosis and management of this patient.

The second case by Pinto et al. [5] highpoints the fundamental role of histology in conjugation with endoscopic findings. A more distracted eye could have easily missed the darker area found in endoscopy or misinterpreted it as a non-significant lesion, and tissue acquisition in adjacent areas possibly lead to the initial misdiagnosis. Repeat endoscopy and biopsies proved to be the right choice of action, and this should be considered when clinical history, endoscopic and histological findings do not match. This case is also a reminder to never forget the previous medical history of a patient, namely, of previous malignant disease, as it might just be the clue needed for final diagnosis.

MM is among the most common carcinomas to metastasize to GI tract and can be spread throughout. Even so, it appears to have particular affinity to the small bow-

Karger@karger.com
www.karger.com/pjg

Correspondence to:
Jéssica Chaves, jessicaraquellimachaves@gmail.com

el, specially to the jejunum and ileum [3, 6]. At a molecular level, the greatest expression of CCL25 in the small bowel, which is a ligand to CCR9 expressed in the melanoma cell surface, may somehow explain the typical (atypical) metastasis to this part of the GI tract [3, 7].

On the other hand, primary GI melanomas can arise from various GI segments, more commonly from the anal canal, rectum, and oesophagus and accounts for a minority of MM, with an estimated incidence of 0.58 cases per million people. They are more frequently encountered in elderly women and tend to be more aggressive and diagnosed at an advance stage – 36% versus 4% comparing to cutaneous melanoma, respectively [8, 9]. A primary GI melanoma might be suspected in the absence of prior history of cutaneous melanoma or if the lesion is isolated without other extraintestinal metastasis, and it can be inferred histologically if a precursor lesion is present in tissue sample [10].

Patients with metastatic MM of the GI tract may experience generalized non-specific GI symptoms such as abdominal pain or constipation, depending primarily on the place affected. Cases of GI occlusion and active bleeding have also been described [2, 3]. Clinical diagnosis of GI primary melanoma or secondary involvement can be challenging, especially if symptoms are mild and non-specific. The time between primary excision and metastatic disease can also be a confounding factor, since most metastases are diagnosed within the first 3 years, but there are some cases reporting metastatic disease 15 years after initial treatment [11].

Imaging studies such as computed tomography or positron emission tomography (PET) may be useful in identifying sites of possible metastatic melanoma and can be ordered during follow-up, particularly in advanced disease. Nevertheless, mainly for computed tomography scan, the sensitivity for detecting metastases is about 60–70% [3].

Endoscopic evaluation, as seen in the 2 case reports explored in this issue, is an irreplaceable tool to obtain a diagnosis and can, with the exception of videocapsule endoscopy, acquire tissue for histological appraisal, which is vital in confirming the diagnosis [2, 3, 12]. Endoscopic appearance is variable and metastatic lesions might be misleading. Polypoid or excavated lesions may be observed, and even though colour could be helpful, they may present themselves as amelanotic, so biopsy of suspected lesions should be performed [3, 12, 13], as seen in the case reported by Pinto et al. [5]. However, as stated previously, it is important to note that metastatic melanoma to the GI tract is much less frequently diagnosed in clinical practice than post-mortem, suggesting that most of the times metastasis is asymptomatic [3, 11]. Thus, if metastatic disease is already present, endoscopic and histological diagnosis of MM metastasis of the GI tract should only be pursued if it modifies management of the patient.

In cases of melanoma of unknown primary (that corresponds to about 3% of all cases of MM), i.e., cases in which, according to Das Gupta criteria [14], cutaneous, ophthalmologic, anal, and genital melanoma have been excluded, the true value of endoscopic evaluation is difficult to establish and more recent consensus argues that it may not be useful to search for the primary tumour in mucosal membranes, eyes, or other organs [15, 16]. In case presented by Soares-Santos et al. [4], the symptoms presented by the patient motivated the endoscopic study and lead to the diagnosis of metastatic MM.

Prognosis of MM has dramatically been transformed since the introduction of new therapeutical targets. Before the introduction of target agents, such as BRAF inhibitors and immunotherapy, MM in advanced stage had a median survival time of 6.2 months, with only 25.5% of the patients alive at 1 year [17]. In the era of immune checkpoint inhibitors and targeted BRAF/MEK inhibitors, the clinical management of metastatic MM has fortunately changed. Most immune checkpoint inhibitors are now being used in the treatment of metastatic MM with or without surgery, improving overall survival. Nivolumab, for instance, had a 1-year survival rate of 73% in patients with non-operable or metastatic MM, with a good safety profile [18]. Immune-related adverse events that can urge with this therapy, and may occur in almost every organ, are usually mild and treatable [3, 18].

Surgery also plays a role in the management of these patients, and so a multidisciplinary approach is recommended. An increase in quality of life and survival is, likewise, seen in patients undergoing resection of GI metastases of MM. Despite this fact, the decision to recommend a surgical procedure must take into account patients' comorbidities, age, and melanoma disease burden [19].

In conclusion, even if metastatic MM of GI tract is not an uncommon condition, its clinical diagnosis is far from optimal. The GI tract may be just too dark to be seen (potentially due to non-specific symptoms and the need for invasive procedures), or the lesions may be just too "white" to be deceptive. A high clinical suspicion must be present in patients presenting with GI symptoms and history of MM. Treatment options are increasing, so is the survival of these patients.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was used for the development of this work.

Author Contributions

Jéssica Chaves performed the literature search and wrote the manuscript. Diogo Libânio reviewed the manuscript and made critical corrections.

Data Availability Statement

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

References

1 Dzwierzynski WW. Melanoma risk factors and prevention. Clin Plast Surg. 2021;48(4):543–50.
2 Sinagra E, Sciumè C. Ileal melanoma, a rare cause of small bowel obstruction: report of a case, and short literature review. Curr Radiopharm. 2020;13(1):56–62.
3 Kohoutova D, Worku D, Aziz H, Teare J, Weir J, Larkin J. Malignant melanoma of the gastrointestinal tract: symptoms, diagnosis, and current treatment options. Cells. 2021;10(2):327.
4 Soares Santos DF, Costa M, Carvalho P, Santos RM, Carvalho A. Gastrointestinal metastatic melanoma: the key for diagnosis. GE Port J Gastroenterol. 2021. https://www.karger.com/DOI/10.1159/000518000.
5 Pinto CMM, Rodriguez M, Souto Moura M, Afonso M, Bastos P, Dinis Ribeiro M. Gastric metastatic melanoma mimicking a hyperplastic lesion. GE Port J Gastroenterol. 2021. https: //www.karger.com/DOI/10.1159/000520211.
6 Patel JK, Didolkar MS, Pickren JW, Moore RH. Metastatic pattern of malignant melanoma. A study of 216 autopsy cases. Am J Surg. 1978;135(6):807–10.
7 Hadjinicolaou AV, Hadjittofi C, Athanasopoulos PG, Shah R, Ala AA. Primary small bowel melanomas: fact or myth? Ann Transl Med. 2016;4(6):113.
8 Zheng Y, Cong C, Su C, Sun Y, Xing L. Epidemiology and survival outcomes of primary gastrointestinal melanoma: a SEER-based population study. Int J Clin Oncol. 2020;25(11):1951–9.
9 Kahl AR, Gao X, Chioreso C, Goffredo P, Hassan I, Charlton ME, et al. Presentation, management, and prognosis of primary gastrointestinal melanoma: a population-based study. J Surg Res. 2021;260:46–55.
10 Syed HR, Shekar S, Aravantagi A. Melanoma and the gastrointestinal (GI) tract: maintaining a high index of suspicion. Cureus. 2021;13(2):e13408.
11 Farshad S, Keeney S, Halalau A, Ghaith G. A case of gastric metastatic melanoma 15 years after the initial diagnosis of cutaneous melanoma. Case Rep Gastrointest Med. 2018;2018:7684964.
12 Urbain D, Aerts M, Reynaert H, Mana F, Neyns B. Small-bowel metastasis of malignant melanoma: video capsule endoscopy appearance. Endoscopy. 2010;42(Suppl 2):E185.
13 Ozturk O, Basar O, Koklu S, Yuksel O, Purnak T, Sokmensuer C. An unusual presentation of malignant melanoma: amelanotic gastric metastasis. Am J Gastroenterol. 2015;110(3):476.
14 DasGupta T, Dowden L, Berg TW. Malignant melanoma of unknown primary origin. Surg Gynec Obst. 1963;117:341–5.
15 Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Basset-Seguin N, et al. European consensus-based interdisciplinary guideline for melanoma. Part 1: diagnostics – update 2022. Eur J Cancer. 2022;170:236–55.
16 Sirvan SS, İhsan Eren H, Kurt Yazar S, Günenç AC, Yeşilada AK, Irmak F, et al. Approach to patients with malignant melanoma of unknown primary origin. Sisli Etfal Hastan Ttip Bul. 2019;53(2):125–31.
17 Korn EL, Liu P-Y, Lee SJ, Chapman J-AW, Niedzwiecki D, Suman VJ, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. J Clin Oncol. 2008;26(4):527–34.
18 Long GV, Atkinson V, Ascierto PA, Robert C, Hassel JC, Rutkowski P, et al. Effect of nivolumab on health-related quality of life in patients with treatment-naïve advanced melanoma: results from the phase III CheckMate 066 study. Ann Oncol. 2016;27(10):1940–6.
19 Sanki A, Scolyer RA, Thompson JF. Surgery for melanoma metastases of the gastrointestinal tract: indications and results. Eur J Surg Oncol. 2009;35(3):313–9.

GE – Portuguese Journal of Gastroenterology

Review Article

GE Port J Gastroenterol 2023;30:4–19
DOI: 10.1159/000526644

Received: March 11, 2022
Accepted: May 23, 2022
Published online: November 7, 2022

Efficacy and Safety of Laparoscopic Endoscopic Cooperative Surgery in Upper Gastrointestinal Lesions: A Systematic Review and Meta-Analysis

Sara Oliveira de Brito[a] Diogo Libânio[b, c] Cláudia Martins Marques Pinto[b]
João Pedro Pinho Osório de Araújo Teixeira[d, e]
João Paulo Meireles de Araújo Teixeira[d, e]

[a]Faculty of Medicine, University of Porto, Porto, Portugal; [b]Gastroenterology Department, Portuguese Oncology Institute of Porto, Porto, Portugal; [c]CINTESIS/Biostatistics and Medical Informatics Department, Porto Faculty of Medicine, Porto, Portugal; [d]General Surgery, São João University Hospital Center, Porto, Portugal; [e]Surgery Department, Faculty of Medicine, University of Porto, Porto, Portugal

Keywords
Laparoscopic endoscopic cooperative surgery · Endoscopic submucosal dissection · Laparoscopic resection · Subepithelial lesions · Meta-analysis

Abstract

Background and Aims: Laparoscopic and endoscopic cooperative surgery (LECS) combines advantages of endoscopy and laparoscopy in order to resect upper gastrointestinal lesions. Our aim was to evaluate the efficacy and safety of LECS in patients with EGJ (esophagogastric junction), gastric and duodenal lesions, as well as to compare LECS with pure endoscopic and pure laparoscopic procedures. ***Methods:*** PubMed, Scopus, and ISI Web of Knowledge were searched. Efficacy (R0, recurrence) and safety (conversion rate, procedure and hospitalization time, adverse events, mortality) outcomes were extracted and pooled (odds ratio or mean difference) using a random-effects model. Study quality was assessed with Newcastle-Ottawa Scale and heterogeneity by Cochran's Q test and I^2. Subgroup analysis according to location was performed. ***Results:*** This meta-analysis included 24 studies/1,336 patients (all retrospective cohorts). No significant differences were found between LECS and preexisting techniques (endoscopic submucosal dissection (ESD)/laparoscopy) regarding any outcomes. However, there was a trend to shorter hospitalization time, longer procedure duration, and fewer adverse events in LECS versus Laparoscopy and ESD. R0 tended to be higher in the LECS group. Hospitalization time was significantly shorter in gastric versus EGJ lesions (mean 7.3 vs. 13.7 days, 95% CI: 6.6–7.9 vs. 8.9–19.3). There were no significant differences in conversion rate, adverse events, or mean procedural time according to location. There was a trend to higher conversion rate and longer procedure durations in EGJ and higher rate of adverse events in duodenal lesions. ***Conclusion:*** LECS is a valid, safe, and effective treatment option in patients with EGJ, gastric, and duodenal lesions, although existing studies are retrospective and prone to selection bias. Prospective studies are needed to assess if LECS is superior to established techniques. ***Key Messages:*** LECS is safe and effective in the treatment of upper gastrointestinal lesions, but there is no evidence of superiority over established techniques.

Karger@karger.com
www.karger.com/pjg

Karger
OPEN ACCESS

Correspondence to:
Sara Oliveira de Brito, up201603819@med.up.pt

Eficácia e segurança da Cirurgia Laparoscópica e Endoscópica Cooperativa em lesões gastrointestinais superiores: revisão sistemática e meta-análise

Palavras Chave
Cirurgia cooperativa Laparoscópica e endoscópica · disseção endoscópica da submucosa · resseção laparoscópica · Lesões subepiteliais · Meta-análise

Resumo
Introdução e objetivos: A Cirurgia cooperativa laparoscópica e endoscópica (LECS) combina vantagens da endoscopia e laparoscopia na resseção de lesões gastrointestinais superiores. O nosso objetivo é avaliar a eficácia e segurança da LECS em pacientes com lesões na junção esofagogástrica (EGJ), estômago e duodeno, e comparar a LECS com procedimentos puramente endoscópicos e laparoscópicos. ***Métodos:*** PubMed, Scopus, ISI Web of Knowledge foram pesquisadas. Dados sobre eficácia (R0, recorrência) e segurança (taxa de conversão, duração do procedimento e hospitalização, recorrência, eventos adversos, mortalidade) foram colhidos e agrupados (odds ratio ou média das diferenças), usando modelo de efeitos randomizados. Qualidade dos estudos foi avaliada pela Escala Newcastle-Ottawa e heterogeneidade pelos testes Q da Cochran e I^2. Foi realizada análise de subgrupos, consoante a localização. ***Resultados:*** Esta meta-análise incluiu 24 estudos/1336 pacientes (todos coortes retrospetivos). Não encontramos diferenças significativas entre LECS e as técnicas pré-existentes (Disseção endoscópica da submucosa (ESD)/Laparoscopia) em nenhum aspeto. Porém, encontramos uma tendência para hospitalização mais curta, procedimentos mais longos e menos efeitos adversos na LECS versus Laparoscopia e ESD. R0 tende a ser maior no grupo LECS. Hospitalização foi significativamente menor em lesões gástricas versus EGJ (média 7.3 vs. 13.7 dias, 95% CI: 6.6–7.9 vs. 8.9–19.3). Não encontramos diferenças significativas na taxa de conversão, eventos adversos nem tempo médio de procedimento. Porém encontramos uma tendência para taxas de conversão maiores e procedimentos mais longos na EGJ e maior taxa de eventos adversos no duodeno. ***Conclusão:*** LECS é um tratamento válido, seguro e eficaz em pacientes com lesões na EGJ, estômago e duodeno, apesar dos estudos retrospetivos existentes estarem propensos a viés de seleção. São necessários estudos prospetivos para avaliar a superioridade da LECS face às técnicas existentes. ***Mensagens-chave:*** LECS é um tratamento seguro e eficaz para lesões gastrointestinais superiores, mas sem evidência de superioridade face às técnicas existentes.

Introduction

Laparoscopic and endoscopic cooperative surgery (LECS) is a procedure, which combines the advantages of endoscopy and laparoscopy. It was proposed by Hiki et al. [1] in 2008 as a technique to resect gastric subepithelial lesions (SELs). Before LECS was developed, SELs were generally treated by laparoscopic wedge resection (LWR). However, gastric SELs may not be recognized from outside of the stomach wall, making it difficult to accurately determine resection lines through LWR [2–4]. This can lead to incomplete or excessive resection, which may lead to increased recurrence or postoperative alterations of the stomach with gastric stasis [2, 4].

The first proposed technique was classical LECS that consists of endoscopic confirmation of the incision lines, followed by an endoscopic mucosal incision, while the seromuscular layer is incised laparoscopically. At the end, the incision line is sutured laparoscopically and the specimen is removed transabdominally [5, 6]. Classical LECS was proposed for SELs without ulceration, regardless of location. Its main benefits are allowing complete resection with minimal margins, preserving gastric motility and postoperative quality of life. Specially in esophagogastric junction SELs, LECS could avoid total or proximal gastrectomy [4]. However, classical LECS also has some limitations: possible peritoneal contamination with tumor cells or gastric juice (due to opening of the gastric wall) and requirement of advanced endoscopic and laparoscopic skills [7, 8].

To overcome these disadvantages and expand LECS for treatment of SELs with ulceration and gastric epithelial neoplasms, some modifications were developed, such as inverted LECS, combination of laparoscopic and endoscopic approaches to neoplasia with nonexposure technique (CLEAN-NET), nonexposed endoscopic wall-inversion surgery (NEWS), and closed-LECS [4, 6, 7, 9].

Inverted LECS decreases the risk of intraperitoneal seeding by inverting the mass into the gastric lumen. Although this risk is not null, there is also intentional perforation. In addition to classical LECS, it allows the resection of masses with less than 5 cm regardless of the location [6, 7, 10].

CLEAN-NET, NEWS, and closed-LECS are only suitable for SELs lesser than 3 cm. CLEAN-NET includes eversion of the mass and nonexposed full-thickness resection after seromuscular incision, preserving the continuity of the mucosa, that works as a barrier. The risk of mucosal laceration in lesions superior to 3 cm justifies the size limitation [9, 11]. NEWS stands on a "suture first and then cut" rule, including a full-thickness resection technique without intentional perforation [8, 12, 13]. The previous 2 types of modified LECS are not indicated for lesions located at the EGJ or pyloric ring. On closed-LECS and NEWS, lesions are retrieved by the transoral route [3, 4, 7, 9, 14, 15].

Endoscopic submucosal dissection (ESD) is the first-line treatment for gastric epithelial lesions without deep submucosal invasion, allowing en bloc resection, independently of size. Despite this, in SELs the risk of perforation is higher since the resection plan is deeper and is associated with long operation times and long learning curves [6, 7, 16]. Modified LECS procedures can also have a role in SELs located in the deep submucosa/muscle layer and in some early gastric cancers that would be technically difficult to treat with ESD. Specifically in the duodenum, where ESD is associated with a high perforation risk (20–30%), LECS is an attractive option since it might be safer than ESD and conventional surgery [4–6].

According to previous studies, LECS is a safe and feasible procedure, with a complication rate lesser than 5%, but there are no studies demonstrating if LECS is in fact better than ESD or conventional surgery, neither showing which is the better LECS procedure, among the classical and the modified ones [2, 4, 6, 17–19].

The aim of this systematic review and meta-analysis was to evaluate efficacy and safety outcomes of LECS for gastric, EGJ, and duodenal lesions and to compare LECS with competing techniques (ESD and conventional surgery) whenever possible.

Methods

This systematic review and meta-analysis followed the principles set in the Preferred Reporting. Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement [20].

Study Search and Selection

Studies were identified through scanning of 3 electronic databases (MEDLINE through PubMed, Scopus, and ISI Web of Knowledge), with the last search performed on March 8, 2021. The search query for PubMed was (gastric OR stomach OR duodenal OR duodenum OR "esophagogastric junction") AND ("laparoscopic and endoscopic cooperative surgery" OR "Laparoscopic-endoscopic cooperative surgery" OR LECS OR D-LECS OR "non-exposed endoscopic wall-inversion surgery" OR "non-exposed endoscopic wall-inversion surgery" OR "Nonexposed wall-inversion surgery" OR "non-exposed wall-inversion surgery" OR CLEAN-NET OR "combination of laparoscopic and endoscopic approaches for neoplasia with non-exposure technique" OR "Closed-LECS" OR "closed laparoscopic and endoscopic cooperative surgery" OR "non-exposure endoscopic-laparoscopic cooperative surgery" OR "inverted LECS"). Queries for other databases were adapted from this query. No time or language restrictions were made in this phase.

After removal of duplicates, two authors (J.T., S.B.) independently screened all titles and abstracts to exclude irrelevant studies. The full text of selected and relevant studies was then evaluated independently by the same two researchers according to the inclusion criteria described below. This phase was performed with Rayyan online platform [21]. Disagreements were solved by consensus between the authors or with the intervention of a third reviewer (D.L.) when required.

Inclusion criteria were: (1) retrospective or prospective, case-control, or cohort studies and clinical trials; (2) including patients submitted to laparoscopic and endoscopic cooperative surgery due to esophagogastric, gastric and/or duodenal lesions (single-arm studies as well as comparative studies with competing techniques were included); (3) evaluating at least one of the following efficacy or safety outcomes: R0/complete resection; need for conversion; procedure time; hospitalization time; recurrence; adverse events; and mortality. Exclusion criteria were: (1) case reports, reviews, letters to editor, surveys, and animal studies; (2) language other than English/Portuguese/Spanish/Italian/French; (3) studies published only in abstract form; (4) studies including less than 10 patients; and (5) studies with patient overlap with other included studies (in this case, the most informative reference was used).

Data Extraction and Quality Evaluation

Data extraction was performed by S.B. and D.L. Data extraction forms included (1) author, publication year, country, study period, study design, setting (2) population characteristics: numbers of participants, tumor location, histological subtypes; (3) type of resection techniques: LECS (NEWS, CLEAN-NET; closed-LECS), LWR, ESD, laparoscopic resection; and (4) outcomes: R0, need for conversion, procedure time (minutes), hospitalization time (days), recurrence, adverse events, and mortality. Data regarding costs and quality of life were also extracted whenever possible.

Quality evaluation was performed using the Newcastle-Ottawa Assessment Scale adapted, for cohort studies, by S.B. and D.L. [22]. Newcastle-Ottawa Scale ranges from 0 to 9 points in double-arm studies and from 0 to 6 points in single-arm studies. No specific value is assigned to high or low quality, although higher scores indicate higher quality and greater methodological aspects.

Data Synthesis and Statistical Analysis

Raw data regarding each outcome (number of events and total) were collected in order to calculate outcome prevalence and standard error. Effect measures included odds ratio (OR) for categorical variables and mean difference (MD) for continuous variables. For continuous outcomes, in some studies, median and range were transformed into mean and standard deviation through the methods proposed by the Cochrane collaboration and Hozo et al. [23, 24]. Meta-analysis was performed with Review Manager 5.4 soft-

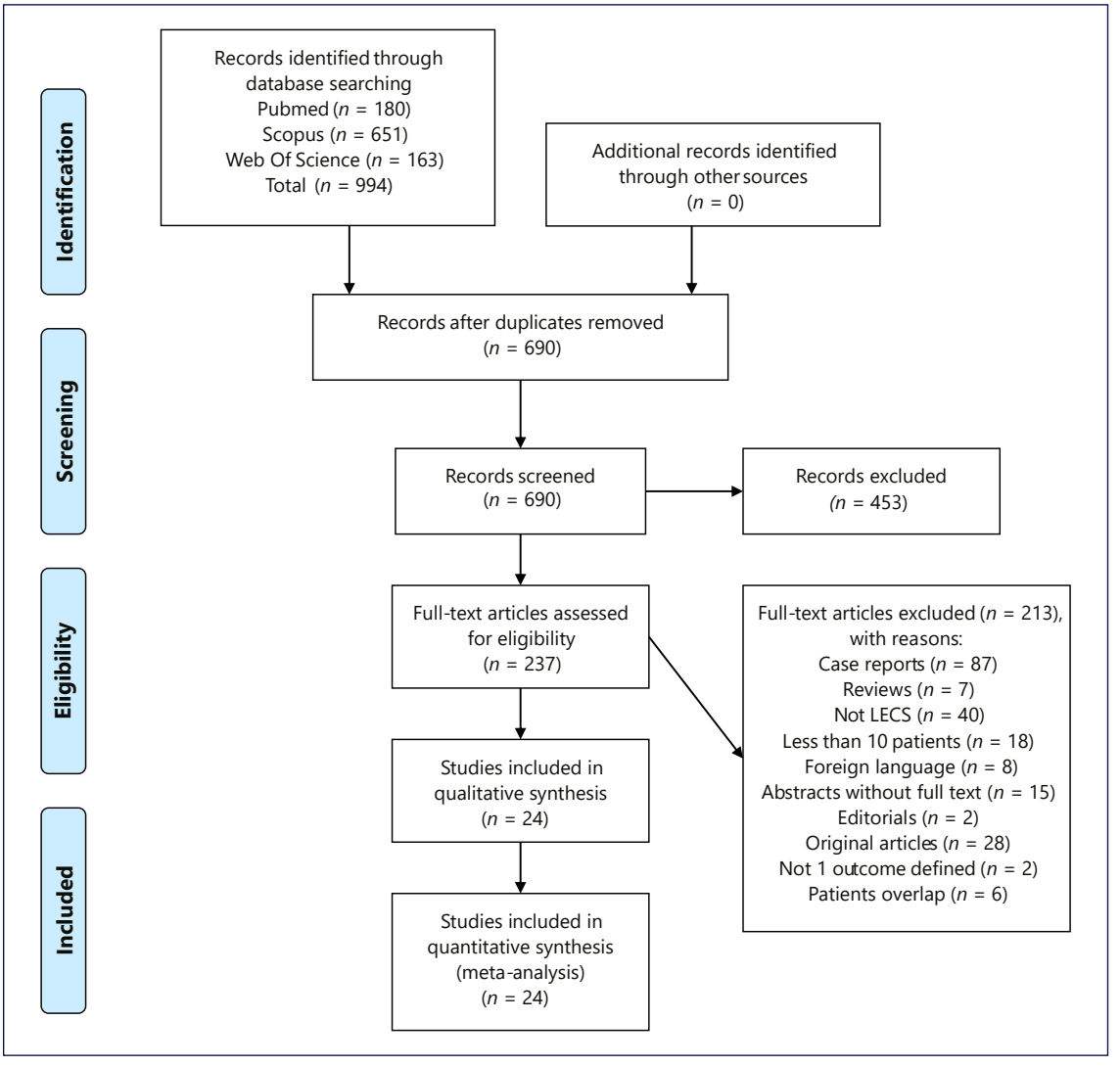


Fig. 1. Flowchart of included studies. LECS, laparoscopic and endoscopic cooperative surgery.

ware [25], using a random-effect model (when at least 3 studies were available for each outcome) [26]. Heterogeneity was evaluated with Cochran *Q* test and I^2, being significant heterogeneity defined as $p < 0.05$ or $I^2 > 40\%$, respectively. Subgroup analysis according to lesion was performed for 4 outcomes (need for conversion, procedure time, hospitalization time, and adverse events). Pooled mean for continuous variables and prevalence for categorical variables were calculated with OpenMetaAnalyst and MetaXL, using a random-effect model [26, 27]. Publication bias was planned if ≥10 studies were included in comparative analysis for the primary outcomes (procedure time and adverse events).

Results

Study Selection

A total of 994 studies were identified through data base search. After removing the duplicates, 690 studies were screened regarding title and abstract and 453 were considered irrelevant. Therefore, the full text of 237 studies was assessed for eligibility by applying inclusion and exclusion criteria. Of those, 24 were included in this systematic review and all were included in meta-analysis. Study flowchart is shown in Figure 1, according to the PRISMA statement [20].

GE Port J Gastroenterol 2023;30:4–19
DOI: 10.1159/000526644

Table 1. General characteristics of included studies

Study and year	Country	Type of study	*N*	Technique	Histological type	Newcastle
Esophagogastric junction						
Aoyama et al. [42], 2020	Japan	Retrospective Single-center	21	LECS (*N* = 13); NEWS (*N* = 4); CLEAN-NET (*N* = 4)	18 Leiomyomas, 2 GISTs, 1 Ectopic pancreas	6*
Hoteya et al. [19], 2014	Japan	Retrospective Single-center	5	LECS	4 Leiomyoma, 1 GIST	6
Ri et al. [48], 2020	Japan	Retrospective Single-center	20	LECS	Not available (all SEL)	7
Stomach						
Hajer et al. [39], 2019	Czech Republic and Austria	Retrospective Two-center	23	NEWS (*N* = 11); LWR (*N* = 12)	**NEWS**: 6 GISTs, 1 Submucosal lipoma, 1 Leiomyoma, 1 Endocrine tumor, 1 Vanek's tumor, and 1 Ectopic pancreatic; **LWR**: 7 GISTs, 1 Leiomyoma, 2 Ectopic pancreatic tissue, 1 Endometriosis, 1 Hyperplasiogenic polyp	6
Kanehira et al. [44], 2020	Japan	Retrospective Single-center	69	CLEAN-NET (*N* = 50); LWR (*N* = 19)	**CLEAN-NET:** 25 GIST; 10 Schwannoma; 6 Leiomyoma; 3 Ectopic pancreas; 3 Granuloma; 1 Carcinoid tumor; 1 Glomus tumor; 1 Cyst; **LWR**: 11 GIST; 7 Leiomyoma; 1 Schwannoma	6
Mahawongkajit and Chanswangphuvana [45], 2020	Thailand	Retrospective Single-center	15	LECS (*N* = 10); NEWS (*N* = 5)	**LECS**: 9 GIST; 1 Leiomyoma **NEWS**: 3 GIST; 1 Schwannoma; 1 Ectopic pancreas	5*
Mitsui et al. [34], 2018	Japan	Retrospective Single-center	28	NEWS	28 GIST	3*
Okubo et al. [47], 2020	Japan	Retrospective Single-center	69	CLEAN-NET (*N* = 25); Laparoscopic distal gastrectomy (*N* = 44)	Not available	7
Aoyama et al. [41], 2020	Japan	Retrospective Single-center	42	NEWS	24 GIST; 6 Ectopic pancreas; 5 Leiomyoma; 3 Neurinoma; 2 Granuloma; 1 Hemangioma; 1 Gastritis cystica profunda; 1 Desmoid fibromatosis	6*
Shoji et al. [37], 2018	Japan	Retrospective Single-center	71	LECS (*N* = 14); NEWS (*N* = 26); LWR (*N* = 31)	**LECS**: 6 GIST; 7 Leiomyoma; 1 other; **NEWS**: 16 GIST; 2 Leiomyoma; 8 others; **LWR**: 27 GIST; 1 Leiomyoma; 3 others	7
Balde et al. [30], 2016	China	Retrospective Single-center	60	LECS (*N* = 30); ESD (*N* = 30);	60 GIST	9
Cao et al. [38], 2019	China	Retrospective Single-center	45	LECS (*N* = 25) ESD (*N* = 20)	45 GIST	5
Hoteya et al. [19], 2014	Japan	Retrospective Single-center	20	LECS	15 GIST; 1 Leiomyoma; 1 Schwannoma; 1 Cavernous hemangioma; 2 Aberrant pancreas	6
Komatsu et al. [32], 2016	Japan	Retrospective Single-center	48	LECS (*N* = 33) LWR (*N* = 15)	Not available	7
Kang et al. [28], 2013	China	Retrospective Single-center	101	LECS	78 GIST; 13 Leiomyoma; 3 Ectopic pancreas; 3 NET; 2 Lipoma; 1 Glomus tumor; 1 Inflammatory pseudotumor	6*
Kikuchi et al. [14], 2017	Japan	Retrospective Single-center	10	Closed-LECS	Not available	5*
Ri et al. [48], 2020	Japan	Retrospective Single-center	194	LECS	Not available (all SEL)	7
Waseda et al. [29], 2014	Japan	Retrospective Single-center	22	LECS	10 GIST; 1 NET; 3 Aberrant pancreas; 3 Leiomyoma; 2 Glomus tumor; 2 Schwannoma; 1 Granuloma	6*

Table 1 (continued)

Study and year	Country	Type of study	*N*	Technique	Histological type	Newcastle
Ojima et al. [36], 2018	Japan	Retrospective Single-center	46	LECS (*N* = 21); EIGS (*N* = 25)	46 GIST	7
Tsujimoto et al. [17], 2012	Japan	Retrospective Single-center	20	LECS	16 GIST, 1 Inflammation for parasite; 1 Leiomyoma; 1 Glomus tumor; 1 Aberrant pancreas	5*
Yin et al. [33], 2017	China	Retrospective Single-center	91	LECS (*N* = 15); Laparoscopic resection (*N* = 30); ESD (*N* = 46)	91 GIST	9
Duodenum						
Kanaji et al. [43], 2020	Japan	Retrospective Single-center	20	D-LECS	16 Adenocarcinoma; 2 NET; 1 Adenoma; 1 Ectopic pancreas	5*
Ichikawa et al. [31], 2016	Japan	Retrospective Single-center	12 (13 lesions)	D-LECS	10 Adenocarcinoma; 2 NET; 1 Adenoma	5*
Nunobe et al. [46], 2020	Japan	Retrospective Multicenter	206	D-LECS	79 Adenoma; 70 Adenocarcinoma; 36 NET; 7 GIST; 6 Hyperplasia of Brunner's gland; 5 Hyperplastic polyp; 1 Ectopic pancreas, 1 Schwannoma; 1 Ulcer formation and malformation of vessels	5*
Ojima et al. [35], 2018	Japan	Retrospective Single-center	68	D-LECS (*N* = 18) D-ESD (*N* = 50)	**D-LECS**: 7 Intramucosal adenocarcinoma; 1 Adenoma; 6 NET; 4 GIST **D-ESD**: 14 Intramucosal adenocarcinoma; 27 Adenoma; 6 NET; 1 Hyperplastic polyp; 2 Lipoma	5
Yanagimoto et al. [40], 2019	Japan	Retrospective Single-center	10	D-LECS	6 Adenocarcinoma; 3 Adenoma; 1 Neuroendocrine tumor	6*
Mahawongkajit and Chanswangphuvana [45], 2020	Thailand	Retrospective Single-center	1	NEWS	1 Neuroendocrine tumor	5*

N, total number of cases; M-A, meta-analysis; LECS, laparoscopic and endoscopic cooperative surgery; NEWS, nonexposed endoscopic wall-inversion surgery; CLEAN-NET, combination of laparoscopic and endoscopic approaches to neoplasia with non-exposure technique; GIST, gastrointestinal stromal tumor; SEL, subepithelial lesions; LWR, laparoscopic wedge resection; ESD, endoscopic submucosal dissection; closed-LECS, closed laparoscopic and endoscopic cooperative surgery; D-LECS, laparoscopic and endoscopic cooperative surgery for duodenal neoplasm. *These are single-arm studies. Therefore, the score potential using Newcastle-Ottawa Quality Assessment Form for Cohort Studies ranges from 0 to 6 points.

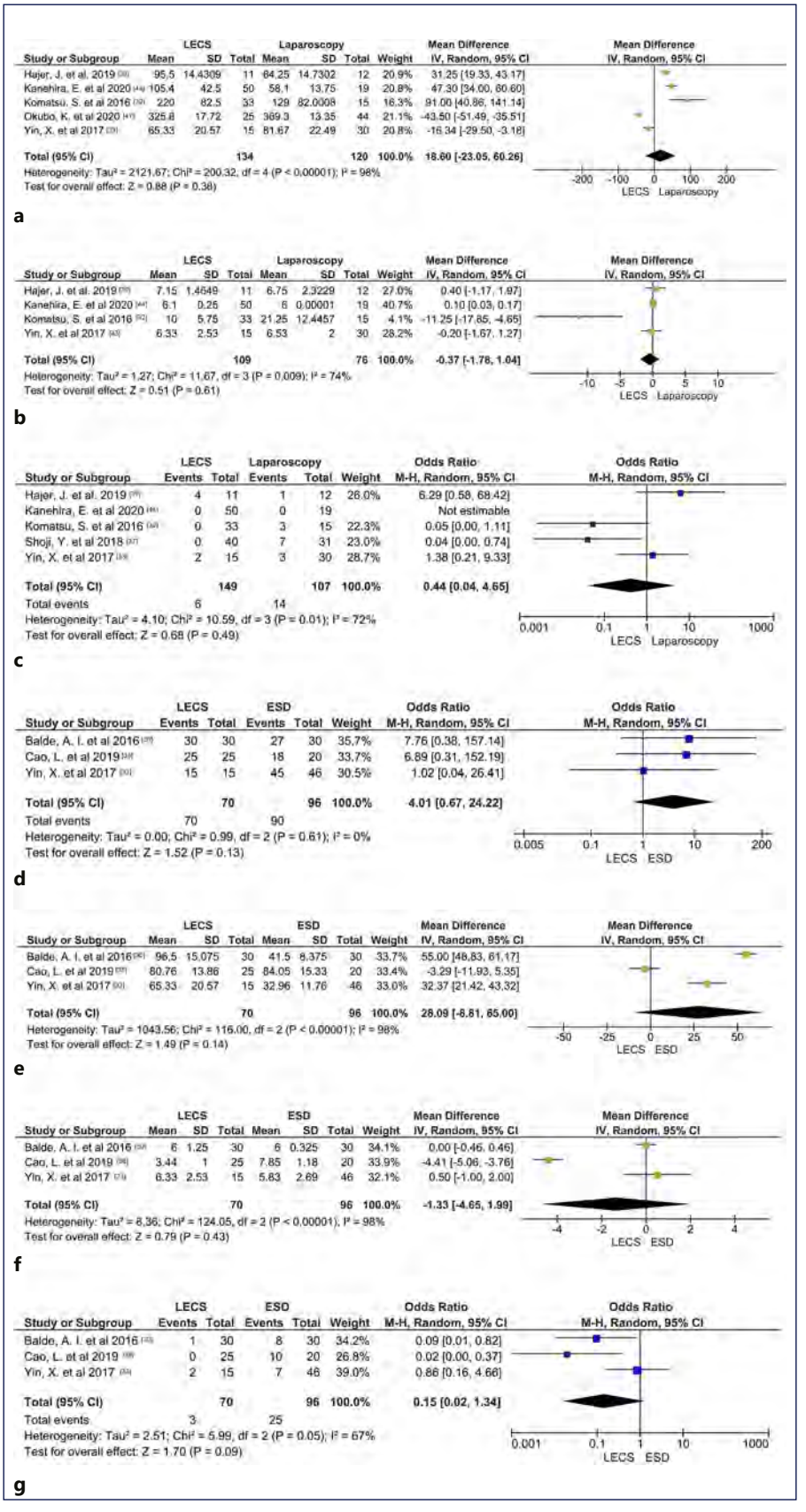


Fig. 2. a–g Forest plots of several outcomes according to surgical technique. **a** Forest plot of procedure time according to surgical technique (Laparoscopic Techniques vs. LECS). **b** Forest plot of hospitalization time according to surgical technique (Laparoscopic Techniques vs. LECS). **c** Forest plot of adverse event according to the surgical technique (Laparoscopic Techniques vs. LECS). **d** Forest plot of R0 according to the surgical technique (ESD vs. LECS). **e** Forest plot of procedure time according to the surgical technique (ESD vs. LECS). **f** Forest plot of hospitalization time according to the surgical technique (ESD vs. LECS). **g** Forest plot of adverse event according to the surgical technique (ESD vs. LECS). LECS, laparoscopic and endoscopic cooperative surgery; ESD, endoscopic submucosal dissection; SD, standard deviation.

Table 2. Comparative studies

Study	Location	*N*	Histology SEL versus EL (%)	Ro	Need for conversion	Procedure time, min	Hospitalization time, days	Recurrence	Adverse events	Mortality
EGJ versus Non-EGJ										
Hoteya et al. [19], 2014	EGJ	5	100% versus 0%	5	0	196±48.6	13.2±3.7	0	0	NR
	Non-EGJ	20	100% versus 0%	20	0	145.9±36.5	9.9±1.4	0	0	NR
Ri et al. [48], 2020	EGJ	20	100% versus 0%	20	8	320.25±102.25	20.5±12.5	NR	4	NR
	Non EGJ	194	100% versus 0%	194	2	195.25±86.321	31.75±30.3442	NR	8	NR
LECS versus Laparoscopic Techniques										
Hajer et al. [39], 2019	NEWS	11	100% versus 0%	11	NR	95.5±14.4309	7.15±1.4649	0	4	0
	LWR	12	92% versus 8%	11	NR	64.25±14.7302	6.75±2.3229	0	1	2
Kanehira et al. [44], 2020	CLEAN-NET	50	100% versus 0%	50	0	105.4±42.5	6.1±0.25	0	0	0
	LWR	19	100% versus 0%	19	0	58.1±13.75	6±0.00001	0	0	0
Shoji et al. [37], 2018	LECS (LECS and NEWS)	40	100% versus 0%	40	NR	NR	NR	0	0	NR
	LWR	31	100% versus 0%	31	NR	NR	NR	0	7	NR
Komatsu et al. [32], 2016	LECS	33	NR	33	NR	220±82.5	10±5.75	0	0	NR
	LWR	15	NR	15	NR	129±82.0008	21.25±12.4457	2	3	NR
Okubo et al. [47], 2020	CLEAN-NET	25	NR	NR	NR	325.8±17.72	NR	NR	NR	NR
	Laparoscopic distal gastrectomy	44	NR	NR	NR	369.3±13.35	NR	NR	NR	NR
Yin et al. [33], 2017	LECS	15	100% versus 0%	15	0	65.33±20.57	6.33±2.53	0	2	0
	Laparoscopic resection*	30	100% versus 0%	30	0	81.67±22.49	6.53±2	1	3	0
LECS versus ESD										
Balde et al. [30], 2016	LECS	30	100% versus 0%	30	0	96.5±15.075	6±1.25	0	1	NR
	ESD	30	100% versus 0%	27	0	41.5±8.375	6±0.325	2	8	NR
Cao et al. [38], 2019	LECS	25	100% versus 0%	25	0	80.76±13.86	3.44±1	0	0	0
	ESD	20	100% versus 0%	18	0	84.05±15.33	7.85±1.18	0	10	0
Yin et al. [33], 2017	LECS	15	100% versus 0%	15	0	65.33±20.57	6.33±2.53	0	2	0
	ESD	46	100% versus 0%	45	0	32.96±11.76	5.83±2.69	0	7	0
Duodenal LECS versus ESD										
Ojima et al. [35], 2018	LECS	18	56% versus 44%	18	0	132.75±57.5	7±1.5	NR	0	0
	ESD	50	16% versus 84%	26	0	41±28	3±12	NR	14	0

N, total number of cases; SEL, subepithelial lesions; EL, epithelial lesions; EGJ, esophagogastric junction; NR, data not reported on the study; LECS, laparoscopic and endoscopic cooperative surgery; NEWS, nonexposed endoscopic wall-inversion surgery; LWR, laparoscopic wedge resection; CLEAN-NET, combination of laparoscopic and endoscopic approaches to neoplasia with nonexposure technique; ESD, endoscopic submucosal dissection. *This includes LWR, proximal, and distal gastrectomy.

Study Characteristics and Quality Evaluation

The main study characteristics are shown in Table 1 [14, 17, 19, 28–48]. Most of the studies (23) were from Asia (96%) and 22 studies (92%) were single-center. All studies were retrospective. The median Newcastle-Ottawa Scale score of included studies was 6 (7 in double-arm studies and 5 in single-arm studies). A total of 1,337 lesions, from 1,336 patients, were included in the analysis, of which 46 (3.4%) were located in the EGJ, 974 (72.9%) in the stomach, and 317 (23.7%) in the duodenum. Half of the studies (12) were single-arm (of which 1 study was about lesions on the EGJ, 6 on the stomach, 4 on the duodenum, and 1 had lesions on both the stomach and the duodenum [45]). The other 12 studies were comparative. One study reported data regarding costs [37] and another one regarding quality of life [47].

Comparative Studies

LECS versus Laparoscopic Techniques

Six studies compared the outcomes of LECS and laparoscopic techniques (4 LECS vs. LWR [32, 37, 39, 44]; 1 LECS vs. laparoscopic gastrectomy [47]; 1 LECS vs. LWR and gastrectomy [33]) in gastric lesions. In meta-analysis, procedure time, hospitalization time, and adverse events were not significantly different between the two groups (shown in Fig. 2a–c), although there was a trend to longer procedure time in LECS' group (MD 18.3 min, 95% CI: −23.1 to 60.3, I^2 = 98%), shorter hospitalization time in LECS' group (MD −0.37, 95% CI: −1.8 to 1.0, I^2 = 74%), and lower adverse events rate in LECS' group (4.0% vs. 13.1%, OR: 0.44, 95% CI: 0.04–4.65, I^2 = 72%). Despite the tendency to longer procedure time in LECS' group, in the 2 studies that compared LECS with Laparoscopic gastrectomy [33, 47], procedure time was higher in laparoscopic techniques' group (shown in Table 2). R0 was 100% in LECS group and 99.6% (1/256) in LWR/laparoscopy's group. R0 was not achieved in 1 case using LWR [39]. The conversion rate was 0% in both groups. Recurrence occurred in 3 of 107 cases (2.8%) in laparoscopic techniques' group [32, 33] and in 0 of 149 cases (0%) in LECS' group. Two deaths were reported among the 61 cases of the laparoscopic group [39], and 0 among the 76 cases of the LECS' group (shown in Table 2). Both reported deaths were not related to the oncological disease neither its treatment. Meta-analysis was not possible in these last outcomes.

LECS versus ESD

Three studies compared the outcomes of LECS and ESD in gastric lesions [30, 33, 38]. In meta-analysis, R0, procedure time, hospitalization time, and adverse events were not significantly different between the two groups (shown in Fig. 2d–g), although there was a trend to higher complete resection rate in LECS's group (100% vs. 94%, OR: 4.01, 95% CI: 0.67–24.22, I^2 = 0%), longer procedure time in LECS' group (MD 28.1, 95% CI: −8.81 to 65.00, I^2 = 98%), shorter hospitalization time in LECS' group (MD −1.33, 95% CI: −4.65 to 1.99, I^2 = 98%), and lower adverse events rate in LECS' group (4,3% vs. 26%, OR: 0.15, 95% CI: 0.02–1.34, I^2 = 67%). The conversion rate was 0% in both groups. Recurrence was noticed in 2 of the 96 cases (2.08%) using ESD [30] and in 0 of the 70 cases using LECS. No deaths were reported in 106 cases (shown in Table 2).

Duodenal LECS versus ESD

One study compared the outcomes of LECS and ESD in duodenal lesions [35]. R0 was 100% in LECS' group, but only 52% in ESD group, corresponding to 26 among the 50 cases. There was no need for conversion in any studies. Procedure duration and hospitalization time were higher in LECS' group. Recurrence was not reported. ESD's group accounted for a total of 14 adverse events (28%), whereas LECS had 0 adverse events among its 18 cases (0%). No deaths were reported (shown in Table 2). Meta-analysis was not performed due to a low number of studies.

Single-Arm Studies regarding LECS

Half of all included studies were noncomparative LECS studies. Twenty-four studies provided data for the calculation of pooled efficacy and safety outcomes. This is shown in Table 3.

EGJ

Three studies provided data on 46 EGJ lesions [19, 42, 48]. R0 resection rate was 100% and pooled conversion rate was 11.3% (95% CI: 0–47.1%, I^2 = 87%). The 8 conversion cases occurred in the same study [48]. Pooled mean procedural time was 246 min (95% CI: 185–307, I^2 = 89%), and pooled mean hospitalization time was 13.7 days (95% CI: 8.0–19.3, I^2 = 91%). Two studies reported recurrence rates [19, 42] and it was 0% (0 in 26 cases). Pooled adverse events' rate was 7.1% (95% CI: 0–24.7%, I^2 = 67%), with all 4 adverse events occurring in the same study [48]. Mortality was 0% (0 in 21 cases).

Gastric

Eighteen studies provided data on 702 gastric lesions [14, 17, 19, 28–30, 32–34, 36–39, 41, 44, 45, 47, 48]. R0

Table 3. Single-arm studies

Study	*N*	Histology SEL/EL (%)	Ro	Need for conversion	Procedure time, min	Hospitalization time, days	Recurrence	Adverse events	Mortality
EGJ									
Aoyama et al. [42], 2020	21	100% versus 0%	21	0	225±48	9.0±1.9	0	0	0
Hoteya et al. [19], 2014	5	100% versus 0%	5	0	196.0±48.6	13.2±3.7	0	0	NR
Ri et al. [48], 2020	20	100% versus 0%	20	8	320.25±102.25	20,5±12,5	NR	4	NR
Stomach									
Hajer et al. [39], 2019	11	100% versus 0%	11	NR	95.5±14.4309	7.15±1.4649	0	4	0
Kanehira et al. [44], 2020	50	100% versus 0%	50	0	105.4±42.5	6,1±0.25	0	0	0
Mitsui et al. [34], 2018	28	100% versus 0%	NR	2	193.107±59.726	NR	NR	1	NR
Okubo et al. [47], 2020	25	NR	NR	NR	325.80±17.72	NR	NR	NR	NR
Mahawongkajit and Chanswangphuvana [45], 2020	15	100% versus 0%	15	NR	NR	NR	0	0	0
Aoyama et al. [41], 2020	42	100% versus 0%	42	NR	198±14.25	7.0±0.425	0	1	0
Shoji et al. [37], 2018	40	100% versus 0%	40	NR	NR	NR	0	0	NR
Balde et al. [30], 2016	30	100% versus 0%	30	0	96.5±15.075	6.0±1.25	0	1	NR
Cao et al. [38], 2019	25	100% versus 0%	25	0	80.76±13.86	3.44±1.00	0	0	0
Hoteya et al. [19], 2014	20	100% versus 0%	20	0	145.9±36.5	9.9±1.4	0	0	NR
Komatsu et al. [32], 2016	33	NR	33	NR	220±82.5	10±5.75	0	0	NR
Kang et al. [28], 2013	101	100% versus 0%	101	0	113±36	NR	0	2	0
Kikuchi et al. [14], 2017	10	NR	NR	1	253±45	9.2±1.5	0	2	NR
Ri et al. [48], 2020	194	100% versus 0%	194	2	181±49.8333	7±17.5	NR	8	NR
Waseda et al. [29], 2014	22	100% versus 0%	22	0	NR	NR	0	2	NR
Ojima et al. [36], 2018	21	100% versus 0%	21	NR	151±53.5	8.5±2.5	1	1	0
Tsujimoto et al. [17], 2012	20	100% versus 0%	20	0	157.5±68.4	11.6±9.5	0	0	0
Yin et al. [33], 2017	15	100% versus 0%	15	0	65.33±20.57	6.33±2.53	0	2	0
Duodenum									
Mahawongkajit and Chanswangphuvana [45], 2020	1	100% versus 0%	1	0	261	NR	0	0	0
Kanaji et al. [43], 2020	20	15% versus 85%	19	0	236.25±56.75	12.5±2.5	0	2	0
Ichikawa et al. [31], 2016	12	15% versus 85%	NR	0	358.5±101.0511	18.5±12.1552	0	4	NR
Nunobe et al. [46], 2020	206	25% versus 75%	196	11	180±90.1667	9±12	0	38	NR
Ojima et al. [35], 2018	18	56% versus 44%	18	0	132.75±57.5	7±1.5	NR	0	0
Yanagimoto et al. [40], 2019	10	10% versus 90%	10	0	256.35±60.6412	8.75±2.0052	0	2	NR

N, total number of patients; SEL, subepithelial lesions; EL, epithelial lesions; EGJ, esophagogastric junction; NR, data not reported on the study.

resection rate was 100%. Pooled conversion rate was 1.0% (95% CI: 0.4–2.2%, I^2 = 0%). The 5 conversion cases occurred in 3 different studies [14, 34, 48]. Pooled mean procedural time was 158 min (95% CI: 118–199, I^2 = 100%), and pooled mean hospitalization time was 7.3 days (95% CI: 6.6–8.0, I^2 = 98%). Fifteen studies reported recurrence rates and it was 0.22% (1 in 455 cases). This case was reported by Ojima et al. [36], in an 85-year-old patient with a 90-mm lesion. Pooled adverse events' rate was 3.5% (95% CI: 1.8–6.0; I^2 = 44%), with a total of 24 adverse events reported in 677 cases. Mortality was reported only in 9 studies and it was 0% (0 in 300 cases).

Duodenal

Six studies provided data on 267 duodenal lesions [31, 35, 40, 43, 45, 46]. R0 resection rate was 95.7%. Incomplete resection was reported in 11 of 255 cases (4.3%), which included 2 studies: Kanaji et al. [43] and Nunobe et al. [46] . Pooled conversion rate was 4.3% (95% CI: 2.2–7.1; I^2 = 0%). Need for conversion was reported in 11

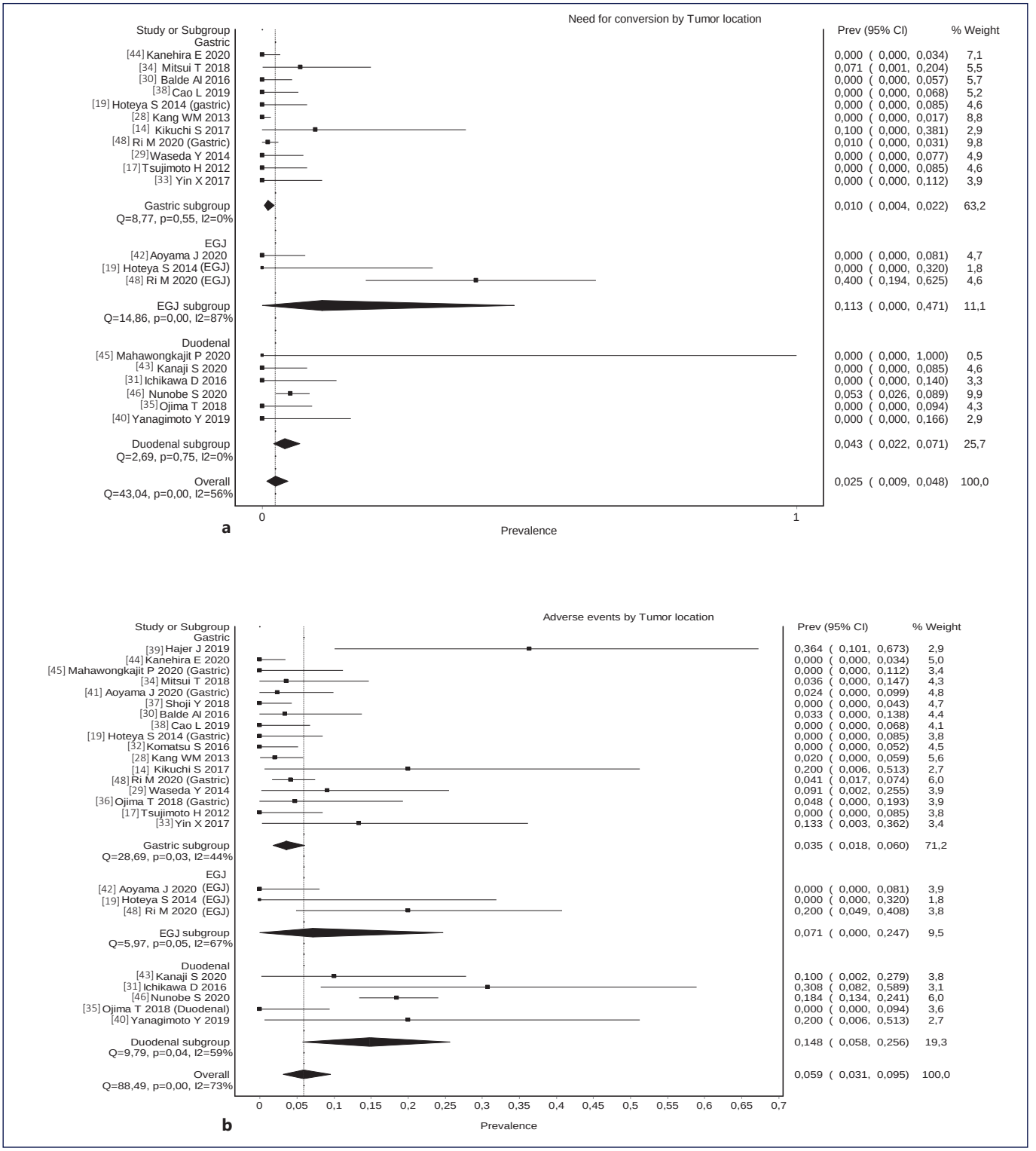
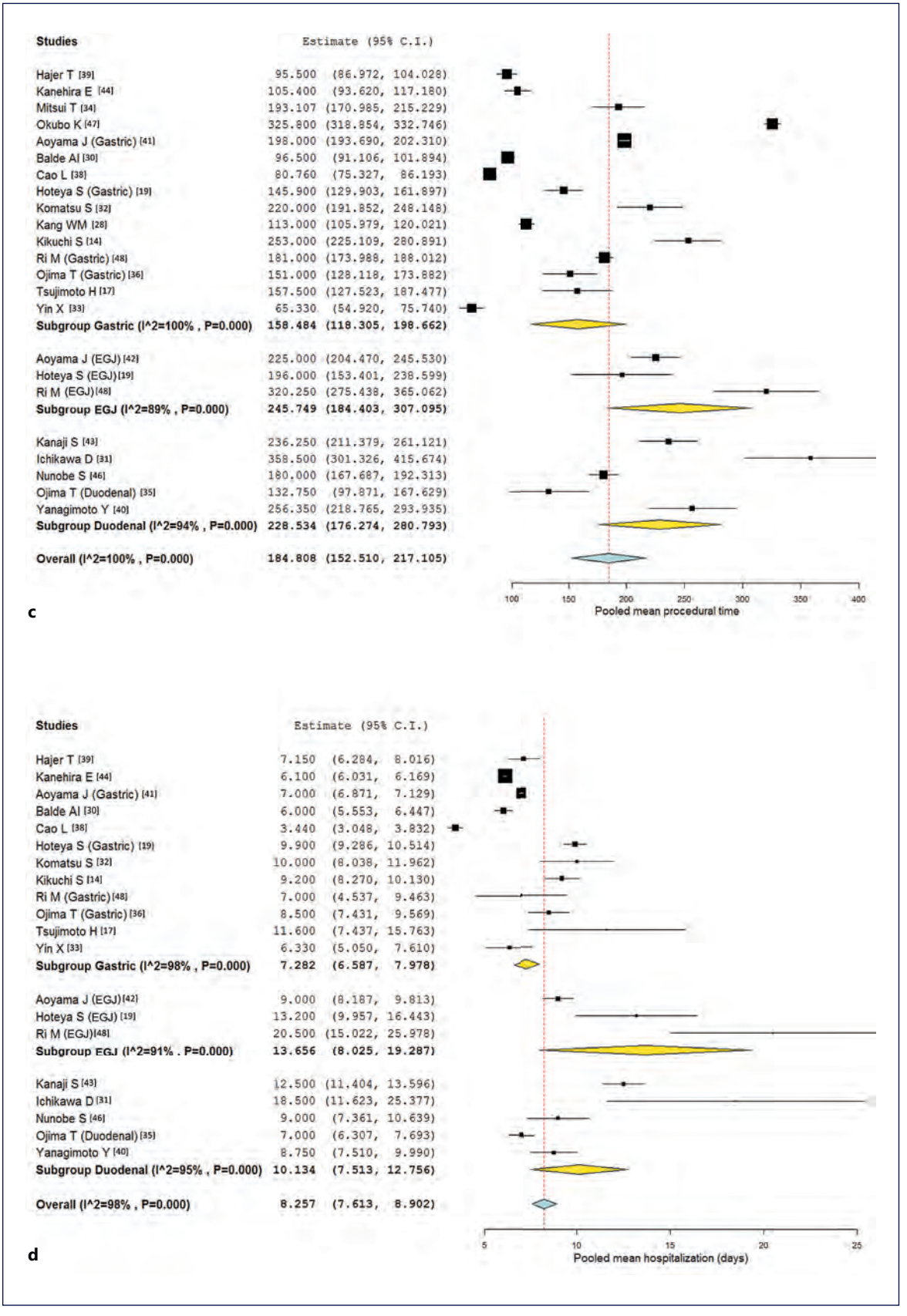


Fig. 3. a–**d** Rates of conversion and adverse events according to location (gastric, EGJ, and duodenal). Forest plots of mean hospitalization time and mean procedure time according to the location (gastric, EGJ and duodenal). **a** Rates of conversion according to the location (gastric, EGJ, and duodenal). **b** Rates of adverse events according to the location. **c** Forest plots of mean hospitalization time according to the location (gastric, EGJ, and duodenal). **d** Forest plots of mean procedure time according to the location (gastric, EGJ, and duodenal). EGJ, esophagogastric junction.

(Figure continued on next page.)


Studies
Estimate (95% C.I.)
Hajer T [39] 95.500 (86.972, 104.028)
Kanehira E [44] 105.400 (93.620, 117.180)
Mitsui T [34] 193.107 (170.985, 215.229)
Okubo K [47] 325.800 (318.854, 332.746)
Aoyama J (Gastric) [41] 198.000 (193.690, 202.310)
Balde AI [30] 96.500 (91.106, 101.894)
Cao L [38] 80.760 (75.327, 86.193)
Hoteya S (Gastric) [19] 145.900 (129.903, 161.897)
Komatsu S [32] 220.000 (191.852, 248.148)
Kang WM [28] 113.000 (105.979, 120.021)
Kikuchi S [14] 253.000 (225.109, 280.891)
Ri M (Gastric) [48] 181.000 (173.988, 188.012)
Ojima T (Gastric) [36] 151.000 (128.118, 173.882)
Tsujimoto H [17] 157.500 (127.523, 187.477)
Yin X [33] 65.330 (54.920, 75.740)
Subgroup Gastric (I^2=100% , P=0.000) 158.484 (118.305, 198.662)
Aoyama J (EGJ) [42] 225.000 (204.470, 245.530)
Hoteya S (EGJ) [19] 196.000 (153.401, 238.599)
Ri M (EGJ) [48] 320.250 (275.438, 365.062)
Subgroup EGJ (I^2=89% , P=0.000) 245.749 (184.403, 307.095)
Kanaji S [43] 236.250 (211.379, 261.121)
Ichikawa D [31] 358.500 (301.326, 415.674)
Nunobe S [46] 180.000 (167.687, 192.313)
Ojima T (Duodenal) [35] 132.750 (97.871, 167.629)
Yanagimoto Y [40] 256.350 (218.765, 293.935)
Subgroup Duodenal (I^2=94% , P=0.000) 228.534 (176.274, 280.793)
Overall (I^2=100% , P=0.000) 184.808 (152.510, 217.105)
100 150 200 250 300 350 400
Pooled mean procedural time
c
Studies
Estimate (95% C.I.)
Hajer T [39] 7.150 (6.284, 8.016)
Kanehira E [44] 6.100 (6.031, 6.169)
Aoyama J (Gastric) [41] 7.000 (6.871, 7.129)
Balde AI [30] 6.000 (5.553, 6.447)
Cao L [38] 3.440 (3.048, 3.832)
Hoteya S (Gastric) [19] 9.900 (9.286, 10.514)
Komatsu S [32] 10.000 (8.038, 11.962)
Kikuchi S [14] 9.200 (8.270, 10.130)
Ri M (Gastric) [48] 7.000 (4.537, 9.463)
Ojima T (Gastric) [36] 8.500 (7.431, 9.569)
Tsujimoto H [17] 11.600 (7.437, 15.763)
Yin X [33] 6.330 (5.050, 7.610)
Subgroup Gastric (I^2=98% , P=0.000) 7.282 (6.587, 7.978)
Aoyama J (EGJ) [42] 9.000 (8.187, 9.813)
Hoteya S (EGJ) [19] 13.200 (9.957, 16.443)
Ri M (EGJ) [48] 20.500 (15.022, 25.978)
Subgroup EGJ (I^2=91% , P=0.000) 13.656 (8.025, 19.287)
Kanaji S [43] 12.500 (11.404, 13.596)
Ichikawa D [31] 18.500 (11.623, 25.377)
Nunobe S [46] 9.000 (7.361, 10.639)
Ojima T (Duodenal) [35] 7.000 (6.307, 7.693)
Yanagimoto Y [40] 8.750 (7.510, 9.990)
Subgroup Duodenal (I^2=95% , P=0.000) 10.134 (7.513, 12.756)
Overall (I^2=98% , P=0.000) 8.257 (7.613, 8.902)
5 10 15 20 25
Pooled mean hospitalization (days)
d

3

cases, in Nunobe et al. [46] . Pooled mean procedural time was 229 min (95% CI: 176–281, I^2 = 94%), and pooled mean hospitalization time was 10.1 days (95% CI: 7.5–12.7, I^2 = 95%). Recurrence rate was 0% (0 in 249 cases). Pooled adverse events' rate was 14.8% (95% CI: 5.8–25.6, I^2 = 59%), with a total of 46 adverse events reported in 267 cases. Mortality was reported only in 3 studies [35, 43, 45] and it was 0% (0 in 39 cases).

Overall, pooled conversion rate was 2.5% (95% CI: 0.9–4.8%, I^2 = 56%). Although there were no statistically significant differences in the conversion rate according to the location, there was a trend to higher conversion in EGJ lesions (11.3%, 95% CI: 0–47.1%, I^2 = 87%), followed by duodenal lesions (4.3%, 95% CI: 2.2–7.1%, I^2 = 0%) and gastric lesions (1.0%, 95% CI: 0.4–2.2%, I^2 = 0%). This is shown in Figure 3. Pooled adverse events' rate was 5.9% (95% CI: 3.1–9.5, I^2 = 73%). Although there were no statistically significant differences in adverse events' rate according to the location, there was a trend to higher rate of adverse events in duodenal lesions (14.8%, 95% CI: 5.8–25.6, I^2 = 59%), followed by EGJ lesions (7.1%, 95% CI: 0–24.7, I^2 = 67%) and gastric lesions (3.5%, 95% CI: 1.8–6, I^2 = 67%). This is shown in Figure 3b. Pooled mean procedural time was 185 min (95% CI: 153–217, I^2 = 100%). Mean procedural time was also not significantly different according to the location. However, the same trend was verified: higher procedural time in EGJ lesions (246 min, 95% CI: 184–307, I^2 = 100%), followed by duodenal lesions (229 min, 95% CI: 176–281, I^2 = 94%) and gastric lesions (158 min, 95% CI: 118–199, I^2 = 100%). This is shown in Figure 3c. Pooled mean hospitalization time was 8.3 days (95% CI: 7.6–8.9, I^2 = 98%). Hospitalization time was significantly shorter in gastric lesions versus EGJ lesions (mean 7.3 vs. 13.7 days, 95% CIs of 6.6–7.9 and 8.9–19.3, respectively). There was higher hospitalization time in EGJ lesions (13.7 days, 95% CI: 8–19.3, I^2 = 91%), followed by duodenal lesions (10.1 days, 95% CI: 7.5–12.8, I^2 = 95%) and gastric lesions (7.3 days, 95% CI: 6.6–8, I^2 = 98%). This is shown in Figure 3d.

Costs

Shoji et al. [37] analyzed the operative costs of 3 techniques: LWR, LECS, and NEWS. NEWS was associated with a significantly lower mean total cost, followed by LECS, and being LWR the most expensive technique. The major cause pointed by the authors for these differences was the cost of suturing devices, such as laparoscopic linear staplers, which were less used in the NEWS' group ($p < 0.001$). Authors also referred that, although a hand-sewn technique used on LECS and NEWS was cheaper, it increased the operative time, resulting in higher personnel and anesthetic expenses.

Quality of Life

Okubo et al. [47] evaluated postoperative quality of life after local resection (CLEAN-NET) and distal gastrectomy, using the Postgastrectomy Syndrome Assessment Scale (PGSAS-45) questionnaire and endoscopic evaluation at 1, 6, and 12 months after surgery. Authors reported significantly endoscopic differences 12 months after gastrectomy, with less esophageal reflux and residual gastritis in the group submitted to CLEAN-NET. CLEAN-NET subgroup also presented better clinical symptoms 12 months after procedure, reporting less indigestion, less dissatisfaction during meals, less dissatisfaction for daily life, and more amount of food ingested per meal, resulting in better nutritional status and body weight ratio.

Histology

Three studies reported histological evaluation of the surgical specimens in the EGJ [19, 42, 48]. All lesions were subepithelial (total of 46 lesions). Regarding gastric lesions, 15 studies reported histological evaluation of 847 surgical specimens [17, 19, 28–30, 33, 34, 36–39, 41, 44, 45, 48]. One lesion (0.1%) was epithelial [39] and the other 846 lesions (99.9%) were subepithelial. Six studies reported histological evaluation of retrieved lesions in the duodenum, making a total of 318 lesions [31, 35, 40, 43, 45, 46]. Seventy-six lesions (24%) were subepithelial and 242 (76%) were epithelial lesions. The location with higher number of epithelial retrieved lesions was the duodenum. This is shown in Tables 2 and 3.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis comparing LECS with laparoscopic techniques (LWR and laparoscopic gastrectomy) and endoscopic techniques (ESD). We found that LECS is an effective and safe therapy for upper GI SELs, with high rates of R0 and low adverse events rates, shorter hospitalization time, and longer procedure time. Additionally, we found that, to date, there is no clear evidence of the benefit of LECS over ESD or LWR/laparoscopy namely in procedural/hospitalization time nor in R0/adverse events, in gastric lesions.

Regarding gastric lesions, no significant differences were found between LECS and preexisting techniques (ESD or LWR/laparoscopy) regarding any outcomes.

This might be explained by the high heterogeneity and low number of comparative studies. However, we could observe some trends in our results: LECS was associated with higher R0, shorter hospitalization time, and longer procedure duration, comparing to ESD. Comparing to laparoscopic techniques, hospitalization time was lower and procedure duration was higher when LECS was the chosen procedure. Although analyzing separately LWR and laparoscopic gastrectomy's procedure duration, we noticed that LECS was shorter than those procedures using laparoscopic gastrectomies and longer than those using LWR. LECS was associated with fewer adverse events comparing with both laparoscopic and endoscopic procedures. Hajer et al. [39] stood out from the other 4 studies [32, 33, 37, 44], which compared adverse events between LECS and LWR/laparoscopy, having a marked deviation to the direction that favors LWR/laparoscopy. It is important to mention that it is a two-center study in which the two compared subgroups were from different hospitals and from different countries. Given that, we cannot assure that both groups have the same characteristics [39].

Regarding duodenal lesions, ESD was associated with nonsignificantly higher rates of incomplete local resection and adverse events, while LECS was associated with nonsignificantly longer procedure duration and hospital stay.

Hospitalization time was significantly shorter in gastric lesions compared to EGJ lesions. There were no statistically significant differences in conversion rate, mean procedural time, or adverse events' rate according to the location. However, there was a trend to higher conversion rate and longer procedure duration in EGJ lesions and higher rate of adverse events in duodenal lesions.

The conversion rate tended to be higher in the EGJ subgroup because Ri et al. [48] reported 8 cases who needed conversion due to esophageal invasion and large defects after lesion resection (more than half of the circumference of the EGJ). This might explain the higher need for conversion presented by this study.

Two studies that reported the need for conversion in gastric lesions [14, 34] used 2 modified procedures: NEWS and closed-LECS, which include transoral removal of the lesion. Several lesions with more than 30 mm were reported, which require conversion to achieve adequate specimen retrieval. Therefore, this may partially explain the higher rates of conversion in these studies.

R0 was nonsignificantly lower in duodenal procedures (95.7% vs. 100%). This can be explained by several technical difficulties such as maintaining an adequate vision field, accessing the narrow duodenal lumen, holding the endoscope on position, and maneuvering it in such limited space [31, 43, 49, 50]. These difficulties can also explain the higher adverse events' rates in the duodenum, comparing with other gastrointestinal locations.

Both procedure and hospitalization durations tended to be longer in the EGJ group, followed by the duodenum. This can be explained by the higher rate of conversion in these locations, as it will inevitably prolong the duration of the procedure and may lead to more complex techniques, such as proximal gastrectomies. EGJ lesions may be difficult to completely resect without excessive removal of surrounding tissues, increasing the conversion rate. Additionally, it also requires hand-suturing, which contributes to longer duration of the procedure [51].

Some other characteristics were approached. LWR was associated with higher operative costs than LECS and its modified procedures [37].CLEAN-NET was associated with better postoperative quality of life than distal gastrectomy [47].

In another meta-analysis on this topic, Cai et al. [52] compared LECS with ESD and included Ojima et al. [36] in their meta-analysis. The procedure used by Ojima et al. [36] in the ESD arm (EIGS) did not fit in our definition of ESD, as it required the opening of the abdominal and gastric walls in order to deliver the endoscope and surgical instruments. Despite these differences, Cai et al. [52] reported higher incidence of complications and lower procedure time in ESD. Our results tended to the same conclusions.

This is the first systematic review and meta-analysis comparing LECS with laparoscopic and endoscopic techniques. We evaluated the safety and efficacy of LECS on three different locations: EGJ, stomach, and duodenum.

This systematic review and meta-analysis has some limitations. First, all studies were observational and retrospective reports (mainly single-center), as no randomized controlled trials exist on this subject, making them prone to selection bias. Although median quality of existing studies is good (6), the risk of bias is not null. Second, high heterogeneity was found in some outcomes, probably due to large variations among techniques. Despite being inspired by the same technique, modified LECS procedures have some differences. Moreover, our sample size was relatively small: we analyzed 1,337 lesions in this systematic review and most studies had a small number of cases, which can decrease their precision. Lastly, the number of relevant studies comparing LECS on EGJ and other locations as well as comparing duodenal LECS with ESD was insufficient to perform meta-analysis.

Conclusion

LECS can be a valid, safe, and effective treatment option in patients with EGJ, gastric, and duodenal lesions. However, we consider that treatment choice must be individualized, taking in account the experience of the center and the clinical expertise of the medical team involved. Prospective studies are needed to confirm if LECS is superior to other established techniques.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on the published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This article did not require funding.

Author Contributions

Sara Oliveira de Brito and Diogo Libânio conceived and designed the study. Sara Oliveira de Brito and João Pedro Pinho Osório de Araújo Teixeira undertook the bibliographic research and, independently, screened the articles. Sara Brito, Diogo Libânio, and João Pedro Pinho Osório de Araújo Teixeira selected for eligibility, determined inclusion, and reviewed the articles included. Sara Oliveira de Brito drafted the manuscript. Diogo Libânio, Cláudia Martins Marques Pinto, and João Paulo Meireles de Araújo Teixeira revised the draft and approved the final manuscript.

Data Availability Statement

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

References

1 Hiki N, Yamamoto Y, Fukunaga T, Yamaguchi T, Nunobe S, Tokunaga M, et al. Laparoscopic and endoscopic cooperative surgery for gastrointestinal stromal tumor dissection. Surg Endosc. 2008 Jul;22(7):1729–35.
2 Namikawa T, Hanazaki K. Laparoscopic endoscopic cooperative surgery as a minimally invasive treatment for gastric submucosal tumor. World J Gastrointest Endosc. 2015 Oct 10;7(14):1150–6.
3 Matsuda T, Nunobe S, Ohashi M, Hiki N. Laparoscopic endoscopic cooperative surgery LECS for the upper gastrointestinal tract. Transl Gastroenterol Hepatol. 2017;2:40.
4 Hiki N, Nunobe S. Laparoscopic endoscopic cooperative surgery (LECS) for the gastrointestinal tract: updated indications. Ann Gastroenterol Surg. 2019 May;3(3):239–46.
5 Hiki N, Nunobe S, Matsuda T, Hirasawa T, Yamamoto Y, Yamaguchi T. Laparoscopic endoscopic cooperative surgery. Dig Endosc. 2015 Jan;27(2):197–204.
6 Kato M, Yahagi N. Advanced endoscopic treatment of gastric and duodenal neoplasms: beyond standard EMR and ESD. Am J Gastroenterol. 2018;113(10):1423–6.
7 Goto O, Takeuchi H, Kitagawa Y, Yahagi N. Endoscopic submucosal dissection (esd) and related techniques as precursors of "new notes" resection methods for gastric neoplasms. Gastrointest Endosc Clin N Am. 2016 Apr;26(2):313–22.
8 Tsai TC, Meireles OR. Combined surgical and endoscopic approaches to full-thickness resection. Tech Gastrointest EndoscTechniques Gastrointest Endosc. 2019 Jan;21(1):26–32.
9 Kim HH, Uedo N. Hybrid NOTES: combined laparo-endoscopic full-thickness resection techniques. Gastrointest Endosc Clin N Am. 2016 Apr;26(2):335–73.
10 Nunobe S, Hiki N, Gotoda T, Murao T, Haruma K, Matsumoto H, et al. Successful application of laparoscopic and endoscopic cooperative surgery (LECS) for a lateral-spreading mucosal gastric cancer. Gastric Cancer. 2012 Jul;15(3):338–42.
11 Inoue H, Ikeda H, Hosoya T, Yoshida A, Onimaru M, Suzuki M, et al. Endoscopic mucosal resection, endoscopic submucosal dissection, and beyond: full-layer resection for gastric cancer with nonexposure technique (CLEAN-NET). Surg Oncol Clin N Am. 2012 Jan;21(1):129–40.
12 Goto O, Mitsui T, Fujishiro M, Wada I, Shimizu N, Seto Y, et al. New method of endoscopic full-thickness resection: a pilot study of non-exposed endoscopic wall-inversion surgery in an ex vivo porcine model. Gastric Cancer. 2011 Jun;14(2):183–7.
13 Goto O, Takeuchi H, Kawakubo H, Matsuda S, Kato F, Sasaki M, et al. Feasibility of non-exposed endoscopic wall-inversion surgery with sentinel node basin dissection as a new surgical method for early gastric cancer: a porcine survival study. Gastric Cancer. 2015 Apr;18(2):440–5.
14 Kikuchi S, Nishizaki M, Kuroda S, Tanabe S, Noma K, Kagawa S, et al. Nonexposure laparoscopic and endoscopic cooperative surgery (closed laparoscopic and endoscopic cooperative surgery) for gastric submucosal tumor. Gastric Cancer. 2017 May;20(3):553–7.
15 Fujishiro M, Furukawa K, Yamamura T, Nakamura M, Honda T, Maeda O, et al. Nonexposed wall-inversion surgery as a novel local resection method for neoplasms in the gastrointestinal tract. Nagoya J Med Sci. 2020 May;82(2):175–82.
16 Wong VWY, Goto O, Gregersen H, Chiu PWY. Endoscopic treatment of subepithelial lesions of the gastrointestinal tract. Curr Treat Options Gastroenterol. 2017 Dec;15(4):603–17.
17 Tsujimoto H, Yaguchi Y, Kumano I, Takahata R, Ono S, Hase K. Successful gastric submucosal tumor resection using laparoscopic and endoscopic cooperative surgery. World J Surg. 2012 Feb;36(2):327–30.
18 Qiu WQ, Zhuang J, Wang M, Liu H, Shen ZY, Xue HB, et al. Minimally invasive treatment of laparoscopic and endoscopic cooperative surgery for patients with gastric gastrointestinal stromal tumors. J Dig Dis. 2013 Sep;14(9):469–73.
19 Hoteya S, Haruta S, Shinohara H, Yamada A, Furuhata T, Yamashita S, et al. Feasibility and safety of laparoscopic and endoscopic cooperative surgery for gastric submucosal tumors, including esophagogastric junction tumors. Dig Endosc. 2014 Jul;26(4):538–44.
20 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21;6(7):e1000097.
21 Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan -a web and mobile app for systematic reviews. Systematic Rev. 2016;5(1):210.

22 Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Oxford; 2000. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
23 Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5(1):113–0.
24 Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions. John Wiley & Sons; 2019. Available from: www.training.cochrane.org/handbook.
25 Manager R. VReview Manager Version 5.4, The Cochrane Collaboration. Denmark: The Nordic Cochrane Centre Copenhagen; 2020. Available from: https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman.
26 Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Stat Softw. 2010;36(3):1–48.
27 Wallace BC, Dahabreh IJ, Trikalinos TA, Lau J, Trow P, Schmid CH. Closing the gap between methodologists and end-users: R as a computational back-end. J Stat Softw. 2012;49(5):1–15.
28 Kang WM, Yu JC, Ma ZQ, Zhao ZR, Meng QB, Ye X. Laparoscopic-endoscopic cooperative surgery for gastric submucosal tumors. World J Gastroenterol. 2013 Sep 14;19(34):5720–6.
29 Waseda Y, Doyama H, Inaki N, Nakanishi H, Yoshida N, Tsuji S, et al. Does laparoscopic and endoscopic cooperative surgery for gastric submucosal tumors preser ve residual gastric motility? Results of a retrospective single-center study. PLoS One. 2014;9(6):e101337.
30 Balde AI, Chen T, Hu Y, Redondo N JD, Liu H, Gong W, et al. Safety analysis of laparoscopic endoscopic cooperative surgery versus endoscopic submucosal dissection for selected gastric gastrointestinal stromal tumors: a propensity score-matched study. Surg Endosc. 2016 Feb;31(2):843–51.
31 Ichikawa D, Komatsu S, Dohi O, Naito Y, Kosuga T, Kamada K, et al. Laparoscopic and endoscopic co-operative surgery for non-ampullary duodenal tumors. World J Gastroenterol. 2016 Dec 21;22(47):10424–31.
32 Komatsu S, Ichikawa D, Kosuga T, Okamoto K, Konishi H, Shiozaki A, et al. Clinical impact of laparoscopy and endoscopy cooperative surgery (LECS) on gastric submucosal tumor after its standardization. Anticancer Res. 2016 Jun;36(6):3041–7.
33 Yin X, Yin Y, Chen H, Shen C, Tang S, Cai Z, et al. Comparison analysis of three different types of minimally invasive procedures for gastrointestinal stromal tumors ≤5 cm. J Laparoendosc Adv Surg Tech A. 2018 Jan;28(1):58–64.
34 Mitsui T, Yamashita H, Aikou S, Niimi K, Fujishiro M, Seto Y. Non-exposed endoscopic wall-inversion surgery for gastrointestinal stromal tumor. Transl Gastroenterol Hepatol. 2018;3:17.
35 Ojima T, Nakamori M, Nakamura M, Hayata K, Katsuda M, Takifuji K, et al. Laparoscopic and endoscopic cooperative surgery versus endoscopic submucosal dissection for the treatment of low-risk tumors of the duodenum. J Gastrointest Surg. 2018 May;22(5):935–40.
36 Ojima T, Nakamura M, Nakamori M, Takifuji K, Hayata K, Katsuda M, et al. Laparoscopic and endoscopic cooperative surgery is a feasible treatment procedure for intraluminal gastric gastrointestinal stromal tumors compared to endoscopic intragastric surgery. Surg Endosc. 2018 Jan;32(1):351–7.
37 Shoji Y, Takeuchi H, Goto O, Tokizawa K, Nakamura R, Takahashi T, et al. Optimal minimally invasive surgical procedure for gastric submucosal tumors. Gastric Cancer. 2018 May;21(3):508–15.
38 Cao L, Zheng KM, Wang HL, Zhao YJ, Yang ZD, Li W. Laparoscopic and endoscopic cooperative dissection for small gastric gastrointestinal stromal tumor without causing injury to the mucosa. Gastroenterol Res Pract. 2019 Dec;2019:7376903.
39 Hajer J, Havlůj L, Kocián P, Klimbacher G, Shamiyeh A, Gürlich R, et al. Comparison of nonexposed endoscopic wall-inversion surgery with endoscopic-navigated laparoscopic wedge resection for gastric submucosal tumours: results of a two-centre study. Gastroenterol Res Pract. 2019;2019:7573031.
40 Yanagimoto Y, Omori T, Jeong-Ho M, Shinno N, Yamamoto K, Takeuchi Y, et al. Feasibility and safety of a novel laparoscopic and endoscopic cooperative surgery technique for superficial duodenal tumor resection: how i do it. J Gastrointest Surg. 2019 Oct;23(10):2068–74.
41 Aoyama J, Goto O, Kawakubo H, Mayanagi S, Fukuda K, Irino T, et al. Clinical outcomes of non-exposed endoscopic wall-inversion surgery for gastric submucosal tumors: long-term follow-up and functional results. Gastric Cancer. 2020 Jan;23(1):154–9.
42 Aoyama J, Kawakubo H, Matsuda S, Mayanagi S, Fukuda K, Irino T, et al. Clinical outcomes of laparoscopic and endoscopic cooperative surgery for submucosal tumors on the esophagogastric junction: a retrospective single-center analysis. Gastric Cancer. 2020 Nov;23(6):1084–90.
43 Kanaji S, Morita Y, Yamazaki Y, Otowa Y, Takao T, Tanaka S, et al. Feasibility of laparoscopic endoscopic cooperative surgery for non-ampullary superficial duodenal neoplasms: single-arm confirmatory trial. Dig Endosc. 2020 Mar;33(3):373–80.
44 Kanehira E, Kanehira AK, Tanida T, Takahashi K, Obana Y, Sasaki K. CLEAN-NET: a modified laparoendoscopic wedge resection of the stomach to minimize the sacrifice of innocent gastric wall. Surg Endosc. 2020 Jan;34(1):290–7.
45 Mahawongkajit P, Chanswangphuvana P. Laparoscopy-assisted endoscopic full-thickness resection of upper gastrointestinal subepithelial tumors: a single-center early experience. Mol Clin Oncol. 2020 May;12(5):461–7.
46 Nunobe S, Ri M, Yamazaki K, Uraoka M, Ohata K, Kitazono I, et al. Safety and feasibility of laparoscopic and endoscopic cooperative surgery for duodenal neoplasm: a retrospective multicenter study. Endoscopy. 2021 Oct;53(10):1065–8.
47 Okubo K, Arigami T, Matsushita D, Sasaki K, Kijima T, Noda M, et al. Evaluation of postoperative quality of life by PGSAS-45 following local gastrectomy based on the sentinel lymph node concept in early gastric cancer. Gastric Cancer. 2020 Jul;23(4):746–53.
48 Ri M, Nunobe S, Makuuchi R, Ida S, Kumagai K, Ohashi M, et al. Is laparoscopic and endoscopic cooperative surgery (LECS) for gastric subepithelial tumor at the esophagogastric junction safe? Asian J Endosc Surg. 2020 Apr;14(2):223–31.
49 Matsumoto S, Yoshida Y. Selection of appropriate endoscopic therapies for duodenal tumors: an open-label study, single-center experience. World J Gastroenterol. 2014 Jul 14;20(26):8624–30.
50 Marques J, Baldaque-Silva F, Pereira P, Arnelo U, Yahagi N, Macedo G. Endoscopic mucosal resection and endoscopic submucosal dissection in the treatment of sporadic non-ampullary duodenal adenomatous polyps. World J Gastrointest Endosc. 2015 Jun 25;7(7):720–7.
51 Matsuda T, Hiki N, Nunobe S, Aikou S, Hirasawa T, Yamamoto Y, et al. Feasibility of laparoscopic and endoscopic cooperative surgery for gastric submucosal tumors (with video). Gastrointest Endosc. 2016 Jul;84(1):47–52.
52 Cai XL, Li XY, Liang C, Xu Y, Zhang MZ, Yu WM, et al. Endoscopic or laparoscopic resection for small gastrointestinal stromal tumors: a cumulative meta-analysis. Chin Med J. 2020 Nov 20;133(22):2731–42.

GE – Portuguese Journal of Gastroenterology

Research Article

GE Port J Gastroenterol 2023;30:20–28
DOI: 10.1159/000520272

Received: May 25, 2021
Accepted: October 14, 2021
Published online: November 25, 2021

Positioning *Aeromonas* Infection in Inflammatory Bowel Disease: A Retrospective Analysis

Tiago Pereira Guedes[a] Joana Alves Silva[a] Sara Neves[b] Daniela Falcão[a]
Paula Costa[c] Paula Lago[a] Isabel Pedroto[a] Marta Salgado[a]

[a]Gastroenterology Department, Centro Hospitalar Universitário do Porto, Porto, Portugal; [b]Infectious Diseases Department, Centro Hospitalar Universitário do Porto, Porto, Portugal; [c]Microbiology Department, Centro Hospitalar Universitário do Porto, Porto, Portugal

Keywords

Aeromonas · Inflammatory bowel disease · Crohn's disease · Ulcerative colitis · GI infections · Immunology · Microbiology and inflammatory bowel disease

Abstract

Background and Aim: *Aeromonas* are Gram-negative rods known to cause a spectrum of diseases. Inflammatory bowel disease (IBD) is an idiopathic complex condition resulting from interaction of multiple factors. Aeromonas infection in association with IBD is still largely unknown. We aim to look for the significance of *Aeromonas* infection and for significant differences between IBD and non-IBD patients. ***Methods:*** A retrospective observational analysis was performed of all patients positive for *Aeromonas* in stool cultures, during a 10-year period, from a tertiary and university hospital. ***Results:*** Fifty patients were included, 56% male with a mean age of 42.1 years. Thirty-eight (76%) were non-IBD and 12 (24%) IBD patients. IBD patients were more frequently under immunosuppressors. Two patients were asymptomatic and 44% developed mild, 44% moderate, and 16.7% severe infection. The main strains isolated were *Aeromonas hydrophila/caviae*. Bacterial co-isolation was found in 4 non-IBD and histological findings of cytomegalovirus in 2 IBD patients. Non-IBD patients presented more frequently with fever and IBD patients with bloody diarrhea and abdominal pain. There was higher tendency for severe infection rate in IBD patients with higher antimicrobial therapy use. Steroids were exclusively used in the IBD group. From IBD, 4 patients had the diagnosis of ulcerative colitis and 9 of Crohn's disease with colonic involvement. Of these patients, 5 received IBD diagnosis after the acute episode of *Aeromonas* infection. ***Conclusions:*** Clinical presentation of *Aeromonas* infection differs between IBD and non-IBD patients. Non-IBD patients had milder severity of infection with less use of antibiotics. *Aeromonas* infection seems to greatly contribute to IBD manifestation.

Tiago Pereira Guedes and Joana Alves Silva contributed equally to this work (co-first authors).

karger@karger.com
www.karger.com/pjg

Correspondence to:
Tiago Pereira Guedes, tiagoapguedes@gmail.com

Infeção por *Aeromonas* e doença inflamatória intestinal: uma análise retrospetiva

Palavras Chave
Aeromonas · Doença inflamatória intestinal · Doença de Crohn · Colite ulcerosa · Infeção gastrointestinal · Imunologia · Microbiologia e doença inflamatória intestinal

Resumo
Introdução: A etiologia da Doença Inflamatória Intestinal (DII) é complexa e resultante da interação de diversos fatores, nomeadamente microbiológicos. A infeção por Aeromonas caracteriza-se por um espectro alargado de manifestações clínicas. O papel da infeção por Aeromonas na DII não está caracterizado. Objetivos: Avaliar o significado da infeção por Aeromonas na DII e as diferenças com a infeção em doentes não-DII. ***Métodos:*** avaliação retrospetiva e observacional de todos os doentes com isolamento microbiológico de Aeromonas em amostras fecais num período de 10 anos, num hospital terciário. ***Resultados:*** foram avaliados 50 doentes, 56% do sexo masculino, com idade média de 42.1 anos. Doze (24%) com diagnóstico de DII e trinta e oito (76%) não-DII. Os doentes com DII encontravam-se mais frequentemente sob imunossupressão. Dois doentes foram assintomáticos, 44% desenvolveram doença ligeira, 44% moderada e 16.7% severa, havendo maior tendência para infeção severa nos DII. Os doentes não-DII apresentaram mais frequentemente febre e os DII diarreia sanguinolenta e dor abdominal. O uso de antimicrobianos foi superior no grupo DII e a utilização de corticoesteroides foi exclusiva nestes doentes. Isolamento concomitante de outros agentes microbiológicos ocorreu em 4 doentes não-DII e 2 com DII tinham histologia compatível com infeção por Citomegalovírus. Da população DII, 4 eram Colite Ulcerosa e 9 Doença de Crohn com envolvimento cólico. Destes, 5 receberam o diagnóstico após a infeção por Aeromonas. ***Conclusão:*** A apresentação clínica da infeção por Aeromonas foi distinta entre as populações DII e não-DII, sendo que os doentes DII apresentaram doença mais severa e maior utilização de antimicrobianos. A infeção na DII ocorreu essencialmente em doentes com envolvimento cólico.

Introduction

The *Aeromonas* genus, belonging to the Aeromonadaceae family, comprises facultatively anaerobic Gram-negative bacteria widely present in aquatic environments, soil, and food goods (such as meat, shellfish, and dairy products), making the gastrointestinal tract an understandable reaching point for *Aeromonas* [1, 2]. However, there has been discordant information concerning its role as a gastrointestinal pathogen, since its isolation in stool from asymptomatic individuals is not uncommon [3]. Of the 17 phenospecies of the genus *Aeromonas*, the most frequently isolated from human feces are *A. hydrophila*, *A. caviae*, *A. veronii*, and *A. trota* [4–6]. The most common manifestation of *Aeromonas* infection is diarrhea, usually acute and self-limited, but other presentations such as bloody diarrhea and abdominal pain, or chronic more indolent diarrhea, have been described [7]. Although most of the infections occur in immunocompromised patients, it can also cause disease in healthy individuals [8].

Although the ultimate cause of inflammatory bowel disease (IBD) is still unknown, there are many components interacting in its network of pathogenic mechanisms like environmental factors, genetic susceptibility, dysregulated immune response, and microbiological factors [9, 10]. Regarding the latter, both alterations in intestinal microbiota and infections by external agents might play a role in IBD onset and its flares [11, 12]. Dysbiosis can also result from commensal flora that, although normal in speciation, possess more subtle virulence factors such as enteroadherence, or the lack of diversity of the fecal microbiome [13, 14].

Considering the specific bacteria related to IBD onset, *Campylobacter* is probably the one with more data, while the heterogeneity of the studies does not allow to draw consistent conclusions [15]. Although data are mainly based on case report studies, some authors have suggested that *Aeromonas* can be a trigger of flares in IBD [16–18] and as well as a trigger to develop de novo chronic colitis in patients with no previous history of IBD [7, 19]. To our knowledge, only 2 recent studies involving IBD patients have tried to correlate the diagnosis and severity of the disease with *Aeromonas* infection [7, 8].

Our aim was to further look for the significance of *Aeromonas* infection as well as for significant differences between IBD and non-IBD patients.

Materials and Methods

Patients and Clinical Information

A retrospective analysis of data was performed of inpatients and outpatients with a positive stool culture for *Aeromonas*, between January 2009 to January 2019, in a tertiary and university hospital. Patients of all ages were included. Clinical data were obtained retrospectively from the electronic medical records.

Baseline data included age at *Aeromonas* fecal detection, sex, comorbidities (namely the presence of IBD and transplantation status), ongoing drugs (namely immunosuppressants), recent travels, and previous abdominal surgery. Clinical characteristics at the time of *Aeromonas* detection were also analyzed: the presence of symptoms attributed to gastrointestinal infection such as nausea, vomiting, diarrhea, number of bowel movements, abdominal pain, and fever; endoscopy findings, if performed; presence of histopathological features of cytomegalovirus (CMV) infection in colon biopsies; other bacterial co-identification in stool cultures; treatment applied (namely antibiotics and steroids); disease severity and/or death related to the infection.

The indication for treatment was done according to the physician's criteria. Disease severity was defined as: (a) mild self-limited gastroenteritis, as a gastrointestinal infection that resolved spontaneously without the need for antibiotics; (b) moderate gastroenteritis, as a gastrointestinal infection that required antibiotic treatment; and (c) severe gastroenteritis, defined by a gastrointestinal infection complicated with septicemia and/or renal impairment. Death related to the infection was defined as the occurrence of death over the duration of infection and/or antibiotic therapy.

Stool samples were processed for bacterial culture using GN broth and selective media: Macconkey agar, Macconkey agar with sorbitol, Salmonella-Shigella agar, CIN (Cefsulodin-Irgasan-Novobiocin) agar, and Campylosel agar. In certain patients, a blood agar with an ampicillin disc was also used. The culture media were incubated at 35 °C and observed daily for 48 h, except for the Campylosel media. Suspected colonies of *Aeromonas* spp. in CIN media and those that grew close to the ampicillin disc and, simultaneously, showed a positive oxidase reaction, were identified. The identification was made in automated systems: phenotypical methods (Vitek2® – bioMérieux) or by mass spectrometry technique (MALDI-TOF MS® – bioMérieux).

IBD and Non-IBD Patients

Data from all patients was analyzed, and two groups (IBD and non-IBD patients) were created for comparison. The IBD group included all patients with the diagnosis of IBD previously and after *Aeromonas* isolation. Individuals for whom both ulcerative colitis (UC) and Crohn's disease (CD) were recorded on successive dates were categorized according to the latest.

Statistical Analysis

Descriptive analysis was performed considering absolute and relative frequencies for categorical variables or mean and standard deviation for quantitative variables. Association between qualitative variables was performed based on the χ^2 test (with Yates' correction) or Fisher' exact test (when assumptions could not be verified in 2 × 2 tables). Group comparison according to quantitative variables was performed using the independent-sample *t* test or Mann-Whitney test (variable with relevant skewness). In all analyses, a significance level of 0.05 was considered and SPSS version 26 was used.

Results

Baseline Characteristics

Stool isolation of *Aeromonas* was identified in 53 patients during the 10-year period of the study. Fifty patients were included and analyzed. Three were excluded due to the absence of minimal clinical information.

Our population consisted mainly of individuals of male sex (54%) with a mean age of 42.1 years (1–89 years old). Fourteen (28%) patients were under 18 years old. Baseline characteristics are presented in Table 1.

Twelve patients (24%) had the diagnosis of IBD, with 7 (14%) having it diagnosed previously and 5 (10%) after *Aeromonas* fecal isolation. Five patients had ongoing chemotherapy treatment during *Aeromonas* isolation and 2 had advanced liver disease. Thirteen patients (26%) were immunosuppressed considering therapeutics as calcineurin inhibitors, AZA, systemic steroids, and biological therapy as infliximab. Six patients (12%) were previously submitted to organ transplantation. At the time of *Aeromonas* isolation, 4 patients were under azathioprine (AZA), 6 under topical or systemic steroids, and 6 under calcineurin inhibitors. Only 1 IBD patient was under combined therapy with infliximab and AZA. Only 1 non-IBD patient was under AZA for autoimmune hepatitis. Also, the only IBD patient under calcineurin inhibitors was a liver transplant recipient.

No patient had recent travel history. Twelve patients (24%) presented a history of previous abdominal surgery, with 3 having a previous hemicolectomy, 1 a cholecystectomy, 3 liver transplants, 1 reno-pancreatic transplant, and 2 gastric bypasses.

Clinical Presentation in IBD and Non-IBD Patients

The clinical and microbiological characteristics at the time of *Aeromonas* isolation are shown in Table 2. From the overall sample, 48/50 (96%) patients were found to have symptoms that could be attributed to the presence of *Aeromonas*. Only 1 IBD and 1 non-IBD patient were considered asymptomatic: concerning the IBD patient, the stool culture was required in the course of the diagnosis of IBD, as part of a protocol required at the first consultation. This patient was sent to IBD consultation due to chronic diarrhea and abdominal pain in the past year but was asymptomatic at the time of consultation. Concerning the non-IBD patient, the stool culture was required in the course of the postrenal transplantation protocol.

The most frequent strains isolated in both groups were *A. hydrophila/caviae* (distinction not possible with the

Table 1. Baseline characteristics

	Total *n* (%) or mean (SD)	IBD *n* (%) or mean (SD)	Non-IBD *n* (%) or mean (SD)	*p* value
Total	50 (100.0)	12 (24.0)	38 (76.0)	–
Age, years	42.1 (28.6)	40.2 (23.5)	42.7 (30.3)	0.794[c]
Female sex	23 (46.0)	4 (33.3)	19 (50.0)	0.498[a]
IBD diagnosis				
Previous to *Aeromonas* isolation	7 (14.0)	7 (58.3)	–	–
Posterior to *Aeromonas* isolation	5 (10.0)	5 (41.7)	–	–
Comorbidities at the moment of *Aeromonas* fecal isolation				
Arterial hypertension	14 (28.0)	3 (25.0)	11 (28.9)	1.000[b]
Dyslipidemia	7 (14.0)	1 (8.3)	6 (15.8)	1.000[b]
Diabetes	4 (8.0)	1 (8.3)	3 (7.9)	1.000[b]
Chronic renal failure	3 (6.0)	0 (0.0)	3 (7.9)	1.000[b]
Cirrhosis	2 (4.0)	0 (0.0)	2 (5.3)	1.000[b]
Cancer	5 (10.0)	0 (0.0)	5 (13.2)	0.319[b]
Transplant	6 (12.0)	1 (8.3)	5 (13.2)	1.000[b]
Ongoing drugs at the moment of *Aeromonas* fecal isolation				
PPI	18 (36.0)	5 (41.7)	13 (34.2)	0.735[b]
Chemotherapy	5 (10.0)	0 (0.0)	5 (13.2)	0.319[b]
Immunosuppressed patients	13 (26.0)	7 (58.3)	6 (18.8)	0.073[b]
Immunosuppressant drugs				
AZA	4 (8.0)	3 (25.0)	1 (2.6)	*0.038*[b]
Topical or systemic steroids	6 (12.0)	4 (33.3)	2 (5.3)	*0.024*[b]
Calcineurin inhibitors	6 (12.0)	1 (8.3)	5 (13.2)	0.294[b]
Biologic therapy (anti-TNF)	1 (2.0)	1 (8.3)	0 (0.0)	0.240[b]
Previous abdominal surgery	12 (24.0)	1 (8.3)	11 (28.9)	0.248[b]

AZA, azathioprine; IBD, Inflammatory bowel disease; PPI, proton pump inhibitors; SD, standard deviation; [a] χ^2 test; [b] Fisher Test; [c] Independent sample Student's *t* test.

routinely used methods). Symptoms presented at the time of *Aeromonas* isolation differ among both groups, with IBD patients presenting more frequently with bloody diarrhea (83.3 vs. 10.5%, $p < 0.001$) and abdominal pain (75.0 vs. 34.2%, $p = 0.032$). The presence of fever was more common among patients without IBD (0.0 vs. 34.2%, $p = 0.022$). IBD patients were more frequently under AZA (25.0 vs. 2.6%, $p = 0.038$) and systemic or topical steroids (33.3 vs. 5.3%, $p = 0.024$) when compared with non-IBD patients. Immunosuppressive therapy with calcineurin inhibitors was more often used in non-IBD patients (8.3 vs. 13.2%, $p = 0.294$).

The majority of patients presented a mild-moderate *Aeromonas* infection with a proportionally higher tendency for severe episodes in IBD patients (27.3 vs. 13.5%, $p > 0.05$). There were 8 (16.7%) severe cases, 7 of which concerned immunocompromised patients. Nineteen patients (41.7% were IBD and 36.8% non-IBD) needed to be admitted to the hospital for management of severe infection and symptomatic control in moderate cases.

Concerning the treatment of the acute episode, IBD patients were more frequently submitted to antibiotics (83.3 vs. 36.8%, $p = 0.013$), and quinolones were the most frequently used class in both (36% overall). Only IBD patients were treated with systemic or topical steroids (33.3 vs. 0.0%, $p = 0.002$), and all of these patients were also under antibiotics. Four (8%) *Aeromonas*-resistant strains were identified (3 [7.9%] in non-IBD vs. 1 [8.3%] in IBD). Other fecal bacteria were identified only in 4 non-IBD patients (10.5%): 3 children, two 1-year-olds and one 8-year-old, presented *Campylobacter jejuni*, and a 73-year-old patient presented also with *Salmonella*. All patients progressed favorably with no deaths observed.

Table 2. Clinical presentation features in IBD and non-IBD patients

	Total *n* (%) or median (SD) or median (IQR)	IBD *n* (%) or median (SD) or median (IQR)	Non-IBD *n* (%) or median (SD) or median (IQR)	*p* value
Aeromonas strain				–
Hydrophila/caviae	32 (64.0)	9 (75.0)	23 (60.5)	–
Hydrophila	12 (24.0)	1 (8.3)	11 (28.9)	
Aeromonas spp.	3 (6.0)	1 (8.3)	2 (5.3)	
Aeromonas veronii	3 (6.0)	1 (8.3)	2 (5.3)	
Symptoms	48 (96.0)	11 (91.7)	37 (97.4)	0.426[b]
Diarrhea	46 (92.0)	10 (83.3)	36 (94.7)	0.240[b]
Bloody diarrhea	14 (8.0)	10 (83.3)	4 (10.5)	***<0.001***[b]
Abdominal pain	22 (44.0)	9 (75.0)	13 (34.2)	***0.032***[a]
Nausea and vomiting	21 (42.0)	4 (33.3)	17 (44.7)	0.717[a]
Fever	13 (26.0)	0 (0.0)	13 (34.2)	***0.022***[b]
Bowel movements/day				–
<5	18 (36.0)	2 (16.7)	16 (42.1)	
5–10	24 (48.0)	9 (75.0)	15 (39.5)	
>10	4 (8.0)	0 (0.0)	4 (10.5)	
Severity				0.582[a]
Mild	21 (44.0)	4 (36.4)	17 (45.9)	
Moderate	21 (44.0)	5 (45.5)	16 (43.2)	
Severe	8 (16.7)	3 (27.3)	5 (13.5)	
Hospital admission	19 (38.0)	5 (41.7)	14 (36.8)	1.000[a]
Treatment				
Antibiotics	24 (48.0)	9 (75.0)	14 (36.8)	***0.013***[a]
Quinolone	18 (36.0)	9 (75.0)	9 (23.7)	–
Carbapenem plus quinolone	3 (6.0)	1 (8.3)	2 (5.3)	
Carbapenem plus vancomycin	1 (2.0)	0 (0.0)	1 (2.6)	
Amoxicillin and clavulanic acid	1 (2.0)	0 (0.0)	1 (2.6)	
Systemic or topical steroids	4 (8.0)	4 (33.3)	0 (0.0)	***0.002***[b]
Other treatments				–
No treatment	18 (36.0)	1 (8.3)	17 (44.7)	
Mesalazine	6 (12.0)	5 (41.7)	1 (2.6)	
Probiotic	2 (4.0)	0 (0.0)	2 (5.3)	
Resistant strains identified	4 (8.0)	1 (8.3)	3 (7.9)	–
Dead	0 (0.0)	–	–	–

IBD, inflammatory bowel disease; IQR, interquartile range; SD, standard deviation; [a] χ^2 test; [b] Fisher test; [c] Independent sample Student's *t* test.

IBD Diagnosis and Aeromonas *Infection*

Clinical characteristics of IBD patients and *Aeromonas* infection are presented in Table 3. From the IBD patient subgroup, 7 had the diagnosis of IBD previously and 5 after the *Aeromonas* isolation. From the latter, only 1 had the infection and subsequent diagnosis of IBD at pediatric age (patient 8, Table 3).

From those with a previously established diagnosis of IBD, 3 were UC patients and 4 CD patients (Table 3). Only 1 patient with CD was under combined therapy with infliximab and AZA (patient 4, Table 3), and the remaining were under AZA monotherapy at the time of *Aeromonas* isolation. UC patients were under mesalamine. One patient (patient 9, Table 3) was under tacrolimus due to a previous liver transplant. Five patients were treated with antibiotics, and 2 of them simultaneously with systemic steroids. One patient was treated only with topical steroids. Three patients needed hospital admission, with one requiring ganciclovir treatment due to concomitant histological features of CMV on colonic biopsy (patient 5,

Table 3. *Aeromonas* isolation in IBD patients

Patient	Age, sex	CD, (MC)/UC	Ongoing IBD treatment	De novo IBD	Main symptoms	Endoscopic/imaging features	Treatment	Hospitalization	*Aeromonas* strain
1	24, F	CD (A2L1B2)	AZA	No	Bloody diarrhea	–	Topical steroids	No	*Aeromonas hydrophila/caviae*
2	28, F	CD (A2L1B1)	AZA Topical steroids	No	Diarrhea, abdominal pain	–	Ciprofloxacin	No	*Aeromonas hydrophila/caviae*
3	36, F	CD (A2L2B1)	None	Yes	Diarrhea, abdominal pain	Colonic mucosa with congestion and aphtoid erosions	Mesalamine	No	*Aeromonas hydrophila*
4	76, M	CD, (A3L1+L4 B2)	Infliximab AZA	No	Abdominal pain, nausea, vomiting	Ileal and jejunal segmental stenosis with transmural hyperenhancement and small loop dilation	Imipenem, systemic steroids	Yes	*Aeromonas hydrophila/caviae*
5	16, M	CD (A1L2B1)	AZA	No	Bloody diarrhea, abdominal pain	Friable and congestive mucosa with erosions	Ciprofloxacin, systemic steroids, ganciclovir	Yes	*Aeromonas hydrophila/caviae*
6	64, F	CD (A3L2B)	None	Yes	Bloody diarrhea, weight loss	Colonic mucosa with deep ulcers on colon	Ciprofloxacin, systemic steroids, ganciclovir	Yes	*Aeromonas spp*
7	31, M	CD (A2L2B1)	None	Yes	Bloody diarrhea	Decreased vascular pattern, erosions	Mesalamine	No	*Aeromonas hydrophila/caviae*
8	15, M	CD A1L2B1	Mesalamine, systemic steroids	Yes	Bloody diarrhea, abdominal pain	Decreased vascular pattern, aphtoid erosions	Ciprofloxacin, mesalamine	Yes	*Aeromonas hydrophila/caviae*
9	27, M	UC	Mesalamine	No	Diarrhea, abdominal pain, weight loss	Mayo endoscopic subscore 2	Ciprofloxacin	Yes	*Aeromonas sobria*
10	62, M	UC	Mesalamine one month previous	Yes	Bloody diarrhea	Mayo endoscopic subscore 2	Ciprofloxacin	No	*Aeromonas hydrophila/caviae*
11	12, F	UC	Mesalamine	No	Bloody diarrhea	–	Ciprofloxacin, mesalamine	No	*Aeromonas hydrophila*
12	62, M	UC	Mesalamine	No	–	–	No additional	No	*Aeromonas spp*

CD, Crohn disease; F, female; IBD, inflammatory bowel disease; UC, ulcerative colitis; M, male; MC, Montreal classification.

Table 3). The only patient under infliximab presented with intestinal sub-occlusion with a quinolone-resistant *A. hydrophila/caviae* isolation. All patients progressed favorably, and none needed to escalate IBD therapy after the *Aeromonas* acute episode. Seven patients were submitted to endoscopic evaluation. However, histological data was compatible with IBD, with no other specific features. Immediately after the acute episode, only clinical and analytical data were used to assess the remission, namely the symptoms reported by the patients, CRP, and calprotectin.

Concerning the 5 patients with a diagnosis of IBD after the episode of *Aeromonas* isolation, 4 of them were diagnosed with colonic CD and 1 with UC. Two of them were admitted to the hospital with 1 showing simultaneous histological features of CMV infection on colonic biopsy (patient 6, Table 3), being treated with antibiotics, systemic steroids, and ganciclovir. The other 3 received the IBD diagnosis in an ambulatory setting due to the persistence of chronic diarrhea in which *Aeromonas* was isolated in the first stool culture requested for the workup. From this subgroup of patients with de novo IBD diagnosis, 2 required posterior escalation therapy to infliximab (patients 6 and 10, Table 3).

Discussion/Conclusion

The pathogenic role of *Aeromonas* in human enterocolitis is still controversial as is the association of *Aeromonas* infection with IBD development or as a flare trigger. To our knowledge, a few case reports have been published, with only 2 similar case series available [7, 8].

The global prevalence of *Aeromonas* gastrointestinal infection ranges from 2 to 88% and carriage status in healthy individuals from 1 to 45% [7]. Stool isolation rates differ depending, among others, on geography, food habits, and isolation methods [20]. The prevalence of infection in developed countries ranges from 0.8 to 7.4% and carriage rate from 0 to 4% [20], indicating a possible higher prevalence in developing countries. Although no specific data exists for Portugal, we had a relatively low number of *Aeromonas* stool isolation considering the period covered. The evolution of *Aeromonas* detection methods through the years may have a role in it, since the majority (56%) of our isolates were identified between 2014 and 2019, coinciding with the introduction of mass spectrometry methods. In this study ($n = 50$), 2 patients were asymptomatic carriers (4%), concordant with the reported carriage rate in healthy individuals in developed countries [20].

The reports of the most predominant clinical species of *Aeromonas* have changed over the years. Improved molecular methods led to the conclusion that 95.4% of the strains associated with the clinical disease were *A. caviae* (37.3%), *A. veronii* (23.5%), *A. dhakensis* (21.5%), and *A. hydrophila* (13.1%) [21]. In our study, the 3 identified species are concordant with the most associated with clinical disease in other studies [7, 8]. Nevertheless, since *A. dhakensis* cannot be identified by the biochemical methods and mass spectrometry used in our laboratory, we cannot exclude that there might be a misidentification as *A. caviae*, *A. hydrophila*, or *A. veronii*. Although our data reinforce the predilection of this finding in non-IBD patients (96.2%), we have interestingly shown higher isolation of *A. hydrophila*. This could be explained by the higher number of patients under 18 years old and different geographical factors. It should, however, be kept in mind that the frequency of each strain differs according to the country. In our study, no relation was found between the strains and severity of the clinical manifestations.

When compared with a recent similar study performed in a tertiary hospital in Spain ($n = 98$) [8], the mean age of our population was lower (42 vs. 62 years-old) as well as the proportion of female sex (46 vs. 51%). This difference can be explained mainly by the fact that only adult patients were involved in the Spanish study. On the other hand, we presented a higher percentage of isolates in patients with previous IBD diagnosis (14 vs. 11%) with very similar cases of CD (8 vs. 7 patients) and an equal number of UC patients ($n = 4$).

The main comorbidities found in our group of patients were malignancies (10%), pharmacological immunosuppression (34%), and liver diseases (4%). *Aeromonas* is known to cause gastrointestinal symptoms in both immunocompetent and immunocompromised individuals with predisposing factors reported, such as diabetes, hematological malignancies, or hepatobiliary diseases [20]. Overall, the severity of the infection in our population was mainly mild-moderate with 17% severe. The percentage of severe infection was greater in IBD patients (27.3 vs. 13.5%), also reported by others [7]. Of the 5 non-IBD patients that presented with severe infection, 2 were undergoing chemotherapy, 2 had previous abdominal surgery, and the last was an HIV patient with no antiretroviral therapy adherence. The reported mortality rate can reach 30% in the set of *Aeromonas'* bacteremia [21]. Fortunately, there were no reported deaths attributed to the infection in our study.

The antibiotic susceptibility profile for *Aeromonas* does not appear to have changed substantially [22]. In the

present study, only 4 isolates were resistant to antibiotics usually active against aeromonads, according to EUCAST breakpoints [23]. Two patients had a strain resistant to ciprofloxacin and cotrimoxazole, another patient to cotrimoxazole, and the last one to ciprofloxacin. There was no identified resistance to carbapenems, a fortunate sign regardless of the reports describing an increased *Aeromonas* resistance to the latter [24]. Resistant strains were more common in non-IBD patients (75 vs. 25%). This could be explained by the fact that the mean age of non-IBD patients was higher, which usually implies a significantly higher exposure to antibiotics and previous hospital admissions.

In our analysis, IBD patients represented 24% of our population with a predominance of male sex and a tendency for younger age when compared to non-IBD patients. In the previous series, IBD patients represented 11–14% of all *Aeromonas*-positive patients with the same age trend [7, 8]. Symptomatic *Aeromonas* infection was seen in almost all patients (96%). Distinctive symptoms between the two groups were the presence of bloody diarrhea and abdominal pain which was significantly more common in IBD patients. This was in line with previous findings suggesting that a colonic involvement in the vast majority of IBD might explain the high rates of bloody diarrhea in these patients [7].

A higher proportion of IBD patients presented a severe clinical infection which followed the trend of previous studies [7]. Three IBD patients presented a more severe disease: one was under tacrolimus after liver transplant due to primary sclerosing cholangitis; the other patient was under combined therapy with infliximab and AZA; finally, a 64-year-old female with de novo CD and severe endoscopic features with concomitant CMV colitis. Almost half of non-IBD patients present a mild disease, which is a very similar result compared to the 44% previously reported [7, 16]. IBD population significantly needed more antibiotic therapy and steroids, following the trend of higher severity of infection. This might be explained by the lower threshold to antibiotic therapy in patients with IBD, namely in immunocompromised, regardless of clinical, analytical, and endoscopic features.

Regarding the place of *Aeromonas* infection in the natural history of the disease, the scarcely reported literature on the subject poses it as a potential trigger to flare and for the de novo IBD diagnosis. In our study, from those with IBD, 7/12 were diagnosed previously to *Aeromonas* isolation. A role for *Aeromonas* as a trigger to IBD flare was previously reported in a patient diagnosed with mild ulcerative proctitis, who presented a severe colitis refractory to steroid therapy with favorable evolution under antibiotic therapy directed to the isolated *Aeromonas* [16]. On the other hand, other reports had postulated a putative role of *Aeromonas* infection for the development of de novo IBD diagnosis [7, 12]. It remains under discussion if the infection prompts IBD development or naturally unmasks an underlying disease with previous subclinical activity. The mechanisms inherent to these interrelationships are unknown, but *Aeromonas*-associated intestinal dysbiosis could possibly lead to reduced bacterial diversity and, in those genetically susceptible, result in IBD onset. In our population, we also found concomitant CMV infection (Table 3, patient 6). Giving the epidemiology of CMV as a flare-causing pathogen in IBD, the endoscopic features (deep ulcers on colon) and the significant prevalence of *Aeromonas* carriage status, it is plausible that the *Aeromonas* isolated was not responsible for causing the disease.

In our population, we observed the subsequent diagnosis of IBD in 5/12 patients after *Aeromonas* infection. Lobatón et al. [7] also described 2 cases of diarrhea and abdominal pain with *Aeromonas* detection simultaneously to CD diagnosis. Similarly, more than 30 years ago, an association was proposed between *Aeromonas* infection and the new onset of 3 cases of UC [19].

Although it represents one of the few studies relating *Aeromonas* infection and IBD patients, there are some limitations to address. The retrospective character of the study, data retrieval from a unicentric microbiology database, and the loss of 3 patients due to insufficient clinical information might bias the interpretation of our results. It is important to mention that only 7 IBD patients with flares were submitted to endoscopic evaluation, which, to some extent, could compromise the conclusion. Also, the analysis of the time between *Aeromonas* isolation and the first signs of IBD would be important in the evaluation of the possible causality between the two diseases in future larger studies. It is important to mention the heterogeneity of the control group, mainly the inclusion of pediatric patients that could compromise the comparisons that were made. The reduced sample and the bias to request stool culture mainly in symptomatic patients do not allow us to infer about the overall and ecological scenario of *Aeromonas* identification in our population.

In conclusion, *Aeromonas* infection appears to play an important role in IBD activity. This infection might contribute as one more piece in the interactome unsolved puzzle for IBD. Our results reinforce that *Aeromonas* in-

fection can be a trigger for IBD flare or de novo IBD diagnosis, supporting the importance of fecal culture analysis. Our results allying with the lack of data on *Aeromonas* infection and IBD might indicate an overlook of this infection.

Statement of Ethics

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

The authors declare that they have followed the protocols of their work center on the publication of patient data.

The authors declare that no patient data appear in this article.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding.

Author Contributions

T.P.G. and J.A.S. equally contributed to the manuscript. T.P.G. and M.S. conceived and designed the study. T.P.G., J.A.S., S.N., D.F. collected, analyzed, and interpreted data. P.C., P.L., I.P., and M.S. performed critical review of the manuscript.

References

1 Zhou Y, Yu L, Nan Z, Zhang P, Kan B, Yan D, et al. Taxonomy, virulence genes and antimicrobial resistance of Aeromonas isolated from extra-intestinal and intestinal infections. BMC Infect Dis. 2019 Feb;19(1):158.

2 Bhowmick UD, Bhattacharjee S. Bacteriological, clinical and virulence aspects of aeromonas-associated diseases in humans. Pol J Microbiol. 2018 Jun;67(2):137–49.

3 Morgan DR, Johnson PC, DuPont HL, Satterwhite TK, Wood LV. Lack of correlation between known virulence properties of Aeromonas hydrophila and enteropathogenicity for humans. Infect Immun. 1985 Oct; 50(1):62–5.

4 Tomás JM. The main Aeromonas pathogenic factors. ISRN Microbiol. 2012 Sep;2012: 256261.

5 Ko WC, Lee HC, Chuang YC, Liu CC, Wu JJ. Clinical features and therapeutic implications of 104 episodes of monomicrobial Aeromonas bacteraemia. J Infect. 2000 May;40(3):267–73.

6 von Graevenitz A. The role of Aeromonas in diarrhea: a review. Infection. 2007 Apr;35(2): 59–64.

7 Lobatón T, Hoffman I, Vermeire S, Ferrante M, Verhaegen J, Van Assche G. Aeromonas species: an opportunistic enteropathogen in patients with inflammatory bowel diseases? A single center cohort study. Inflamm Bowel Dis. 2015 Jan;21(1):71–8.

8 Elorza A, Rodríguez-Lago I, Martínez P, Hidalgo A, Aguirre U, Cabriada JL. Gastrointestinal infection with Aeromonas: incidence and relationship to inflammatory bowel disease. Gastroenterol Hepatol. 2020 Dec;43(10): 614–9.

9 de Souza HS, Fiocchi C, Iliopoulos D. The IBD interactome: an integrated view of aetiology, pathogenesis and therapy. Nat Rev Gastroenterol Hepatol. 2017 Dec;14(12):739–49.

10 Baumgart DC, Carding SR. Inflammatory bowel disease: cause and immunobiology. Lancet. 2007 May;369(9573):1627–40.

11 Orel R, Kamhi Trop T. Intestinal microbiota, probiotics and prebiotics in inflammatory bowel disease. World J Gastroenterol. 2014 Sep;20(33):11505–24.

12 Lobatón T, Domènech E. Bacterial Intestinal Superinfections in Inflammatory Bowel Diseases Beyond Clostridum difficile. Inflamm Bowel Dis. 2016 Jul;22(7):1755–62.

13 Barnich N, Carvalho FA, Glasser AL, Darcha C, Jantscheff P, Allez M, et al. CEACAM6 acts as a receptor for adherent-invasive E. coli, supporting ileal mucosa colonization in Crohn disease. J Clin Invest. 2007 Jun;117(6): 1566–74.

14 Nishikawa J, Kudo T, Sakata S, Benno Y, Sugiyama T. Diversity of mucosa-associated microbiota in active and inactive ulcerative colitis. Scand J Gastroenterol. 2009;44(2):180–6.

15 Castaño-Rodríguez N, Kaakoush NO, Lee WS, Mitchell HM. Dual role of Helicobacter and Campylobacter species in IBD: a systematic review and meta-analysis. Gut. 2017 Feb; 66(2):235–49.

16 Baliellas Comellas C, Xiol Quingles X, Castellote Alonso J, Torras Torra J. [Severe occurrence of idiopathic ulcerative colitis caused by Aeromonas sobria]. Rev Esp Enferm Dig. 1991 Jun;79(6):442–3.

17 de Sola Earle C, Montiel Quezel-Guerraz N, Hidalgo Rojas L, Sánchez Cantos A, García Alegría J. Gastroenteritis aguda grave por Aeromonas en paciente colectomizado por enfermedad de Crohn. Rev Esp Enferm Dig. 1997 Jan;89(1):48–50.

18 Ahishali E, Pinarbasi B, Akyuz F, Ibrisim D, Kaymakoglu S, Mungan Z. A case of Aeromonas hydrophila enteritis in the course of ulcerative colitis. Eur J Intern Med. 2007 Sep; 18(5):430–1.

19 Willoughby JM, Rahman AF, Gregory MM. Chronic colitis after Aeromonas infection. Gut. 1989 May;30(5):686–90.

20 Igbinosa IH, Igumbor EU, Aghdasi F, Tom M, Okoh AI. Emerging Aeromonas species infections and their significance in public health. ScientificWorldJournal. 2012;2012:625023.

21 Fernández-Bravo A, Figueras MJ. An Update on the Genus Aeromonas: Taxonomy, Epidemiology, and Pathogenicity. Microorganisms. 2020 Jan;8(1):129.

22 Janda JM, Abbott SL. The genus Aeromonas: taxonomy, pathogenicity, and infection. Clin Microbiol Rev. 2010 Jan;23(1):35–73.

23 EUCAST. Clinical breakpoints and dosing of antibiotics [Internet]. [cited 2021 Feb 27]. Available from: https://www.eucast.org/clinical_breakpoints/

24 Sinclair HA, Heney C, Sidjabat HE, George NM, Bergh H, Anuj SN, et al. Genotypic and phenotypic identification of Aeromonas species and CphA-mediated carbapenem resistance in Queensland, Australia. Diagn Microbiol Infect Dis. 2016 May;85(1):98–101.

GE – Portuguese Journal of Gastroenterology

Research Article

GE Port J Gastroenterol 2023;30:29–37
DOI: 10.1159/000520530

Received: August 5, 2021
Accepted: October 8, 2021
Published online: November 30, 2021

Development of a Model to Predict Liver Decompensation prior to Transarterial Chemoembolization Refractoriness in Patients with Intermediate-Stage Hepatocellular Carcinoma

Joel Ferreira-Silva[a] Pedro Costa-Moreira[a, b] Helder Cardoso[a, b]
Rodrigo Liberal[a, b] Pedro Pereira[a, b] Guilherme Macedo[a, b]

[a]Gastroenterology Department, Hospital de São João, Porto, Portugal; [b]Faculty of Medicine of the University of Porto, Porto, Portugal

Keywords
Hepatocellular carcinoma · Transarterial chemoembolization · Child-Pugh class

Abstract

Introduction: Transarterial chemoembolization (TACE) is the first-line treatment for patients with intermediate-stage hepatocellular carcinoma (HCC). For patients without an adequate response, current finding suggests that treatment with molecular target agents, approved for advanced stage, might present benefits. However, this requires a preserved liver function. This study aims to evaluate possible predictors of early deterioration of hepatic reserve, prior to TACE refractoriness, in a cohort of patients treated with TACE. ***Methods:*** Retrospective analysis of 99 patients with Child-Pugh class A and intermediate-stage HCC who underwent TACE as the first-line treatment. All patients were submitted to a biochemical and medical evaluation prior to initial TACE and every month afterward. Response to initial TACE was evaluated at 1 month. The time to Child-Pugh class deterioration before TACE refractoriness was assessed. ***Results:*** Ninety-nine patients were included. Objective response rate (ORR) to initial TACE was assessed as present in 59 (63.4%) and as absent in 34 (36.6%) patients. Liver decompensated before TACE refractoriness in 51 (51.5%) patients, and the median time to liver decompensation was 14 (IQR 8–20) months after first TACE. In multivariate analysis, beyond up-to-7 criteria (HR 2.4, $p = 0.031$), albumin <35 mg/dL (HR 3.5, $p < 0.001$) and absence of ORR (HR 2.4, $p = 0.020$) were associated with decreased overall survival free of liver decompensation. Moreover, beyond up-to-7 criteria, albumin <35 mg/dL and absence of ORR associated negatively with 6-month survival free of liver decompensation. Our model created using those variables was able to predict liver decompensation at 6 months with an AUROC of 0.701 ($p = 0.02$). ***Conclusions:*** The absence of ORR after initial TACE, beyond up-to-7 criteria and albumin <35 mg/dL, was a predictive factor for early liver decompensation before TACE refractoriness in our population. Such patients might benefit from treatment escalation to systemic therapy, in monotherapy or in combination with TACE.

karger@karger.com
www.karger.com/pjg

Karger
OPEN ACCESS

Correspondence to:
Joel Ferreira-Silva, jom_73@hotmail.com

Desenvolvimento de um modelo preditor de descompensação hepática pré refratariedade a quimioembolização transarterial em doentes com carcinoma hepatocelular em estadio intermediário

Palavras Chave
Carcinoma hepatocellular · Quimioembolização transarterial · Classe Child-Pugh

Resumo
Introdução: A quimioembolização transarterial (TACE) é o tratamento de primeira linha para doentes com carcinoma hepatocelular (HCC) em estadio intermédio. Em doentes sem resposta adequada, a evidência atual sugere que o tratamento com agentes de alvo molecular, aprovado para estágio avançado, pode apresentar benefícios. Porém, isso requer função hepática preservada. O objetivo deste estudo é avaliar possíveis preditores de deterioração precoce da reserva hepática, antes da refratariedade ao TACE, em uma coorte de doentes tratados com TACE. ***Métodos:*** Análise retrospectiva de noventa e nove doentes com Child-Pugh classe A e HCC em estadio intermédio que foram submetidos a TACE como tratamento de primeira linha. Todos os doentes foram submetidos a uma avaliação bioquímica e médica antes do TACE inicial e a cada mês após. A resposta ao TACE inicial foi avaliada em 1 mês. O tempo para a deterioração da classe Child-Pugh antes da refratariedade a TACE foi avaliado. ***Resultados:*** Noventa e nove doentes foram incluídos. A resposta radiológica objetiva (ORR) ao TACE inicial foi avaliada como presente em 59 (63.4%) e ausente em 34 (36.6%) doentes. Descompensação hepática ocorreu, antes da refratariedade a TACE, em 51 (51.5%) doentes e o tempo médio para a descompensação hepática foi de 14 (IQR 8–20) meses, após o primeiro TACE. Na análise multivariada, além dos critérios *up-to-7* (HR 2,4, $p = 0.031$), albumina <35 mg/dL (HR 3,5, $p < 0.001$) e ausência de ORR (HR 2,4, $p = 0.020$) foram associados a diminuição da sobrevida livre de descompensação hepática. Além disso, a sobrevida de 6 meses livre de descompensação hepática apresentou associação, além dos critérios *up-to-7*, albumina <35 mg/dL e ausência de ORR. Foi criado um modelo com essas variáveis, capaz de prever a descompensação hepática com AUROC de 0,701 ($p = 0.02$). ***Conclusões:*** A ausência de ORR após TACE inicial, além dos critérios *up-to-7* e albumina <35 mg/dL foram fatores preditivos para descompensação hepática antes da refratariedade a TACE na nossa população. Esses doentes podem beneficiar do escalonamento do tratamento para a terapia sistêmica, em monoterapia ou em combinação com TACE.

Introduction

Transarterial chemoembolization (TACE) is the first-line treatment for patients with non-resectable hepatocellular carcinoma (HCC) in the absence of decompensated cirrhosis, large tumor size (>10 cm), comorbidities, portal vein thrombosis, or extrahepatic spread [1–3]. The survival benefit of TACE in patients with intermediate-stage HCC is well established [4]. However, this therapy frequently loses its therapeutic efficacy over time, despite repeated procedures, leading to TACE refractoriness [5].

For patients without an adequate response after TACE, the concept of therapeutic stage migration can be considered [6]. Systemic therapy (ST) has been demonstrated to be effective in patients after TACE failure [7]. Furthermore, recent studies suggest that, in patients with HCC and TACE refractoriness, ST might improve the prognosis, when compared with repeated TACE procedures [8–10]. Moreover, several studies demonstrate a benefit of systemic treatment as an adjuvant to TACE [11]. As such, ST can be considered in patients with intermediate-stage HCC [1, 7]. However, ST, similar to locoregional therapy, requires preserved liver function, and patients that develop early deterioration of liver function following TACE are deprived of ST as a therapeutic option [12]. To complicate matters, up to 25% of patients with TACE refractoriness develop Child-Pugh B/C after initial TACE [8, 9]. Furthermore, it has previously been described that repeated TACE procedures are associated with deterioration of hepatic reserve, even though recent studies might challenge the relevance of this association [11, 13]. Defining predictors of early liver decompensation in patients with HCC proposed to TACE could potentially help in better treatment selection in such patients. Previous works fail to propose predictors of early deterioration of liver function before TACE refractoriness.

This study aims to evaluate possible predictors of overall and 6-month survival free of liver decompensation before TACE refractoriness in a cohort of Western patients with intermediate-stage HCC submitted to TACE.

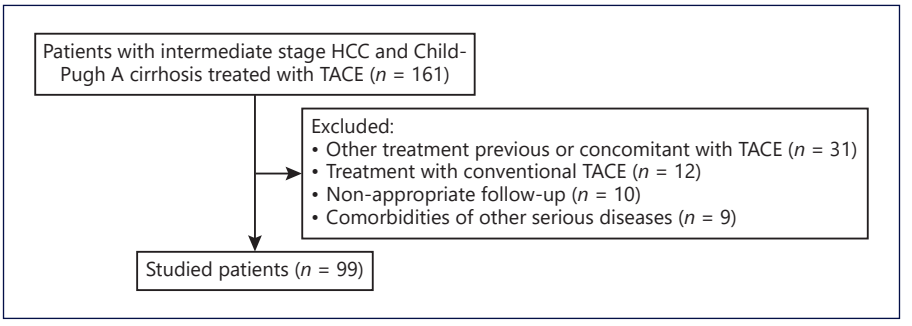


Fig. 1. Flowchart regarding patient selection. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

Material and Methods

Study Design

We performed a retrospective study of all consecutive patients with intermediate-stage HCC submitted to drug-eluting polyvinyl alcohol microspheres TACE (DEM-TACE), as proposed by a multidisciplinary board, in a tertiary center between January 2010 and October 2020. This study was carried out in compliance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Ethical Committee of our center. The requirement for written informed consent was waived. Inclusion criteria where: (i) radiological or histological evidence of HCC in accordance with the diagnosis criteria of American Association for the Study of Liver Diseases guidelines, (ii) intermediate-stage HCC in accordance with Barcelona Clinic Liver Cancer staging system, (iii) Child-Pugh class A cirrhosis before DEM-TACE, and (iii) treatment with TACE. Exclusion criteria were: (i) comorbidities of other serious diseases (American Society of Anesthesiologists physical status >2), (ii) lack of appropriate follow-up (clinical evaluation or radiological tumor evaluation within 3 months after initial DEM-TACE), (iii) other treatment previous or concomitant with TACE, and (iv) treatment with conventional TACE [14]. All patients were submitted to a biochemical and medical evaluation before initial TACE.

Transarterial Chemoembolization Procedure and Subsequent Follow-Up

After catheter insertion in the celiac artery, guided by angiography, a microcatheter injects contrast into the common hepatic artery, identifying the arteries that feed the tumor. The microcatheter is then advanced as far as possible in the segmental or subsegmental branches feeding the tumor. Drug-eluting microspheres loaded with doxorubicin are injected into the tumor's supply arteries until blood flow is obstructed. The selection of doxorubicin dose is determined by our institution's protocol.

Objective response rate (ORR) to TACE was evaluated 1 month after each procedure with magnetic resonance or computer tomography scan, in accordance with modified response evaluation criteria in solid tumors (mRECIST) [15]. Subsequently, every 3 months imaging was performed and intrahepatic recurrences or presence of viable tumors dictated additional treatment, TACE, or other indicated treatment depending on TACE refractoriness criteria.

Adverse events were accessed retrospectively in patient records and were classified according to Common Terminology Criteria of Adverse Events (CTCAE) 5.0 [16]. Only CTCAE grade ≥3 adverse events were recorded.

Definition of TACE Responder, Liver Decompensation, and TACE Refractoriness

ORR was defined as (i) present in patients with complete response or partial response and as (ii) absent in patients with stable disease or progressive disease in accordance with mRECIST criteria. Liver decompensation was defined as irreversible exacerbation from Child-Pugh class A to Child-Pugh class B or C after first TACE. TACE refractoriness, in accordance with the Japan Society of Hepatology, was defined as (i) ≥2 TACE procedures with each reevaluation showing progression in tumor number or insufficient response of the treated tumors (viable lesions >50%) or (ii) appearance of extrahepatic spread or vascular invasion [17].

Outcomes

The primary outcome was overall survival free of liver decompensation, defined as the time interval from the first TACE to liver decompensation. Secondary outcomes were 6-month survival free of liver decompensation, overall survival free of TACE refractoriness (time interval from the first TACE to TACE refractoriness), and overall survival (time from the first TACE to death).

Statistical Analysis

All variables were presented as categorical variables, with counts and percentages. Overall survival free of liver decompensation was defined as the time interval between initial TACE and development of liver decompensation. Patients who survived without liver decompensation at the last follow-up date (December 10, 2020) or were lost to follow-up were censored. Patients with TACE refractoriness before liver decompensation were censored at the time of TACE refractoriness. Overall survival free of liver decompensation rates were estimated using the Kaplan-Meier method and compared using the log-rank test. Multivariable analysis, using Cox-regression, was performed for the analysis of the following outcomes: overall and 6-month survival free of liver decompensation, overall survival free of TACE refractoriness, and overall survival. All variables statistically significant in the previous univariable analysis were included in this analysis. Multiple imputations had been performed with 5 independent draws for missing values. The interactions between predictors were also tested.

Possible models for risk stratification of overall survival free of liver decompensation were then developed based on the above analyses and performance was measured by likelihood ratio chi-square. A ROC curve analysis was developed to determine the best cut-off value for the model. Kaplan-Meier analysis compared overall survival free of liver decompensation between the two groups created.

Table 1. Baseline characteristics

Parameter	*n* (%)
Sex	
Female	20 (20.2%)
Male	79 (79.8%)
Age, years	
<60	24 (24.2%)
60–70	21 (21.2%)
>70	54 (54.5%)
Etiology	
Alcohol	42 (42.4%)
HCV	34 (34.3%)
HBV	7 (7.1%)
NASH	5 (5.1%)
Others	11 (11.1%)
Tumor size, mm	
<50	86 (86.8%)
50–70	7 (7.1%)
>70	6 (6.1%)
Number of nodules	
1	58 (58.6%)
2	25 (25.3%)
3	8 (8.1%)
>3	8 (8.1%)
Up-to-7	
Within	81 (81.8%)
Beyond	18 (18.2%)
Albumin, g/L	
≤35	43 (43.4%)
>35	56 (56.6%)
Bilirubin, mg/dL	
<2	78 (78.8%)
≥2	21 (21.2%)
Platelets, $\times 10^9$	
≥150	43 (43.4%)
<150	56 (56.6%)
AFP, ng/mL	
<20	61 (61.6%)
≥20	38 (38.4%)
ORR	
Present	41 (41.4%)
Absent	58 (58.6%)
TACE procedures	
1	32 (32.3%)
2	34 (34.3%)
3	17 (17.2%)
≥4	16 (16.2%)
Doxorubicin, mg	
<35	22 (22.2%)
35–70	28 (28.3%)
≥70	49 (49.5%)

HCV, hepatitis C virus; HBV, hepatitis B virus; NASH, non-alcoholic steatohepatitis; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; ORR, objective radiological response at 1 month after first transarterial chemoembolization; TACE, transarterial chemoembolization.

Differences were considered statistically significant when corresponding p values were less than 0.05. All statistical analyses were performed using SPSS Version 23 (IBM Corporation, Chicago, IL, USA).

Results

Patients' Baseline Characteristics

From a total of 161 patients with intermediate-stage HCC and Child-Pugh A cirrhosis treated with TACE, 99 patients were included (Fig. 1). Mean age was 73 (IQR 59–86) years, 78 (79%) were male. Median follow-up time was 40 (IQR 11–62) months. The etiology of hepatic disease was alcohol in 42%, chronic hepatitis C in 34%, chronic hepatitis B (HBV) in 7%, non-alcoholic steatohepatitis in 5%, and others in 11% (Table 1). Median tumor size was 37 mm (10–180 mm). Median tumor number of nodules was 1.6 (IQR 1–2). Eighty-one patients (82%) were within up-to-7 criteria and 18 patients (18%) were beyond up-to-7 criteria. Median albumin was 35.5 g/L (IQR 34–38), median bilirubin was 1 mg/dL (IQR 0.7–1.5), median alpha-fetoprotein was 10.9 ng/mL (IQR 4–70), and median international normalized ratio was 1.2 (IQR 1.1–1.3). No patient presented ascites or hepatic encephalopathy.

Overall and 6-Month Survival Free of Liver Decompensation before TACE Refractoriness

Liver function deteriorated to Child-Pugh B/C before TACE refractoriness in 51 (51.5%) patients and median time to liver decompensation was 14 (IQR 8–20) months, after first TACE. In univariable analysis, overall survival free of liver decompensation was significantly longer in patients within versus beyond up-to-7 criteria (median, 40.9 vs. 20.3, $p = 0.041$), albumin >35 versus ≤35 mg/dL (median, 43.7 vs. 24.5 months, $p < 0.001$), bilirubin <2 versus ≥2 mg/dL (median, 43.9 vs. 18.9 months, $p = 0.029$), and presence versus absence of ORR (median, 56.7 vs. 27.6 months, $p = 0.002$) (Table 2). In multivariable analysis, beyond up-to-7 criteria (HR 2.4, $p = 0.031$), albumin <35 mg/dL (HR 3.5, $p < 0.001$), and absence of ORR (HR 2.4, $p = 0.020$) presented a negative association with overall survival free of liver decompensation (Table 3). Moreover, 6-month survival free of liver decompensation presented a negative association, in multivariable analysis, with beyond up-to-7 criteria (HR 3.7, $p = 0.012$), albumin <35 mg/dL (HR 4.4, $p = 0.006$), and absence of ORR (HR 2.6, $p = 0.025$) (Table 2).

Table 2. Univariable analysis for overall survival free of liver decompensation, 6-month survival free of liver decompensation, survival free of TACE refractoriness, and overall survival

Parameter	OS free of LD (median, 95% CI), months	*p* value	6-month survival free of LD (median, 95% CI), months	*p* value	Survival free of TACE refractoriness (median, 95% CI), months	*p* value	OS (median, 95% CI), months	*p* value
Sex		0.764		0.0661		0.857		0.626
Female	30.3 (12.2–48.4)		5.6 (5.1–6.2)		33.0 (12.0–53.9)		35.4 (18.1–42.8)	
Male	27.2 (8.4–46.3)		5.4 (5.2–5.7)		29.0 (10.6–47.4)		44.4 (27.2–51.5)	
Age, years		0.095		0.234		0.270		**0.017**
<60	43.6 (25.7–61.2)		5.2 (4.6–5.7)		21.0 (12.2–25.7)		46.5 (21.8–61.2)	
60–70	20.3 (11.4–28.2)		5.4 (4.7–5.9)		18.0 (11.2–24.7)		29.3 (13.0–35.6)	
>70	35.4 (29.2–42.5)		5.5 (4.9–6.1)		39.0 (12.8–49.2)		43.5 (27.2–49.9)	
Etiology		**0.011**		0.223		0.070		**0.006**
Alcohol	25.4 (6.4–43.5)		5.7 (5.4–5.9)		25 (9.6–40.3)		37.7 (21.4–43.9)	
HCV	58.2 (21.7–94.3)		5.4 (4.9–5.9)		49 (32.1–65.9)		52.9 (31.0–64.8)	
HBV	9.6 (3.4–14.6)		4.8 (4.1–5.6)		19 (10.2–39.0)		32.7 (5.0–30.4)	
NASH	39.3 (18.3–59.7)		5.2 (4.6–5.7)		39 (9.3–68.6)		41.0 (19.7–52.3)	
Others	19.4 (8.1–38.5)		5.4 (4.7–5.9)		38 (9.3–40.2)		35.0 (8.7–51.2)	
Tumor size, mm		0.079		0.483		**0.008**		0.427
<50	38.2 (28.9–47.4)		5.7 (5.4–5.9)		38.0 (23.0–52.2)		43.7 (26.9–50.5)	
50–70	30.9 (13.9–47.9)		5.4 (4.9–5.9)		18 (8.2–27.7)		38.4 (19.5–47.4)	
>70	5.3 (3.1–7.4)		4.6 (3.3–5.8)		8 (3.8–12.1)		37.9 (10.3–55.4)	
Number of nodules		**0.032**		0.194		**0.010**		0.122
1	45.8 (34.6–56.9)		5.7 (5.5–5.9)		41.0 (19.3–62.6)		50.1 (30.9–59.2)	
2	21.1 (10.9–31.3)		4.9 (4.4–5.6)		12.0 (2.7–21.6)		33.6 (16.3–40.9)	
3	21.1 (7.8–34.3)		4.9 (3.5–6.2)		29.0 (17.0–62.4)		30.5 (11.0–39.9)	
>3	16 (2.5–25.4)		3.6 (3.4–6.2)		20.0 (13.7–46.9)		34.9 (12.3–47.6)	
Up-to-7		**0.041**		**0.007**		**0.001**		**0.005**
Within	40.9 (31.5–50.3)		5.6 (5.4–5.8)		39 (27.0–50.9)		46.9 (29.6–54.2)	
Beyond	20.3 (9.9–30.7)		4.8 (4.1–5.4)		6 (3.4–8.5)		27.9 (10.3–35.6)	
Albumin, g/L		**<0.001**		**0.006**		0.711		**0.019**
≤35	20.4 (10.1–30.7)		5.6 (5.4–5.8)		29.0 (16.7–41.3)		37.5 (19.4–45.7)	
>35	40.9 (34.5–47.2)		4.8 (4.1–5.4)		39.0 (17.3–60.7)		45.9 (28.9–52.9)	
Bilirubin, mg/dL		**0.029**		0.655		0.477		0.667
<2	43.9 (33.8–54.1)		5.4 (5.0–5.8)		31.0 (17.2–44.7)		45.6 (25.9–55.3)	
≥2	18.9 (7.4–30.3)		5.5 (5.2–5.9)		29.0 (12.8–54.2)		39.9 (27.3–50.6)	
Platelets, $\times 10^9$		0.067		**0.027**		0.144		0.660
≥150	39.0 (30.9–47.1)		5.7 (5.2–6.4)		20.0 (15.2–24.8)		21.0 (16.7–25.3)	
<150	15.0 (5.1–24.8)		5.2 (4.1–5.7)		39.9 (31.1–46.9)		28.0 (15.6–40.4)	
AFP, ng/mL		0.355		0.892		0.358		0.401
<20	43.6 (31.4–55.7)		5.3 (4.6–6.1)		40.0 (35.9–44.0)		43.3 (24.6–51.9)	
≥20	27.3 (17.3–37.4)		5.6 (5.1–6.1)		19.0 (15.3–22.7)		41.3 (22.1–50.4)	
ORR		**0.002**		**0.014**		**0.002**		0.080
Present	56.8 (43.5–70.0)		5.6 (5.2–5.8)		57.3 (43.5–70.0)		39.6 (22.4–46.8)	
Absent	27.7 (19.3–36.0)		4.8 (4.1–5.7)		31.7 (19.3–38.0)		49.6 (28.8–60.4)	
TACE procedures		0.074		0.651		0.131		0.743
1	21.3 (8.6–34.5)		5.3 (4.5–6.2)		17.0 (0.5–33.5)		43.4 (24.6–51.9)	
2	39.7 (29.8–54.3)		5.5 (5.2–6.4)		39.0 (22.7–55.3)		42.1 (22.1–50.4)	
3	23.6 (14.6–35.3)		5.3 (4.7–6.1)		20.0 (17.2–22.7)		39.3 (22.4–46.8)	
≥4	41 (31.2–56.2)		5.4 (5.3–6.3)		41.0 (35.6–46.4)		46.5 (28.8–60.4)	
Doxorubicin, mg		0.457		0.934		0.333		0.663
<35	38.4 (19.3–57.5)		5.5 (5.0–6.1)		38.0 (23.1–52.9)		48.0 (21.7–64.3)	
35–70	25.9 (15.7–36.1)		5.4 (4.8–6.0)		17.0 (11.8–22.1)		36.4 (16.8–45.9)	
≥70	35.9 (29.9–48.2)		5.5 (5.1–5.7)		39.0 (21.4–56.6)		41.0 (24.6–47.5)	

OS, overall survival; LD, liver decompensation; CI, confidence interval; HCV, hepatitis C virus; HBV, hepatitis B virus; NASH, non-alcoholic steatohepatitis; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; ORR, objective radiological response at 1 month after first transarterial chemoembolization; TACE, transarterial chemoembolization.

Table 3. Multivariable analysis for overall survival free of liver decompensation, 6-month survival free of liver function deterioration, survival free of TACE refractoriness, and overall survival

Parameter	OS free of LD		6-month survival free of LD		Survival free of TACE refractoriness		OS	
	hazard ratio (95% CI)	*p* value	hazard ratio (95% CI)	*p* value	hazard ratio (95% CI)	*p* value	hazard ratio (95% CI)	*p* value
Age, years								
≤70	1	–	1	–	1	–	1	–
>70	2.6 (0.7–8.6)	0.246	1.7 (0.6–7.1)	0.275	1.9 (0.5–6.5)	0.623	2.4 (1.3–8.1)	**0.012**
Etiology								
Others	1	–	1	–	1	–	1	–
HBV	4.0 (0.8–11.1)	0.123	1.7 (0.4–8.1)	0.483	1.2 (0.2–9.5)	0.844	1.4 (0.8–5.1)	0.237
Up-to-7								
Within	1	–	1	–	1	–	1	–
Beyond	2.4 (1.1–5.5)	**0.031**	3.7 (1.3–10.1)	**0.012**	3.9 (1.8–8.3)	**0.001**	2.4 (1.2–4.7)	**0.011**
Albumin, g/L								
>35	1	–	1	–	1	–	1	–
≤35	3.5 (1.9–6.7)	**<0.001**	4.4 (1.5–12.8)	**0.006**	1.3 (0.6–2.5)	0.503	1.7 (1.0–2.9)	**0.042**
Bilirubin, mg/dL								
<2	1	–	1	–	1	–	1	–
≥2	1.0 (0.9–1.2)	0.843	0.9 (0.5–1.4)	0.537	1.1 (0.4–2.5)	0.983	0.9 (0.8–1.1)	0.387
Platelets, $\times 10^9$								
≥150	1	–	1	–	1	–	1	–
<150	2.4 (1.1–5.5)	0.343	3.1 (0.8–9.1)	0.127	1.7 (0.6–7.1)	0.275	1.8 (0.7–2.8)	0.387
ORR								
Present	1	–	1	–	1	–	1	–
Absent	2.4 (1.1–5.2)	**0.020**	2.8 (1.2–8.1)	**0.025**	2.7 (1.1–3.5)	**0.025**	1.6 (0.8–2.5)	0.074

OS, overall survival; LD, liver decompensation; CI, confidence interval; HBV, hepatitis B virus; ORR, objective radiological response at 1 month after first transarterial chemoembolization.

Table 4. Six-month survival free of liver decompensation for patients stratified as low- or high-risk in accordance with out model

Model classification	6-month SFLD (median, 95% CI), months	*p* value
Low-risk	26.1	0.002
High-risk	50.9	

SFLD, survival free of liver decompensation.

Using up-to-7-criteria, albumin, and ORR, we created a model predictive of 6-month survival free liver decompensation. The model formula is: 1.601 (if beyond up-to-7 criteria) – 0.428 (if albumin >35 mg/dL) – 0.464 (if presence of ORR) – 1.285.

ROC curve presented an AUROC 0.701 ($p = 0.006$) for the prediction of liver decompensation at 6 months. Using the cut-off value of –1.49, the model presented a sensitivity of 81% and a specificity of 72% for liver decompensation at 6 months.

We used the cut-off value of –1.49 to classify patients as low-risk (<–1.49) and high-risk (≥–1.49) in accordance with the model developed. Patients classified as high-risk ($n = 52$) presented a higher prevalence of liver decompensation (35%) when compared with patients classified as low-risk (10%). This difference was statistically significant in chi-square test ($p = 0.022$). Furthermore, in Kaplan-Meyer analysis, high-risk patients presented smaller overall survival free of liver decompensation when compared to low-risk patients (median, 26.1 vs. 50.9 months, $p = 0.002$) (Fig. 2; Table 4).

Transarterial Chemoembolization Treatment Outcome

The median TACE procedures per patient was 2 (IQR 1–3) and 41 patients (41%) presented ORR after first TACE. Fifty (51%) patients developed TACE refractoriness during follow-up and the median time to TACE refractoriness was 33 (IQR 11.7–54.3) months. Twelve (12.1%) patients presented post chemoembolization syndrome. No other major (CTCAE grade ≥3) complications related to TACE were registered.

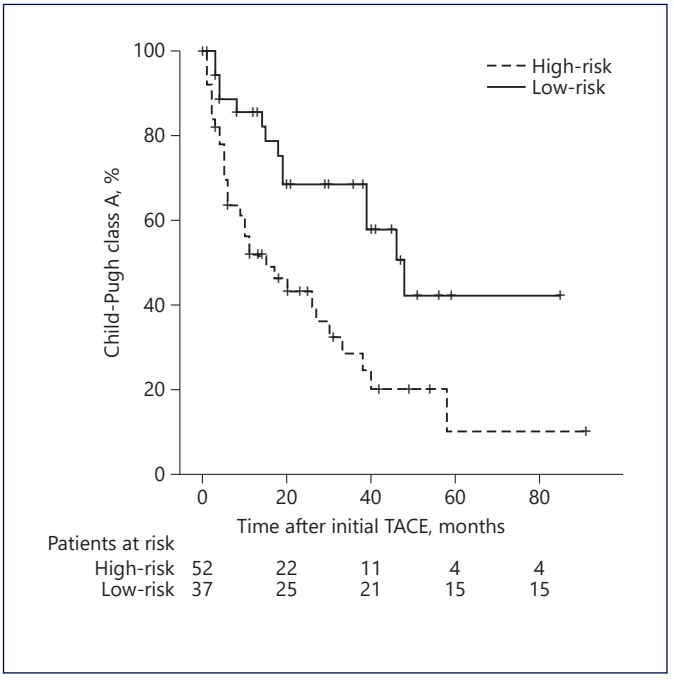


Fig. 2. Kaplan-Meier curves for the time to Child-Pugh class deterioration in patients with intermediate-stage hepatocellular carcinoma who underwent transarterial chemoembolization (TACE) as first-line treatment. Comparing patients classified as high-risk and low-risk in accordance with our model using the cut-off value of –1.49.

In univariable analysis, up-to-7 criteria, number of nodules, total tumor size, and absence of ORR were identified as predictive factors associated with survival free of TACE refractoriness (Table 2). In multivariable analysis, beyond up-to-7 criteria and absence of ORR were identified as predictive factors of survival free of TACE refractoriness (Table 3).

Overall Survival

Presence of liver decompensation at 6 months after initial TACE was negatively associated with overall survival. Median survival was 38.7 (IQR 31.2–46.1) months for patients with Child-Pugh A and 12 (IQR 8.6–15.3) months for patients with Child-Pugh B/C at 6-month evaluation post first TACE procedure. This difference was statistically significant ($p < 0.001$). Moreover, albumin <35 and beyond up-to-7 criteria were also negatively associated with overall survival in univariable analysis (Table 2). In multivariable analysis, beyond up-to-7 criteria (HR 2.4, $p = 0.011$) and albumin <35 mg/dL (HR 1.7, $p < 0.042$) were negatively associated with overall survival (Table 3).

Discussion

Based on our findings, we suggest that baseline albumin <35 g/L, beyond up-to-7 criteria, and absence of response to initial TACE are predictors of liver decompensation to Child-Pugh B/C before TACE refractoriness, in patients with intermediate-stage HCC submitted to TACE. Moreover, early (6 months) liver decompensation was associated with baseline albumin <35 g/L, beyond up-to-7 criteria, and absence of response to initial TACE. Indeed, our model created using those variables was able to predict liver decompensation after initial TACE, and patients classified as high risk presented shorter survival free of liver decompensation.

Previous studies associated different markers of liver function and tumor burden as predictors of liver decompensation. However, those studies did not attempt to focus on predictors of liver decompensation before TACE refractoriness [18–20]. Furthermore, previous studies fail to analyze a specific population of patients with intermediate-stage HCC or a population exclusively treated with DEM-TACE. Identification of predictors of liver decompensation previous to TACE refractoriness is specifically useful in patients with intermediate-stage HCC, since the concept of therapeutic stage migration could be anticipated in such patients before TACE refractoriness. Furthermore, DEM-TACE, as opposed to conventional TACE or transarterial embolization is currently the most commonly used locoregional procedure in intermediate-stage HCC, with a better security profile and, in some studies, better efficacy [21–23]. Facciorusso et al. report a meta-analysis that evaluated the efficacy and safety of TACE versus bland embolization [23]. In this study no differences in survival were identified. However, despite the apparently worst security profile of conventional TACE versus bland embolization, DEM-TACE in particular appears to present lower rates of adverse events. Indeed, in our population, only twelve patients presented postembolization syndrome and no other complications were registered. Also, being a single-center study, TACE procedures were standardized and the choice of anticancer agents was uniformized.

The ORR is proposed as a prognostic tool and is useful in the selection of retreatment strategies [1]. Assessment for retreatment with TACE (ART) score is a scoring system using radiological response to initial TACE as a tool useful in the selection of patients that do not benefit from additional TACE [24, 25]. Our findings suggest ORR might also be useful to predict early liver dysfunction before TACE refractoriness.

Cumulative TACE procedure has been previously identified as a risk factor for liver decompensation [13, 26]. However, the number of TACE procedures and cumulative doxorubicin dose did not present an association with overall survival free of liver decompensation in our population. This could be explained by the type of locoregional therapy used. In our population, only DEM-TACE was used, contrary to previous studies. DEM-TACE presents less toxicity to liver function as opposed to conventional TACE [21, 22].

The concept of TACE refractoriness is useful to consider the opportunity to switch from TACE retreatment to ST [8, 17]. Previous studies demonstrated an association between liver decompensation and TACE refractoriness [18]. Indeed, in our population, beyond up-to-7 criteria and absence of ORR were independently associated with both liver decompensation and TACE refractoriness. As such, patients beyond up-to-7 criteria, with absence of ORR, or with albumin <35 g/L not only have a smaller window of opportunity to initiate ST but have a greater probability of TACE refractoriness.

Several randomized controlled trials evaluating efficacy and safety of ST plus TACE or TACE alone in patients with intermediate-stage HCC have been done and others are currently in progress [11, 27]. Such studies have, so far, suggested a benefit in progression-free survival with this combination. However, the sub-population of patients who benefit the most from this combination is not yet described. We hypothesize that patients classified as high-risk of liver decompensation, using our model, might benefit from inclusion in such studies.

Furthermore, overall survival in patients with HCC treated with locoregional therapy is influenced by both recurrence and successive treatments. Previous studies demonstrate that a significant portion of patients experience HCC recurrence after locoregional therapy [28]. In patients with recurrence with advance-stage HCC, ST is the only palliate treatment available. Such patients are deprived of this option in the presence of liver decompensation. Patients classified as high-risk of liver decompensation, using our model, present an increased risk of liver decompensation and in consequence, might have an increased risk of being deprived of adequate treatment in case of HCC recurrence.

As a retrospective study, there are some limitations from the presence of possible bias. Moreover, sample size limited the number of variables included in multivariable analysis, and only significant variables in univariable analysis were included. Further prospective large studies are necessary to confirm our results.

In conclusion, our findings suggest that in patients with intermediate-stage HCC and Child-Pugh class A, beyond up-to-7 criteria, albumin <35 mg/dL, and absence of ORR to initial TACE are predictors of early liver decompensation before TACE refractoriness. We created a model using those variables that is able to predict liver decompensation. Patients classified as high risk using this model have a smaller window of opportunity for alternative therapies and might benefit from inclusion in TACE plus ST combination therapy or ST monotherapy clinical trials.

Statement of Ethics

This study was carried out in compliance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Ethical Committee of our center. The requirement for written informed consent was waived.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have no funding to declare.

Author Contributions

J.F.-S. conceived the study. J.F.-S. and H.C. designed the study. J.F.-S. and P.C.-M. performed data collection. J.F.-S., H.C., R.L., and P.P. undertook the bibliographic research and drafted the manuscript. G.M. critically revised the draft and approved the final paper.

References

1 Galle PR, Tovoli F, Foerster F, Wörns MA, Cucchetti A, Bolondi L. The treatment of intermediate stage tumours beyond TACE: from surgery to systemic therapy. J Hepatol. 2017 Jul;67(1):173–83.
2 Raoul JL, Sangro B, Forner A, Mazzaferro V, Piscaglia F, Bolondi L, et al. Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. Cancer Treat Rev. 2011 May;37(3):212–20.
3 de Lope CR, Tremosini S, Forner A, Reig M, Bruix J. Management of HCC. J Hepatol. 2012;56 Suppl 1:S75–87.

4 Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018 Aug;68(2):723–50.
5 Burrel M, Reig M, Forner A, Barrufet M, de Lope CR, Tremosini S, et al. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. J Hepatol. 2012 Jun;56(6):1330–5.
6 Vitale A, Trevisani F, Farinati F, Cillo U. Treatment of Hepatocellular Carcinoma in the Precision Medicine Era: From Treatment Stage Migration to Therapeutic Hierarchy. Hepatology. 2020 Dec;72(6):2206–18.
7 Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol. 2012 Oct;57(4):821–9.
8 Ogasawara S, Chiba T, Ooka Y, Kanogawa N, Motoyama T, Suzuki E, et al. Efficacy of sorafenib in intermediate-stage hepatocellular carcinoma patients refractory to transarterial chemoembolization. Oncology. 2014; 87(6):330–41.
9 Arizumi T, Ueshima K, Minami T, Kono M, Chishina H, Takita M, et al. Effectiveness of sorafenib in patients with transcatheter arterial chemoembolization (TACE) refractory and intermediate-stage hepatocellular carcinoma. Liver Cancer. 2015 Dec;4(4):253–62.
10 Peck-Radosavljevic M, et al. Outcomes of patients (pts) with hepatocellular carcinoma (HCC) treated with transarterial chemoembolization (TACE): Global OPTIMIS final analysis. American Society of Clinical Oncology; 2018.
11 Kudo M, Ueshima K, Ikeda M, Torimura T, Tanabe N, Aikata H, et al.; TACTICS study group. Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. Gut. 2020 Aug; 69(8):1492–501.
12 Abou-Alfa GK, Amadori D, Santoro A, Figer A, De Greve J, Lathia C, et al. Safety and efficacy of sorafenib in patients with hepatocellular carcinoma (HCC) and Child-Pugh A versus B cirrhosis. Gastrointest Cancer Res. 2011 Mar;4(2):40–4.
13 Hiraoka A, Kumada T, Kudo M, Hirooka M, Koizumi Y, Hiasa Y, et al.; Real-life Practice Experts for HCC (RELPEC) Study Group and HCC 48 Group (hepatocellular carcinoma experts from 48 clinics). Hepatic function during repeated TACE procedures and prognosis after introducing sorafenib in patients with unresectable hepatocellular carcinoma: multicenter analysis. Dig Dis. 2017;35(6):602–10.
14 Mayhew D, Mendonca V, Murthy BV. A review of ASA physical status - historical perspectives and modern developments. Anaesthesia. 2019 Mar;74(3):373–9.
15 Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. in Seminars in liver disease. 2010. ©Thieme Medical Publishers.
16 Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol. 2003 Jul;13(3):176–81.
17 Kudo M, Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y, et al.; Liver Cancer Study Group of Japan. JSH Consensus-Based Clinical Practice Guidelines for the Management of Hepatocellular Carcinoma: 2014 Update by the Liver Cancer Study Group of Japan. Liver Cancer. 2014 Oct;3(3-4):458–68.
18 Kohla MA, Abu Zeid MI, Al-Warraky M, Taha H, Gish RG. Predictors of hepatic decompensation after TACE for hepatocellular carcinoma. BMJ Open Gastroenterol. 2015 Jun;2(1):e000032.
19 Yasui Y, Tsuchiya K, Kurosaki M, Takeguchi T, Takeguchi Y, Okada M, et al. Up-to-seven criteria as a useful predictor for tumor downstaging to within Milan criteria and Child-Pugh grade deterioration after initial conventional transarterial chemoembolization. Hepatol Res. 2018 May;48(6):442–50.
20 Eso Y, Takai A, Takahashi K, Ueda Y, Taura K, Marusawa H, et al. Combination of Mac-2 binding protein glycosylation isomer and up-to-seven criteria as a useful predictor for Child-Pugh grade deterioration after transarterial chemoembolization for hepatocellular carcinoma. Cancers (Basel). 2019 Mar;11(3): 405.
21 Ferrer Puchol MD, la Parra C, Esteban E, Vaño M, Forment M, Vera A, et al. Quimioembolización del hepatocarcinoma: partículas cargadas frente a quimioembolización convencional. Radiologia (Madr). 2011;53(3): 246–53.
22 Kloeckner R, Weinmann A, Prinz F, Pinto dos Santos D, Ruckes C, Dueber C, et al. Conventional transarterial chemoembolization versus drug-eluting bead transarterial chemoembolization for the treatment of hepatocellular carcinoma. BMC Cancer. 2015 Jun;15(1):465.
23 Facciorusso A, Bellanti F, Villani R, Salvatore V, Muscatiello N, Piscaglia F, et al. Transarterial chemoembolization vs bland embolization in hepatocellular carcinoma: A meta-analysis of randomized trials. United European Gastroenterol J. 2017 Jun;5(4):511–8.
24 Yin W, Ye Q, Wang F, Liang J, Xu B, Zhang X, et al. ART score and hepatocellular carcinoma: an appraisal of its applicability. Clin Res Hepatol Gastroenterol. 2016 Dec;40(6): 705–14.
25 Tseng CL, Lai WJ, Huang CJ, Huang YH, Su CW, Lee IC, et al. The Effectiveness of ART Score in Selecting Patients for Transarterial Chemoembolization Retreatment: A Cohort Study in Taiwan. Medicine (Baltimore). 2015 Nov;94(47):e1659–1659.
26 Miksad RA, Ogasawara S, Xia F, Fellous M, Piscaglia F. Liver function changes after transarterial chemoembolization in US hepatocellular carcinoma patients: the LiverT study. BMC Cancer. 2019 Aug;19(1):795.
27 Hindson J. Combined TACE and sorafenib for HCC treatment. Nat Rev Gastroenterol Hepatol. 2020 Feb;17(2):66–66.
28 Facciorusso A, Del Prete V, Antonino M, Crucinio N, Neve V, Di Leo A, et al. Post-recurrence survival in hepatocellular carcinoma after percutaneous radiofrequency ablation. Dig Liver Dis. 2014 Nov;46(11):1014–9.

GE – Portuguese Journal of Gastroenterology

Research Article

GE Port J Gastroenterol 2023;30:38–48
DOI: 10.1159/000520562

Received: August 4, 2021
Accepted: October 14, 2021
Published online: December 14, 2021

Anastomotic Leaks following Esophagectomy for Esophageal and Gastroesophageal Junction Cancer: The Key Is the Multidisciplinary Management

Raquel Ortigão[a] Brigitte Pereira[b] Rui Silva[a] Pedro Pimentel-Nunes[a, c] Pedro Bastos[a] Joaquim Abreu de Sousa[d] Filomena Faria[b] Mário Dinis-Ribeiro[a, c] Diogo Libânio[a, c]

[a]Gastroenterology Department, Portuguese Oncology Institute of Porto, Porto, Portugal; [b]Intensive Care Unit, Portuguese Oncology Institute of Porto, Porto, Portugal; [c]MEDCIDS, Faculty of Medicine, University of Porto, Porto, Portugal; [d]Surgery Department, Portuguese Oncology Institute of Porto, Porto, Portugal

Keywords
Esophageal cancer · Esophagectomy · Anastomotic leakage · Endoscopic treatment

Abstract
Introduction: Anastomotic leakage after esophagectomy is associated with high mortality and impaired quality of life. ***Aim:*** The objective of this work was to determine the effectiveness of management of esophageal anastomotic leakage (EAL) after esophagectomy for esophageal and gastroesophageal junction (GEJ) cancer. ***Methods:*** Patients submitted to esophagectomy for esophageal and GEJ cancer at a tertiary oncology hospital between 2014 and 2019 (n = 119) were retrospectively reviewed and EAL risk factors and its management outcomes determined. ***Results:*** Older age and nodal disease were identified as independent risk factors for anastomotic leak (adjusted OR 1.06, 95% CI 1.00–1.13, and adjusted OR 4.89, 95% CI 1.09–21.8). Patients with EAL spent more days in the intensive care unit (ICU; median 14 vs. 4 days) and had higher 30-day mortality (15 vs. 2%) and higher in-hospital mortality (35 vs. 4%). The first treatment option was surgical in 13 patients, endoscopic in 10, and conservative in 3. No significant differences were noticeable between these patients, but sepsis and large leakages were tendentially managed by surgery. At follow-up, 3 patients in the surgery group (23%) and 9 in the endoscopic group (90%) were discharged under an oral diet ($p = 0.001$). The in-hospital mortality rate was 38% in the surgical group, 33% in the conservative group, and 10% in endoscopic group ($p = 0.132$). In patients with EAL, the presence of septic shock at leak diagnosis was the only predictor of mortality ($p = 0.004$). ICU length-of-stay was non-significantly lower in the endoscopic therapy group (median 4 days, vs. 16 days in the surgical group, $p = 0.212$). ***Conclusion:*** Risk factors for EAL may help change pre-procedural optimization. The results of this study suggest including an endoscopic approach for EAL.

Deiscências anastomóticas após esofagectomia por neoplasia esofágica / juncional: a importância da abordagem multidisciplinar

Palavras Chave
Cancro esofágico · Esofagectomia · Deiscência anastomótica · Tratamento endoscópico

karger@karger.com
www.karger.com/pjg

Correspondence to:
Raquel Ortigão, raquel.ortigao@hotmail.com

Resumo

Introdução: A deiscência anastomótica após esofagectomia está associada a uma elevada taxa de mortalidade e qualidade de vida comprometida. ***Objetivo:*** Avaliar a eficácia da abordagem da deiscência de anastomose esofágica após esofagectomia por neoplasia do esófago e da junção esofagogastrica (JEG). ***Métodos:*** Foram revistos retrospetivamente todos os doentes submetidos a esofagectomia por neoplasia do esófago e da JEG num hospital terciário entre 2014 e 2019 (n = 119) e analisados os fatores de risco e as diferentes abordagens na deiscência anastomótica. ***Resultados:*** A idade avançada e a presença de metastização ganglionar foram identificados como fatores de risco independentes para deiscência anastomótica (OR 1.06, 95% IC 1.00–1.13 e 4.89, IC 1.09–21.8). Os doentes com deiscência anastomótica estiveram mais dias internados na unidade de cuidados intensivos (UCI) (mediana 14 vs. 4 dias) e tiveram uma mortalidade aos 30 dias e intra-hospitalar mais elevada (15% vs. 2% e 35% vs. 4%, respectivamente). A primeira abordagem terapêutica foi cirúrgica em 13 doentes, endoscópica em 10 e conservadora em 3. Não foram encontradas diferenças estatisticamente significativas entre estes doentes, com uma tendência para a presença de sépsis e de deiscências de maior dimensão nos doentes abordados cirurgicamente. Durante o seguimento, 3 doentes do grupo cirúrgico (23%) e 9 do grupo endoscópico (90%) tiveram alta hospitalar sob dieta oral (p = 0.001). A taxa de mortalidade intra-hospitalar foi de 38% no grupo cirúrgico, 33% no grupo conservador e 10% no grupo endoscópico (p = 0.132). Nos doentes com deiscência anastomótica, a presença de choque sético ao diagnóstico foi o único preditor de mortalidade (p = 0.004). O tempo de internamento na UCI não foi significativamente menor no grupo submetido a tratamento endoscópico (mediana de 4 dias vs. 16 dias no grupo cirúrgico, p = 0.212). ***Conclusão:*** A identificação de fatores de risco para deiscência anastomótica após esofagectomia pode ajudar a alterar a optimização pré-procedimento. Os resultados deste estudo sugerem incluir uma abordagem endoscópica nos doentes com deiscência anastomótica.

Introduction

Esophageal cancer is the sixth leading cause of cancer-related death overall, mainly due to diagnosis in advanced stages [1]. Even when esophageal cancer is resectable, esophagectomy carries a high risk of death (3.6–4.5%) compared with most surgically treated cancers [2–4]. Many efforts have been made to improve the esophagectomy technique and to reduce postoperative complications, but esophageal anastomotic leakage (EAL) remains a frequent and feared postoperative complication, associated with high mortality and impaired quality of life. However, improvement of surgical techniques and management of complications has led to a steady decrease in postoperative mortality over the years [5–8].

Some factors have been associated with EAL development, such as patients' nutritional status and comorbidities, cancer stage, surgical procedure, and neoadjuvant therapy, but there are some controversies in the literature about the significant risk factors for this adverse event [9, 10]. The identification of patients at risk for EAL can thus help in postsurgical management.

EAL treatment success relies on early diagnosis, but optimal treatment remains controversial. The treatment decision is dependent on the characteristics of the leak and the severity of the patient's condition. In the past, surgical revision with re-anastomosis or esophageal deviation was the treatment of choice. Since the emergence of endoscopic techniques, several potential endoscopic interventions have been used, such as clipping, self-expandable metal stents (SEMS), endoscopic vacuum therapy (EVT), and endoscopic suturing devices [11–13].

While there are several studies evaluating the success of endoscopic and surgical treatment, there are few comparative studies evaluating treatment outcomes of different management strategies specifically following oncological esophagectomy. The aim of this study was to assess anastomotic leakage rates after esophagectomy for esophageal and gastroesophageal junction cancer (GEJ), to identify possible risk factors for EAL, and compare the outcomes of patients with EAL according to management strategy.

Materials and Methods

Patients and Methods

This was a retrospective cohort study including consecutive patients submitted to esophagectomy for esophageal or GEJ cancer between January 2014 and December 2019 in Instituto Português de Oncologia do Porto – Francisco Gentil. All the patients submitted to esophagectomy are initially managed in ICU where an electronic registry of all admissions ensure consecutive sampling. Data collection was performed through analysis of electronic medical records and patient charts.

Patient demographic characteristics were collected along with the following clinical, surgical, and pathological characteristics:

history of diabetes or hypertension, smoking and alcohol habits, tumor location, histological type, surgical approach (Ivor-Lewis, McKeown, transhiatal, Sweet, and total esophagogastrectomy), type of reconstruction, anastomosis technique, surgeon's experience, year of procedure, clinical TNM stage, neoadjuvant treatment, APACHE II (Acute Physiology and Chronic Health Evaluation) score on the first postoperative day, mean length-of-stay in the intensive care unit (ICU), need for invasive ventilation, in-hospital mortality, and 1-year survival rate. Patients with and without EAL were compared in terms of these factors.

Definition and Management of Anastomotic Leaks

An anastomotic leak was defined as a "full thickness gastrointestinal defect involving the esophagus, anastomosis, staple line, or conduit irrespective of presentation or method of identification" according to the Esophagectomy Complications Consensus Group definition [14]. An anastomotic leak was classified as contained if no communication existed with the pleural space or only minimal extension into the mediastinal space occurred. Contrarily, an uncontained leak was defined as a relatively large amount of contrast extravasating into the pleural space or draining into the chest tube, the presence of an abscess, mediastinitis, pyothorax, and sepsis [15].

The diagnosis of anastomotic leak was made through oral contrast computed tomography (CT), upper digestive endoscopy, or contrast esophagography. The combination of the patient's clinical status with the availability of each exam at the time of suspected diagnosis were the factors with the greatest impact on the selection of the diagnostic exam to be performed. Patient management depended on the characteristics of the leak, clinical status, and the availability of emergent endoscopic facilities, as well as multidisciplinary judgement. Thr treatment strategy was classified as conservative, surgical, and/or endoscopic. Conservative treatment included intravenous antibiotics, restriction of oral intake, and enteral or parenteral nutrition. Surgical (re-operation) treatment included primary repair of the leak with decortication and drainage, resection of the leak with re-anastomosis, as well as esophageal deviation with cervical esophagostomy. Endoscopic treatment included through-the-scope (TTS) endoclip, over-the-scope clip (OTSC), SEMS, or EVT.

Successful closure of the leak was defined as the state in which endoscopy, CT, or contrast esophagography confirmed complete healing and the patient presented no clinical signs of leak. Time to oral intake was defined as the period from the first treatment of the leak to the day of oral diet start, with oral intake being progressively resumed except if diagnostic exams evidenced persistent leak. Patients who died before starting oral intake were not included in this analysis. A failure to seal the leak was defined as persistent leak after the end of treatment or the need of another treatment strategy. Time to oral intake, ICU length-of-stay, and in-hospital mortality were compared between the conservative, endoscopic, and surgical treatment group. ICU length-of-stay was calculated excluding patients who died during ICU stay.

Statistical Analysis

All statistical analyses were performed using IBM SPSS version 26. Data are presented as the number and percentages for categorical variables. Continuous variables are presented as the mean and standard deviation (SD) or as the median and interquartile range (Q25–Q75). Univariable analysis was performed using the χ^2 test or Fisher exact test, while continuous variables were compared using Student's *t* test or Mann-Whitney test if non-parametric data. The multivariable model included age, sex, and variables with $p < 0.2$ in univariable analysis. For all comparisons, $p < 0.05$ was considered to indicate statistical significance.

Results

Patients

From January 2014 to December 2019, 119 patients underwent esophagectomy for esophageal and GEJ cancer. We excluded 4 patients from the analysis (3 patients with late esophageal pulmonary fistulas more than 1 year after esophagectomy, and 1 patient who had esophageal melanoma metastasis), except for incidence rate measurement.

All the patients were admitted to ICU after surgery for intensive medical surveillance. Patients were predominantly male (85.2%) and the mean age was 64.1 years (SD 9.2). Squamous cell carcinoma was the most frequent histology (77/115, 67.0%), with adenocarcinomas accounting for 33.0%. In more than half of the patients (52.2%), the tumor did not extend beyond the muscularis propria (≤T2). Seventy-nine patients (68.7%) had disease at least in one lymph node (N+).

Eighty-four patients (73.0%) received neoadjuvant chemoradiation therapy. The esophagectomy was performed through the McKeown approach in 80 (69.6%), transhiatal approach in 15 (13.0%), Ivor-Lewis approach in 12 (10.4%), Sweet approach in 6 (5.2%), and total esophagogastrectomy in 2 (1.7%).

The esophagectomy was performed with cervical anastomosis in 98 patients and with intrathoracic anastomosis in 21 patients. The stomach was used as a conduit to re-establish gastrointestinal continuity in 100 cases (gastric pull-up). The esophageal anastomosis was hand sewn in 71.6%, mechanical in 22.1%, and hybrid in 6.3%. Table 1 shows the clinicopathological and surgical characteristics of the patients.

Incidence and Characteristics of Anastomotic Leakage

Considering all patients submitted to esophagectomy ($n = 119$), 26 patients (21.8%) had an anastomotic leak. There were no significant differences according to anastomosis location (21/95 in cervical location vs. 5/20 in intrathoracic, $p = 0.988$). The leak rate was stable throughout the study period.

The median time interval from surgery to diagnosis of the anastomotic leakage was 5.5 days (IQR 3–11). At the

Table 1. Clinicopathological and surgical data of patients who underwent esophagectomy and differences between those developing leaks

	All (n = 115)	Leak (n = 26)	No Leak (n = 89)	p	Multivariable analysis	
					OR, 95% CI	p
Mean age ± SD, years	64.1±9.2	67.42±10.08	63.12±8.71	**0.035**	**1.064 (1.000–1.132)**	**0.049**
Male sex, *n* (%)	98 (85.2)	21 (80.8)	77 (86.5)	0.468	1.377 (0.364–5.210)	0.637
Hypertension, *n* (%)	59 (51.3)	17 (65.4)	42 (47.2)	0.103	0.412 (0.144–1.175)	0.097
Diabetes mellitus, *n* (%)	22 (19.1)	5 (19.2)	17 (19.1)	0.988	2.297 (0.623–8.464)	0.212
Alcoholism, *n* (%)	63 (54.8)	13 (50.0)	50 (56.2)	0.578		
Ex or current smoker, *n* (%)	87 (75.7)	20 (76.9)	67 (75.3)	0.864		
Histological type, *n* (%)						
Adenocarcinoma	38 (33.0)	11 (42.3)	27 (30.3)	0.254		
SCC	77 (67.0)	15 (57.7)	62 (69.7)			
Tumor location, *n* (%)						
Adenocarcinoma						
EGJ–Siewert I	30 (26.1)	20 (76.9)	10 (11.2)	0.428		
EGJ–Siewert II	5 (4.3)	1 (3.8)	4 (4.5)			
Cardia–Siewert III	3 (2.6)	0 (0)	3 (3.4)			
SCC						
Upper third	2 (1.7)	0 (0)	2 (2.2)	0.241		
Middle third	32 (27.8)	9 (34.6)	23 (25.8)			
Lower third	43 (37.3)	6 (23.1)	37 (41.6)			
T category, *n* (%)				**0.020**		0.074
T1/T2	54 (47.0)	7 (27.0)	47 (52.9)		0.389 (0.138–1.097)	
T3/T4	61 (53.0)	19 (73.0)	42 (47.2)		1	
N category, *n* (%)				**0.047**		**0.038**
N+	79 (68.7)	22 (84.6)	57 (64.0)		4.891 (1.095–21.842)	
N0	36 (31.3)	4 (15.4)	32 (36.0)		1	
Neoadjuvant therapy, *n* (%)						
No	27 (23.5)	5 (19.2)	22 (24.7)			
QT	87 (75.7)	20 (76.9)	67 (75.3)	0.864		
RT	85 (73.9)	20 (76.9)	65 (56.5)	0.691		
Surgical procedure, *n* (%)				0.282		
McKeown	80 (69.6)	17 (65.4)	63 (70.8)			
Transhiatal	15 (13.0)	4 (15.4)	11 (12.4)			
Ivor-Lewis	12 (10.4)	5 (19.2)	7 (7.9)			
Sweet	6 (5.2)	0 (0)	6 (6.7)			
Total esophagogastrectomy	2 (1.7)	0 (0)	2 (2.2)			
Anastomosis location, *n* (%)				0.988		
Cervical	95 (82.6)	21 (80.8)	74 (83.1)			
Intrathoracic	20 (17.4)	5 (19.2)	15 (16.9)			
Anastomosis technique, *n* (%)*				0.354		
Mechanical	21 (22.1)	5 (20.8)	16 (22.5)			
Hand sewn	68 (71.6)	16 (66.7)	52 (73.2)			
Hybrid	6 (6.3)	3 (12.5)	3 (4.2)			
Surgeon's experience				0.347		
<10 esophagectomies	44 (38.2)	12 (46.2)	32 (36.0)			
≥10 esophagectomies	71 (61.7)	14 (53.8)	57 (64.0)			
Conduit for anastomosis, *n* (%)						
Stomach	100 (87)	26 (100)	74 (83.1)	0.080		
Jejunum	13 (11.3)	0 (0)	13 (14.6)			
Colon	2 (1.7)	0 (0)	12 (13.5)			
Length of ICU stay, median (IQR)	4.0 (3.0–8.0)	14.0 (4.0–24.3)	4.0 (3.0–6.0)	**<0.001**		
Score APACHE II, median (IQR)	12.0 (10.0–14.0)	13.5 (11.8–15.3)	12.0 (9.0–14.0)	**0.047**		
Need for mechanical ventilation, *n* (%)	26 (22.6)	15 (57.7)	11 (12.4)	**<0.001**		
In-hospital mortality	13 (11.3)	9 (34.6)	4 (4.5)	**<0.001**		
30-day mortality	6 (5.2)	4 (15.4)	2 (2.2)	**<0.001**		

IQR, interquartile range; SCC, squamous cell carcinoma; EGJ, esophagogastric junction. N+ refers to N1-N3 regional lymph node tumor extension, according to TNM classification. Bold values are significant. * Anastomosis technique was not registered in 20 patients.

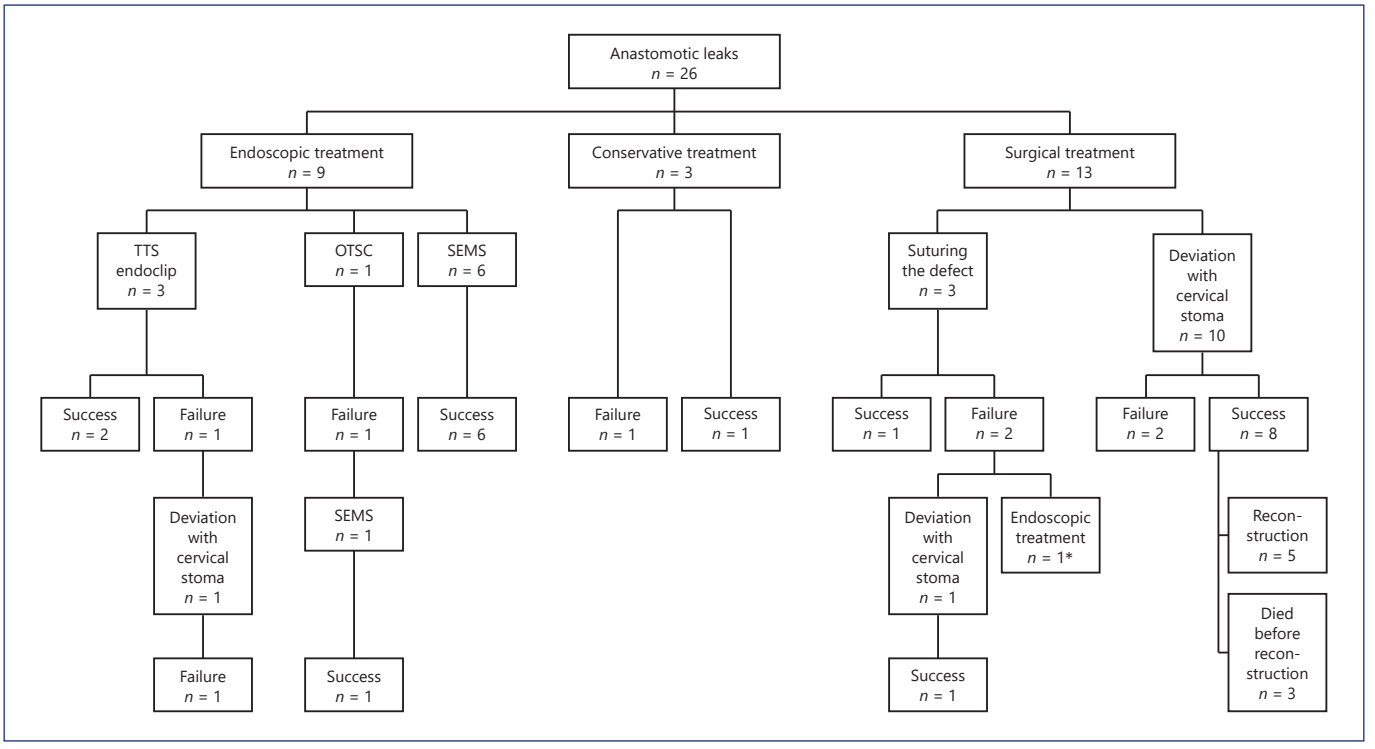


Fig. 1. Management of patients with EAL. * Initially two OTSC, followed by placement of two SEMS and EVT. TTS, through-the-scope clip; OTSC, over-the-scope clip; SEMS, self-expandable metal stents; EVT, endoscopic vacuum therapy.

time of diagnosis, the mean C-reactive protein was 268 ± 103 mg/L. Thirteen patients (50%) developed septic shock due to EAL.

The EAL was most of the times diagnosed through radiological exams (12 by CT, 3 by radiographic contrast examination) and in 11 patients by upper digestive endoscopy. The leak size was described in 21 patients. Eight patients had a defect of less than 25% of anastomotic circumference, 9 patients had a defect up to 25–50%, and 4 had a defect >50%. In 1 patient the leakage was associated with esophago-respiratory fistula.

The leak was limited to the mediastinum in 15 patients (57.7%), of which 10 were contained. The remaining 5 were considered uncontained with mediastinitis. The leak extended into the pleural space in 11 patients (42.3%), all being considered non-contained. During the follow-up period, 3 patients had fistula formation.

Risk Factors for Anastomotic Leak

Univariable analysis revealed that EAL was significantly associated with older age ($p = 0.035$), T and N tumor category (OR 3.037 [1.161–7.943] and OR 3.088 [1.078–9.751], respectively). Multivariable analysis revealed that age and nodal disease were independent risk factors for EAL (Table 1).

Patients with EAL spent more days in the ICU than patients without leak (median 14 vs. 4 days, respectively; $p < 0.001$). The median APACHE II score on postoperative day 1 was significantly higher in patients with leak (13.5 vs. 12.0, $p = 0.047$). In-hospital mortality (34.6 vs. 4.5%) and 30-day mortality (15.4 vs. 2.2%) were significantly higher in the leak group (OR 11.25 [3.10–40.78] and OR 7.909 [1.36–46.00], respectively). Also, APACHE II score on postoperative day 1 was significantly associated with in-hospital mortality ($p = 0.007$).

Treatment Strategy

Fourteen patients needed surgical reintervention, one after failure of endoscopic treatment (Fig. 1). The leak was revised by suturing the defect in 3 patients, with successful closure in 1 patient. Ten patients were treated by surgical deviation, taking down the conduit and creating a cervical stoma. After this procedure, 3 patients died during hospitalization (2 of them in the first 30 days). Five

Table 2. Characteristics of patients submitted to endoscopy and surgery

	Surgical treatment (n = 13)	Endoscopic treatment (n = 10)	p
Age, mean ± SD, years	65.0±11.6	69.0±10.0	0.185
Male sex, *n* (%)	11 (84.6)	8 (80.0)	0.772
Score APACHE II, median (IQR)	14.0 (12.0–16.5)	13.0 (9.8–15.8)	0.471
C-reactive-protein, mean ± SD, mg/L	277.6±91.4)	252.0±118.8)	0.564
Septic shock, *n* (%)	9 (69.2)	3 (30.0)	0.062
Leak location, *n* (%)			0.099
Cervical	6 (46.2)	8 (80.0)	
Thoracic	7 (53.8)	2 (20.0)	
Leakage size[1], *n* (%)			0.113
<25%	2/10 (20.0)	5/9 (55.5)	
25–50%	5/10 (50.0)	4/9 (44.4)	
>50%	3/10 (30.0)	0/9 (0.0)	
Cavity drainage, *n* (%)	8 (61.5)	5 (50.0)	0.580

[1] In the surgical group, leak size was described in 9 of 13 patients, and in the endoscopic group in 9 of 10 patients.

patients underwent new anastomosis reconstruction, which was performed during the same hospitalization in 2 patients and both were discharged under an oral diet. In the other 3 patients reconstruction was carried out electively and 1 of them died 5 days after the procedure with mediastinitis as a result of new leak. One patient developed stenosis after reconstruction (1/4).

Endoscopic treatment was chosen as the primary treatment in 10 patients. TTS-endoclips were used in 3 patients, OTSC in 1 patient, and SEMS in 6 patients. TTS-endoclips were only used in small leaks (less than 10 mm), with success in 2 of the 3 patients. OTSC was used as the first treatment in only 1 patient with a leak with 15 mm. Due to persistent leakage a SEMS was placed 1 week later with success.

Endoscopic stenting was used as first-line therapy in 6 patients (4 partially covered SEMS and 2 fully covered SEMS) and as rescue treatment in 2 patients (1 fully covered SEMS and 1 partially covered SEMS). Technical placement of the stent was successful in all cases. All the patients who received endoscopic stenting as first treatment had clinical success and started oral intake before hospital discharge.

Complications related to stent insertion occurred in 5 patients (62.5%): 2 cases of stent migration (1 fully covered SEMS and 1 partially covered SEMS) and 3 cases of esophageal stenosis (3 partially covered SEMS). One of the stent migrations was successfully managed with endoscopic repositioning and the other patient was managed with removal and insertion of another stent. All stents were removed between 4 and 8 weeks after placement.

EVT was used in 1 patient. This patient was initially submitted to surgical reintervention (suture of anastomosis) without success, and subsequently endoscopic treatment was performed, first with 2 OTSC and then with placement of 2 fully covered SEMS. After 38 days of hospitalization the patient was discharged on an oral diet. Two months later the patient returned to the hospital to have the stents removed and EAL with mediastinum contamination was diagnosed. EVT was used as rescue therapy. Thirteen sponges were used and the treatment lasted 31 days. The patient needed hospitalization for 74 days. One month after leak healing the patient started endoscopic dilatation due to esophageal stenosis.

Outcomes according to Treatment Strategy

In brief, the initial management was conservative in 3 patients, endoscopical treatment in 10 patients, and surgical in 13 patients (Fig. 1). Concomitant drainage of an infected cavity was performed in 50% of endoscopic-treated patients (4 percutaneous drainage and 1 surgical drainage) and in 62% of surgical group (7 drainage at the time of surgery and 1 percutaneous drainage).

The patient demographics (age and sex), clinical severity variables (PCR at the diagnosis of leak, APACHE II score on postoperative day, presence of septic shock) and leak characteristics (leak location and size and presence of a concomitant cavity) did not significantly differ between patients submitted to endoscopic and surgical treatment (Table 2). Patients submitted to conservative treatment were excluded from this analysis because of its small size.

Table 3. Outcomes after anastomotic leak according to treatment

Primary treatment	Conservative treatment ($n = 3$)	Endoscopic treatment ($n = 10$)	Surgical treatment ($n = 13$)	p[e]
Discharge under oral intake, *n* (%)	2 (66.7)	9 (90)	3 (23.1)	**0.001**
Time until oral intake[a], median (IQR), days	16; 56[d]	10 (3–14)	35 (11–262.5)	**0.030**
Length of ICU stay[b], median (IQR), days	27 (12–68)	4 (3–13.5)	16 (6.3–24.0)	0.212
Length of hospital stay[c], median (IQR), days	36; 207[d]	36 (21-56.5)	35 (23.8–52)	0.885
In-hospital mortality, *n* (%)	1 (33.3)	1 (10)	5 (38.5)	0.132

IQR, interquartile range. Bold values are significant. [a] Patients who died before starting oral intake were not included in this analysis (conservative treatment: 2 patients; endoscopic treatment: 9 patients; surgical treatment: 5 patients). [b] Patients who were not discharged from the ICU were excluded (conservative treatment: 3 patients; endoscopic treatment: 10 patients; surgical treatment: 10 patients). [c] Patients who died during hospitalization were excluded (conservative treatment: 2 patients; endoscopic treatment: 9 patients; surgical treatment: 8 patients). [d] Absolute numbers presented (sample of 2 patients). [e] Analysis of statistically significant differences between patients submitted to endoscopic and surgical treatment.

Table 4. Predictors of mortality and prolonged hospital stay

	Mortality		p	Prolonged hospital stay (≥30 days)[1]		p
	yes ($n = 7$)	no ($n = 19$)		yes ($n = 13$)	no ($n = 6$)	
Age, mean ± SD, years	71.6±8.0	65.6±11.3	0.203	64.3±8.7	68.0±16.3	0.673
Male sex, *n* (%)	7 (100.0)	15 (78.9)	0.187	11 (84.6)	4 (66.7)	0.372
Score APACHE II, median (IQR)	15.0 (12.0–17.0)	12.0 (10.0–15.0)	0.210	13.0 (10.0–14.5)	12.0 (10.5–16.5)	0.894
C-reactive-protein, mean ± SD, mg/L	270.3±98.9	266.9±107.4	0.943	287.9±106.4	224.3±115.8	0.251
Septic shock, *n* (%)	7 (100.0)	7 (36.8)	**0.004**	5 (38.5)	2 (33.3)	0.829
Leak location, *n* (%)			0.780			0.419
Cervical	4 (57.1)	12 (63.2)		9 (69.2)	3 (50.0)	
Thoracic	3 (42.9)	7 (36.8)		4 (30.8)	3 (50.0)	
Leakage size[2], *n* (%)			0.911			0.680
<25%	3/7 (42.9)	5/14 (35.7)		3/10 (30.0)	2/4 (50.0)	
25-50%	3/7 (42.9)	6/14 (42.8)		5/10 (50.0)	1/4 (25.0)	
>50%	1/7 (14.3)	3/14 (21.4)		2/10 (20.0)	1/4 (25.0)	
Abscess, *n* (%)	3 (42.9)	11 (57.9)	0.495	6 (46.2)	5 (83.3)	0.127
Treatment, *n* (%)			0.301			0.784
Endoscopic	1 (14.3)	9 (47.4)		6 (46.2)	3 (50.0)	
Surgical	5 (71.4)	8 (42.1)		6 (46.2)	2 (33.3)	
Conservative	1 (14.3)	2 (10.5)		1 (7.7)	1 (16.7)	

The bold value is significant.
[1] Patients who died during hospitalization were excluded. [2] Leak size was described in 21 patients.

Outcomes between the conservative, endoscopic and surgical treatment regarding time to oral diet, length of ICU and hospital stay, and in-hospital mortality are summarized in Table 3. The median ICU length-of-stay was non-significantly longer in the surgical group (16 days) compared to the endoscopic group (4 days; $p = 0.212$), but the median hospital length-of-stay was similar in both groups (36 days in endoscopic group vs. 35 days in surgical group). There were no predictive factors for prolonged hospital stay (Table 4).

Excluding patients who died during hospitalization, oral intake before discharge was possible in 15 patients, 2 (100%) in the conservative group, 9 (100%) in the endoscopy group, and 3 (60%) in the surgery group. The other 2 patients in the surgical group were discharged under enteral feeding by tube jejunostomy. The median time

interval to oral intake was 10 days (3–14) after endoscopic treatment and 35 days (11–262.5) after surgical treatment ($p = 0.030$).

Overall, in-hospital mortality was 33.3% (1/3) in the conservative group, 10% (1/10) in the endoscopic group, and 38.4% (5/13) in the surgical group. The only predictor of mortality following EAL was the presence of septic shock at leak diagnosis ($p = 0.004$; Table 4).

Follow-up was complete in all 17 survivors and ranged from 1.3 to 6.2 years. The 1-year survival rate was 88.2%.

Discussion

Esophagectomy remains a challenging and difficult surgical procedure, associated with important mortality. In our cohort, the 30-day mortality rate was 5.2%, with patients with EAL responsible for two thirds. In addition, in-hospital mortality was greater among patients with EAL (34.6%) compared to those without this complication (4.5%). The overall anastomotic leakage rate of 21.8% observed in our center is in agreement with previous studies (rates ranging from 6 to 30%) [3, 16–18]. Identifying possible risk factors for esophageal leak may provide opportunities to improve preoperative patient conditions and also to choose the most adequate surgical procedure.

A correlation between higher age and EAL was found in univariate and multivariate analysis. However, most previous studies have not found a significant correlation between age and EAL [19, 20].

Patients with hypertension, diabetes mellitus, and alcoholic or smoking habits were not significantly predisposed to EAL, although there seems to be a tendency for hypertension among those with leak. These results are not consistent with previous studies [19, 21]. In fact, Kassis et al. [3] identified various risk factors, such as congestive heart failure, coronary and peripheral artery disease, smoking habits, and cervical anastomosis, all of them with a potential to compromise microvascular supply to the healing of anastomosis. T and N categories of clinical TNM staging were both risk factors for EAL. A possible explanation for this association may be the fact that these patients may require a longer and more extensive surgery.

In agreement with the remaining literature, we also did not find neoadjuvant therapy as a risk factor for anastomotic leak [3, 19, 22, 23]. Since clinical T3 or T4 and the presence of regional lymph node metastasis at diagnosis were significantly associated with EAL, TNM reassessment after neoadjuvant therapy would allow for further understanding of the impact of neoadjuvant therapies on the postoperative prognosis.

The surgical procedure and surgeon's experience were not significantly associated with EAL. However, patients submitted to Ivor-Lewis had a higher rate of EAL (41.7%) than patients submitted to the McKeown procedure (21.3%). The anastomosis technique was not a risk factor for EAL, as described in a meta-analysis published in 2014. However, 67% of the EAL patients had hand-sewn esophagogastric anastomosis [24]. A recent systematic review with meta-analysis revealed that patients undergoing a transthoracic approach were associated with significantly lower rates of EAL [23]. Surprisingly, in our study, the EAL rate was similar in patients with intrathoracic anastomosis (25%) compared with cervical anastomosis (22.1%). These results may be due to the limited number of intrathoracic anastomosis. In fact, many surgeons prefer a cervical anastomosis since a wider oncological resection margin can be achieved and eventual anastomosis dehiscence is usually less severe.

EAL was significantly associated with an increased length of ICU stay and in-hospital mortality. We only measured the APACHE II score on the first day after surgery, therefore it does not reflect patient status at the time of leak diagnosis. Even so, patients with higher APACHE II scores revealed a higher risk of EAL, which means that these patients on the first postoperative day already had clinical and analytical changes that raise the hypothesis of a surgical complication. According to our results, a higher APACHE II score should influence the time of surveillance in ICU. Schniewind et al. [25] recorded patients' APACHE II scores at the time of treatment initiation. In this study, the APACHE II score were 14, 15, 11, and 5 in the EVT, surgery, SEMS, and conservative groups, elucidating that patients with a higher score needed a more interventional treatment.

Currently, there is no standardized treatment algorithm for patients with EAL. The management of EAL should be individualized and guided by the magnitude of the leak and the severity of the clinical condition. The therapeutic decision also depends on medical preferences of the physician in charge and the availability of treatment at the time of diagnosis. Some authors suggested possible therapeutic strategies. Patients with asymptomatic localized radiological cervical leak could be managed conservatively [26]. In addition, endoscopic clipping may be a successful treatment for small leaks, but in larger defects its efficacy is limited. In the most

severe cases, two major therapeutics have been encouraged: insertion of SEMS or surgical exploration. A systematic review published in 2017 suggested SEMS-based therapy as an alternative to surgical treatment, excluding cases such as patients with anatomical leaks unfit for SEMS, patients with endoscopic signs of conduit necrosis, or septic patients. They concluded that the overall postprocedural in-hospital mortality is at least double that following SEMS introduction [27]. In our cohort study, in 8 patients the medical team decided to use SEMS (6 as the first-treatment and 2 as second-line therapy). Complete healing of the leak was achieved in 7 patients (success rate of 87.5%), similar to reported in previous studies (ranging from 70 to 81%) [27–29]. In 1 patient, the stent was introduced late in the course of the disease, which may explain the therapeutic failure. Esophageal stenosis was the most common complication related to stent removal and occurred in 3 patients (37.5%). All of them occurred in patients with partially covered SEMS. Stent migration occurred in 2 patients (25%). Despite the small number of patients with SEMS, the rate of complications related to stent insertion are in line with previous studies [30].

Recently, EVT has been described as a new effective treatment option. In contrast to stent placement, EVT requires multiple endoscopic procedures. In our study, the only patient treated with EVT needed 10 endoscopies in only 1 month. Nevertheless, EVT allows visualizing the wound cavity and optimal drainage, being very effective on sepsis control in patients with mediastinitis. A meta-analysis published in 2020 compared EVT and SEMS for EAL and revealed a significantly higher success rate of EVT in healing EAL, a shorter duration of treatment, and a lower in-hospital mortality rate [12].

In our series, 3 patients were submitted to leak suture, with successful closure in only 1 of them. Ten patients were treated with surgical deviation by taking down the conduit if not viable and creating a cervical stoma. Three patients died during hospitalization due to sepsis. The other 7 patients had hospital discharge, 2 with anastomosis reconstruction and 5 with jejunostomy. Although the leak is easily controlled with this procedure, the right time to perform esophageal reconstruction is a difficult decision, forcing patients to remain on an artificial diet sometimes for more than a year. In the operative group, 61.5% died before starting oral intake. The time to oral intake was significantly longer in the surgical group when compared to the endoscopic group. Crestanello et al. [16], described the management of 47 patients with EAL. A surgical approach was made in 20 patients and esophageal diversion was the chosen procedure in only 2 patients. Reinforcement of the anastomosis and anastomotic repair were the most performed procedures. In-hospital mortality was lower (15%) compared with rates observed in our center.

Despite the small number of patients in each treatment group, there were no statistically significant differences between the groups of patients treated surgically and endoscopically. However, there was a tendency towards surgical treatment in patients with dehiscence of more than 50% of the circumference of the anastomosis or with septic shock. It is noteworthy in our study that a higher rate of in-hospital mortality was observed in patients who underwent surgical intervention (38.5%) as compared with endoscopic (10%) and conservative treatments (33%). Taking into account the outcomes of the leak patients, we consider that surgical intervention is indicated for patients with dehiscence of >75% of the anastomosis, unstable patients, or when endoscopic treatment fails.

The retrospective nature of our cohort presented limitations mainly in the collection of potential risk factors. An example is nutritional status data, such as weight and albumin, which were not consistently recorded pre-ICU admission. The same applies to history of cardiac arrhythmia or chronic obstructive pulmonary disease, clinical factors associated with leak occurrence previously in the literature. Given that diagnostic exams and therapeutic decisions are dependent on medical judgement and equipment availability, there may be regional differences in the decision-making standards. This unicenter design could therefore limit the generalizability of findings.

Considering the postoperatory mortality rate in our cohort, identification of risk factors for EAL may help change preoperative management.

We recommend that once EAL is diagnosed, individualized treatment should be given according to the size of the leak, extent of the contaminated cavity, and status of the patient. Analysis of EAL treatment favors, in our opinion, endoscopic treatment instead of an aggressive approach. Further investigation is needed to determine which factors make us decide for endoscopic treatments, mainly SEMS and EVT, instead of surgical approach.

Statement of Ethics

The study was reviewed and approved by the local ethics committee (Comissão de Ética e Saúde do IPO-Porto).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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

Author Contributions

R.O. and D.L. designed the study; R.O. and F.F. participated in the acquisition of the data; R.O. participated in the analysis and interpretation of the data and drafted the initial manuscript; D.L., B.P., R.S., P.P.-N., P.B., J.A.d.S., and M.D.-R. revised the article critically for important content.

Data Availability Statement

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

References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394–424.

2 Schieman C, Wigle DA, Deschamps C, Nichols Iii FC, Cassivi SD, Shen KR, et al. Patterns of operative mortality following esophagectomy. Dis Esophagus. 2012 Sep-Oct;25(7):645–51.

3 Kassis ES, Kosinski AS, Ross P Jr, Koppes KE, Donahue JM, Daniel VC. Predictors of anastomotic leak after esophagectomy: an analysis of the society of thoracic surgeons general thoracic database. Ann Thorac Surg. 2013 Dec;96(6):1919–26.

4 Yibulayin W, Abulizi S, Lv H, Sun W. Minimally invasive oesophagectomy versus open esophagectomy for resectable esophageal cancer: a meta-analysis. World J Surg Oncol. 2016 Dec;14(1):304.

5 Lagarde SM, de Boer JD, ten Kate FJ, Busch OR, Obertop H, van Lanschot JJ. Postoperative complications after esophagectomy for adenocarcinoma of the esophagus are related to timing of death due to recurrence. Ann Surg. 2008 Jan;247(1):71–6.

6 Low DE. Evolution in surgical management of esophageal cancer. Dig Dis. 2013;31(1):21–9.

7 Mariette C, Markar SR, Dabakuyo-Yonli TS, Meunier B, Pezet D, Collet D, et al.; Fédération de Recherche en Chirurgie (FRENCH) and French Eso-Gastric Tumors (FREGAT) Working Group. Hybrid Minimally Invasive Esophagectomy for Esophageal Cancer. N Engl J Med. 2019 Jan;380(2):152–62.

8 Schuchert MJ, Abbas G, Nason KS, Pennathur A, Awais O, Santana M, et al. Impact of anastomotic leak on outcomes after transhiatal esophagectomy. Surgery. 2010 Oct;148(4):831–8.

9 Aoyama T, Atsumi Y, Hara K, Tamagawa H, Tamagawa A, Komori K, et al. Risk factors for postoperative anastomosis leak after esophagectomy for esophageal cancer. In Vivo. 2020 Mar-Apr;34(2):857–62.

10 Hall BR, Flores LE, Parshall ZS, Shostrom VK, Are C, Reames BN. Risk factors for anastomotic leak after esophagectomy for cancer: A NSQIP procedure-targeted analysis. J Surg Oncol. 2019 Sep;120(4):661–9.

11 Hampe J, Schniewind B, Both M, Fritscher-Ravens A. Use of a NOTES closure device for full-thickness suturing of a postoperative anastomotic esophageal leakage. Endoscopy. 2010 Jul;42(7):595–8.

12 Scognamiglio P, Reeh M, Karstens K, Bellon E, Kantowski M, Schön G, et al. Endoscopic vacuum therapy versus stenting for postoperative esophago-enteric anastomotic leakage: systematic review and meta-analysis. Endoscopy. 2020 Aug;52(8):632–42.

13 Grimminger PP, Goense L, Gockel I, Bergeat D, Bertheuil N, Chandramohan SM, et al. Diagnosis, assessment, and management of surgical complications following esophagectomy. Ann N Y Acad Sci. 2018 Dec;1434(1):254–73.

14 Low DE, Alderson D, Cecconello I, Chang AC, Darling GE, D'Journo XB, et al. International Consensus on Standardization of Data Collection for Complications Associated With Esophagectomy: Esophagectomy Complications Consensus Group (ECCG). Ann Surg. 2015 Aug;262(2):286–94.

15 Guo J, Chu X, Liu Y, Zhou N, Ma Y, Liang C. Choice of therapeutic strategies in intrathoracic anastomotic leak following esophagectomy. World J Surg Oncol. 2014 Dec;12(1):402.

16 Crestanello JA, Deschamps C, Cassivi SD, Nichols FC 3rd, Allen MS, Schleck C, et al. Selective management of intrathoracic anastomotic leak after esophagectomy. J Thorac Cardiovasc Surg. 2005 Feb;129(2):254–60.

17 Gronnier C, Tréchot B, Duhamel A, Mabrut JY, Bail JP, Carrere N, et al.; FREGAT Working Group-FRENCH-AFC. Impact of neoadjuvant chemoradiotherapy on postoperative outcomes after esophageal cancer resection: results of a European multicenter study. Ann Surg. 2014 Nov;260(5):764–70.

18 Zhai C, Liu Y, Li W, Xu T, Yang G, Lu H, et al. A comparison of short-term outcomes between Ivor-Lewis and McKeown minimally invasive esophagectomy. J Thorac Dis. 2015 Dec;7(12):2352–8.

19 Gooszen JA, Goense L, Gisbertz SS, Ruurda JP, van Hillegersberg R, van Berge Henegouwen MI. Intrathoracic versus cervical anastomosis and predictors of anastomotic leakage after oesophagectomy for cancer. Br J Surg. 2018 Apr;105(5):552–60.

20 Van Daele E, Van de Putte D, Ceelen W, Van Nieuwenhove Y, Pattyn P. Risk factors and consequences of anastomotic leakage after Ivor Lewis oesophagectomy. Interact Cardiovasc Thorac Surg. 2016 Jan;22(1):32–7.

21 Aminian A, Panahi N, Mirsharifi R, Karimian F, Meysamie A, Khorgami Z, et al. Predictors and outcome of cervical anastomotic leakage after esophageal cancer surgery. J Cancer Res Ther. 2011 Oct-Dec;7(4):448–53.

22 Cooke DT, Lin GC, Lau CL, Zhang L, Si MS, Lee J, et al. Analysis of cervical esophagogastric anastomotic leaks after transhiatal esophagectomy: risk factors, presentation, and detection. Ann Thorac Surg. 2009 Jul;88(1):177–84.

23 Kamarajah SK, Lin A, Tharmaraja T, Bhargwada Y, Bundred JR, Nepogodiev D, et al. Risk factors and outcomes associated with anastomotic leaks following esophagectomy: a systematic review and meta-analysis. Dis Esophagus. 2020 Mar;33(3):33.

24 Castro PM, Ribeiro FP, Rocha AF, Mazzurana M, Alvarez GA. Hand-sewn versus stapler esophagogastric anastomosis after esophageal ressection: systematic review and meta-analysis. Arq Bras Cir Dig. 2014 Jul-Sep;27(3):216–21.

25 Schniewind B, Schafmayer C, Voehrs G, Egberts J, von Schoenfels W, Rose T, et al. Endoscopic endoluminal vacuum therapy is superior to other regimens in managing anastomotic leakage after esophagectomy: a comparative retrospective study. Surg Endosc. 2013 Oct;27(10):3883–90.
26 Larburu Etxaniz S, Gonzales Reyna J, Elorza Orúe JL, Asensio Gallego JI, Diez del Val I, Eizaguirre Letamendia E, et al. Cervical anastomotic leak after esophagectomy: diagnosis and management. Cir Esp. 2013 Jan;91(1):31–7.
27 Persson S, Rouvelas I, Irino T, Lundell L. Outcomes following the main treatment options in patients with a leaking esophagus: a systematic literature review. Dis Esophagus. 2017 Dec;30(12):1–10.
28 Plum PS, Herbold T, Berlth F, Christ H, Alakus H, Bludau M, et al. Outcome of self-expanding metal stents in the treatment of anastomotic leaks after Ivor Lewis esophagectomy. World J Surg. 2019 Mar;43(3):862–9.
29 Dasari BV, Neely D, Kennedy A, Spence G, Rice P, Mackle E, et al. The role of esophageal stents in the management of esophageal anastomotic leaks and benign esophageal perforations. Ann Surg. 2014 May;259(5):852–60.
30 van Boeckel PG, Sijbring A, Vleggaar FP, Siersema PD. Systematic review: temporary stent placement for benign rupture or anastomotic leak of the oesophagus. Aliment Pharmacol Ther. 2011 Jun;33(12):1292–301.

GE – Portuguese Journal of Gastroenterology

Research Article

GE Port J Gastroenterol 2023;30:49–56
DOI: 10.1159/000521465

Received: July 26, 2021
Accepted: November 27, 2021
Published online: March 22, 2022

Comparison between Two Types of 22-Gauge Fine-Needle Biopsy for Solid Pancreatic Tumors

Cesar Jaurrieta-Rico[a] Katia Picazo-Ferrera[a] Raul Aguilar-Solis[a]
Daniel Escobedo-Paredes[a] Antonio Bandala-Jaques[b]
Viridiana Chavez-Gomez[c] Angelica Hernandez-Guerrero[a]
Juan Octavio Alonso-Larraga[a]

[a]Endoscopy Department, Instituto Nacional Cancerologia, Mexico City, Mexico; [b]Department of Biomedical Cancer Research, Instituto Nacional de Cancerologia, Mexico City, Mexico; [c]Pathology Department, Instituto Nacional Cancerologia, Mexico City, Mexico

Keywords
Biopsy · fine-needle · Pancreatic neoplasms · Endosonography

Abstract

Background: Tissue sampling using endoscopic ultrasound-guided fine-needle aspiration is the gold standard for diagnosing malignant pancreatic tumors; however, its sensitivity and specificity are highly variable. Thus, fine-needle biopsy using cutting needles has been developed to overcome current limitations and improve diagnostic yield. Our study compared two fine-needle biopsy needles for tissue sampling for pancreatic solid lesions. ***Materials and Methods:*** Samples obtained from patients with pancreatic solid lesions using the 22-gauge fine-needle biopsy needles (Franseen needle or reverse bevel needle) were retrospectively analyzed. The primary outcomes were diagnostic yield and sample adequacy. The secondary outcome was diagnostic performance. The analysis was performed using 2×2 tables to calculate sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy for each needle type. Proportions were compared using the Z test. For quantitative variables, a comparative analysis was performed using Student's *t* test. Qualitative and unpaired outcome variables were described using Fisher's exact test. ***Results:*** Sixty-three patients with pancreatic lesions were included in the analysis. The fine-needle biopsy Franseen and reverse bevel groups included 33 and 30 patients, respectively. An adequate sample was obtained in 97% of patients in the Franseen needle group versus 80% in the reverse bevel needle group; the diagnostic yields in these groups were 93.9 and 66.7%, respectively. Neither differences between needle passes nor complications were noted. The sensitivity and specificity were 93.5 and 100%, respectively, in the fine-needle biopsy Franseen group, versus 71 and 100%, respectively, in the reverse bevel needle group. ***Conclusions:*** The Franseen needle was more effective for sampling pancreatic tumors than the reverse bevel needle.

Karger@karger.com
www.karger.com/pjg

Karger
OPEN ACCESS

Correspondence to:
Cesar Jaurrieta-Rico, cesar.jaur@gmail.com
Juan Octavio Alonso-Larraga, joctavioalonso@yahoo.com.mx

Biópsia por agulha fina com 22-gauge: estudo comparativo em lesões sólidas pancreáticas

Palavras Chave
Biopsia · agulha-fina · Neoplasia pancreática · Ecoendoscopia

Resumo
Introdução: A aquisição de tecido através de punção com agulha fina guiada por ecoendoscopia é o padrão para o diagnóstico de neoplasias pancreáticas malignas; contudo, a sua sensibilidade e especificidade é altamente variável. A biópsia por agulha fina (FNB) usando agulhas cortantes foi desenvolvida para ultrapassar as limitações atuais. Este estudo comparou duas agulhas de FNB na aquisição de tecido de lesões pancreáticas sólidas. ***Métodos:*** Amostras obtidas de doentes com lesões pancreáticas sólidas utilizando agulha de FND de 22 gauge (Franseen ou reverse bevel) foram avaliadas retrospetivamente. Os outcomes primárias foram a rentabilidade diagnóstica e a adequabilidade das amostras. O outcome secundário foi a performance diagnóstica. A análise estatística foi realizada através de tabelas de contingência 2 × 2 para cálculo da sensibilidade, especificidade, valor preditivo positivo e negativo e acuidade para cada tipo de agulha. As proporções foram calculadas utilizando o teste-Z. Para variáveis quantitativas foi realizada análise comparativa com teste t-Student. Variáveis qualitativas e não pareadas foram comparadas com teste exato de Fisher. ***Resultados:*** Foram incluídos 63 doentes com lesões pancreáticas (33 no grupo FNB Franseen e 30 no grupo reverse bevel). Foram obtidas amostras adequadas em 97% do grupo Franseen vs 80% no grupo reverse bevel, sendo a rentabilidade diagnóstica de 93.9 e 66.7%, respetivamente. Não houve diferenças no número de passagens nem nas complicações. A sensibilidade e especificidade foram, respetivamente, de 93.5 e 100% no grupo Franseen versus 71 e 100% no grupo reverse bevel. ***Conclusões:*** A agulha Franseen foi mais efetiva na aquisição de amostras de lesões pancreáticas do que a agulha reverse bevel.

Introduction

Ultrasound-guided fine-needle aspiration (EUS-FNA) is considered the diagnostic standard for malignant pancreatic tumors; however, its sensitivity and specificity are widely variable, ranging from 73 to 96.5% and from 71.4 to 100%, respectively [1]. Several factors can affect the outcome of EUS-FNA such as the needle caliber and design, application of suction, use of stylet, onsite cytopathological evaluation of specimens, number of passes, location and size of the tumor, and experience of the endosonographer. The main disadvantage of FNA is that the sampled tissue does not necessarily retain the cellular architecture of the stroma, which is critical for establishing the diagnosis. Recent developments in needle design have permitted the acquisition of core biopsies to overcome the limitations of FNA and preserve the cellular architecture, thereby improving diagnostic performance [2]. This new tissue acquisition technique is denominated fine-needle biopsy (FNB). Two recently introduced FNB needles include the reverse bevel needle Echotip ProCore® (Cook Medical Inc., Limerick, Ireland) and Franseen tip needle Acquire® (Boston Scientific Co., Natick, MA, USA). FNB needles have special relevance in oncology, as this technique of tissue acquisition allows molecular tumor profiling for targeted therapy and more frequent immunohistochemical staining than FNA needles [3, 4].

Randomized clinical controlled trials have revealed that the reverse bevel needle has a threefold better ability to obtain histological core samples and a higher diagnostic yield than the standard FNA needle (92 vs. 30%, $p = 0.006$, 20 vs. 75%, $p = 0.010$, respectively) [5, 6]. Although a systematic review and meta-analysis identified no difference in diagnostic accuracy between these two needles, the reverse bevel needle required fewer passes [7]. Moreover, the Franseen needle was linked to a diagnostic accuracy rate of 96%, versus 88% for the FNA standard needle, as well as a higher mean histology cell block score with fewer needle passes (2.88 vs. 3.82; $p < 0.001$) [8]. More recently, a randomized clinical trial compared a 22-gauge Franseen needle and 20-gauge reverse bevel needle, revealing higher diagnostic accuracy for the Franseen needle (87 vs. 67%; $p = 0.02$) [9]. However, the difficulty in using a higher-gauge needle may affect tissue sampling in certain endoscopic positions. Thus, the main objective of our study was to compare the diagnostic yield of two different FNB needles with the same caliber in the EUS-guided sampling of pancreatic solid lesions.

Materials and Methods

This was a retrospective observational study in which we compared a cohort of patients with pancreatic solid lesions who underwent sampling using a 22-gauge FNB reverse bevel needle and a 22-gauge FNB Franseen needle between September 2016 and March 2020 at Instituto Nacional de Cancerologia in Mexico City, Mexico. This study was approved by the Instituto Nacional de Cancerologia Investigation Committee with the approval No. 2020/0115. Men and women ≥18 years old were eligible for enrollment. We excluded patients who met any of the following criteria: presence of cystic lesions, pregnancy, international normalized ratio >1.5, partial thromboplastin time >42 s, platelet count <50,000, surgically altered anatomy, anticoagulant treatment, hemodynamic instability, and less than 6 months of follow-up.

Patients were divided into two groups according to the FNB needle used for sampling. Clinical and demographics variables such as age, sex, tumor size and localization, number of needle passes, biopsy route, complications, tissue adequacy, and diagnostic yield were analyzed.

The quality of the tissue sample and diagnostic yield were reported by pathologists dedicated to pancreatobiliary pathology. Sample adequacy was defined as the presence of sufficient tissue to allow complete histological evaluation.

Tissue samples submitted for cytopathological analysis were interpreted using the criteria established by the Papanicolaou Society System for pancreatobiliary cytopathology classification as follows: category I (nondiagnostic), category II (negative for malignancy), category III (atypical), category IV (benign neoplastic, other neoplastic), category V (suspicious for malignancy), and category VI (positive for malignancy) [10]. Tissue samples submitted for histopathological analysis were interpreted by surgical pathologists. Pathologists were blinded to the type of needle used.

EUS Tissue Sampling Technique

All procedures were performed under intravenous sedation using a combination of propofol and fentanyl. An Olympus Linear Echo-endoscope (Olympus GF-UCT180, Tokyo, Japan) was used with an EU-2 Premier and EU-2 Premier-Plus processor. All procedures were performed by two expert endosonographers who had performed >1,000 studies.

Once the lesion was identified under ultrasonographic examination, it was punctured using an FNB needle with stylet. After puncture, the stylet was removed, and 5 mL of suction was applied. Sampling was performed using the fanning technique, and each pass consisted of 10–15 back-and-forth movements. Once the pass was completed, the needle was removed for tissue preparation. Considering previous studies that found no benefit in diagnostic yield after taking more than two passes, a goal of two passes was considered the standard, and additional passes were performed at the discretion of the endoscopist after visual inspection of the obtained tissue.

Tissue Processing

Once the needle was removed, a smear was extended on glass slides, dried in air, and then preserved using Hemacolor® stain (Merck KGaA, Darmstadt, Germany). A second smear was then extended on a glass slide, immediately immersed in 96% ethyl alcohol, fixed for at least 10 min, and dyed with the Pap smear technique using the integrated Tissue-Tek Prisma® platform (Sakura Finetek USA Inc., Torrance, CA, USA).

The additional tissue was placed in a 96% ethanol-based solution with polyethylene glycol and rifampicin (Carbowax®) for at least 30 min, centrifuged, decanted, and placed in a centrifugal plastic tube to be fixed with 10% formalin to create cell blocks. Cell blocks were then placed on rice paper inside inclusion capsules and processed to generate paraffin blocks. The needle was routinely irrigated with Carbowax® to place any residual tissue in the solution. There was no pathologist or cytotechnologist present in the endoscopic room during the procedure.

The samples sent for histological analysis were placed in 10% formalin and then processed for paraffin inclusion. Subsequently, sections were generated and dyed with hematoxylin and eosin for histopathological analysis.

Statistical Analysis

SPSS software for Windows v.25 (IBM Corp., Armonk, NY, USA) was used for analysis. A sample size was calculated for a two-queue hypothesis with a type I error rate set to 0.05, study power of 90%, and β-magnitude of 20%. The required sample calculated for each group was 95 patients. The analysis was performed using 2 × 2 tables to calculate sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy for each needle type. Proportions were compared using a Z test. For quantitative variables, a descriptive analysis was performed using Student's *t* test. Qualitative and unpaired outcome variables were described using Fisher's exact test. $p < 0.05$ denoted statistical significance. We performed a multiple logistic regression model to determine the probability of reaching diagnosis according to the type of needle used. We adjusted our model by age, size of the tumor, and biopsy route. We did not include site of tumor in the analysis, as we found it to be colinear with biopsy route.

For statistical analysis and the construction of 2 × 2 tables, biopsies under categories I–IV were considered negative for malignancy. Biopsies under categories V and VI were considered positive. Biopsies considered positive for malignancy in patients who had a favorable evolution after 6 months were considered false positives. Biopsies negative for malignancy in patients who experienced progression of neoplastic disease within 6 months were considered false negatives, as were those in patients diagnosed with malignancy using other sampling methods such as surgery or image-guided biopsy or by repeating a EUS-guided FNA/FNB.

Results

In total, 63 patients with solid pancreatic lesions were identified. The Franseen needle group included 33 patients (mean age, 61.36 ± 14.12 years), including 19 females (57.6%). The most common tumor location in this group was the head of the pancreas (66.7%), and the mean tumor size was 39.45 ± 23.58 mm. The reverse bevel needle group included 30 patients (mean age, 63.37 ± 12.35 years), 19 of whom were female (63.3%). The most common tumor location in this group was the head of the pancreas (70%), and the mean tumor size was 37.13 ± 14.1 mm.

Table 1. Baseline characteristics

Characteristics	FNB Franseen (n = 33), n (%)	FNB reverse bevel (n = 30), n (%)	p
Age	61.36±14.12	63.37±12.35	0.553
Gender			
Male	14 (56)	11 (44)	0.797
Female	19 (50)	19 (50)	
Localization			
Head	22 (66.7)	21 (70)	0.689
Uncinate process	3 (9.1)	2 (6.7)	
Neck	2 (6.1)	4 (13.3)	
Body	5 (15.2)	3 (10)	
Tail	1 (3)	0 (0)	
Size, mm	39.45±23.58	37.13±14.1	0.641
Ultrasonographic appearance			
Homogeneous	28 (84.9)	28 (93.3)	0.466
Heterogeneous	5 (15.1)	2 (6.7)	

FNB, fine-needle biopsy.

Table 2. Main results

Characteristics	FNB Franseen (n = 33), n (%)	FNB reverse bevel (n = 30), n (%)	p
Technical success	33 (100)	30 (100)	
Adequate sample			
Yes	32 (97)	24 (80)	0.047
No	1 (3)	6 (20)	
Diagnostic yield	31 (93.9)	20 (66.7)	0.009
Number of passes	2.06±0.34	2.20±0.48	0.199
Number of procedures for diagnosis	1.06±0.242	1.33±0.479	0.008
Biopsy route			
Transgastric	25 (75.7)	23 (76.6)	0.933
Transduodenal	8 (24.3)	7 (23.4)	0.933
Complication	0	0	

FNB, fine-needle biopsy.

There were no significant differences in age, gender, tumor location and size, and ultrasonographic features between groups. Baseline characteristics are presented in Table 1.

The technical success rate was 100% in both groups. The rate of sample adequacy was 97% in the Franseen needle group, compared with 80% in the reverse bevel needle group (p = 0.047). The diagnostic yield in the Franseen needle group was 93.9%, versus 66.7% in the reverse bevel needle group (p = 0.009). The mean numbers of passes were 2.06 ± 0.34 in the FNB Franseen needle group and 2.20 ± 0.48 in the reverse bevel needle group. No complications were recorded in either group. The main results are presented in Table 2.

In the Franseen needle group, 29 of 33 biopsies were true positives for malignancy, whereas the remaining 4 patients consisted of 2 true negatives and 2 false negatives, resulting in a sensitivity and a specificity of 93.5 (95% confidence interval [CI] = 78.58–99.21) and 100% (95% CI = 15.81–100), respectively. The Franseen needle group had a positive predictive value of 100% and a negative predictive value of 50% (95% CI = 20.74% to 79.26%.

In the reverse bevel needle group, 20 of 30 biopsies were true positives for malignancy, whereas the remaining biopsies included eight false negatives and two true negatives, resulting in a sensitivity and a specificity of 71 (95% CI = 51.33–86.78) and 100% (95% CI = 15.81–100), respectively. The reverse bevel group had a positive pre-

Table 3. Sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy for each needle group

	FNB Franseen, %	FNB reverse bevel, %
Sensitivity	93.5	71.4
Specificity	100	100
PPV	100	100
NPV	50	20
Diagnostic accuracy	93.9	73.3

PPV, positive predictive value; NPV, negative predictive value; FNB, fine-needle biopsy.

Table 4. Histological diagnosis

Diagnosis	FNB Franseen (n = 33), n (%)	FNB reverse bevel (n = 30), n (%)	p
Adenocarcinoma	27 (81.8)	25 (83.3)	0.876
Neuroendocrine tumor	3 (9.0)	3 (10)	0.893
Lymphoma	1 (3.0)	1 (3.3)	0.946
Biliary intraepithelial neoplasia	1 (3.0)	0	0.342
Mucinous cystadenocarcinoma	1 (3.0)	0	0.342
Fibrosis	0	1 (3.3)	0.296

FNB, fine-needle biopsy.

Table 5. Adjusted multiple logistic regression

Variable	OR	95% CI	p
Type of needle[a]	0.753	0.625–0.901	0.004
Age[b]	1.007	0.998–1.016	0.155
Tumor size[b]	1.000	0.994–1.003	0.931
Biopsy route[c]	0.984	0.777–1.247	0.896

OR, odds ratio; CI, confidence interval. [a] Procore reference. [b] Continuous. [c] Transduodenal reference.

dictive value of 100% and a negative predictive value of 20% (95% CI = 12.22–30.99%). The results of sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy for each needle group are presented in Table 3.

In the Franseen needle group, 2 patients repeated EUS-guided biopsy, and the second biopsy was positive for malignancy in both cases. Percutaneous tomography-guided biopsy was requested for 1 patient in the Franseen needle group diagnosed with lymphoma to obtain additional tissue for immunohistochemistry staining.

In the reverse bevel needle group, of the 10 patients with nondiagnostic EUS samples, 5 repeated EUS-guided biopsy to establish the diagnosis. Two patients required a second sampling technique, and they were diagnosed via CT-guided biopsy. Two patients were proposed for best supportive care after a nondiagnostic result, but with evidence of progressive neoplastic disease, and they died within 6 months of follow-up. One patient was diagnosed by surgery.

The most common pathological diagnosis was adenocarcinoma in 82.5% of patients, followed by neuroendocrine tumor in 9.5% of patients. Diagnostic data are summarized in Table 4.

In multiple regression analysis, using the reverse bevel needle, compared to the Franseen needle, resulted in a lower risk of reaching diagnosis, accounting for the other factors. With the reverse bevel needle, we found 0.75 times the risk of reaching diagnosis, compared to the Franseen needle. Furthermore, age, tumor size, and biopsy route did not show significance when assessing their odds for reaching diagnosis. The results of regression analysis are presented in Table 5.

Discussion/Conclusion

This comparative study regarding the diagnostic performance of two FNB needles focused specifically on needle design, as the groups were balanced in terms of needle gauge, sampling technique, lesion size, and number of pass-

es. To our knowledge, this is the first comparative analysis between the 22-gauge FNB Franseen needle and 22-gauge FNB reverse bevel needle. Our results illustrated that the FNB Franseen needle is better than the FNB reverse bevel needle regarding sample adequacy and diagnostic yield.

In particular, we observed high diagnostic performance in the Franseen needle group. A meta-analysis of pancreatic solid lesions sampled using only 22-gauge Franseen needles recorded a pooled rate of diagnostic yield of 92.7% (95% CI = 86.4–96.2) and noted no difference in conducting the rapid on-site evaluation [11]. A second recent meta-analysis comparing FNB needle performance reported a sample adequacy rate of 97% (95% CI = 94.8–99.3) and a diagnostic accuracy rate of 95% (95% CI = 92.5–97.5) for pancreatic lesions sampled using FNB Franseen needles, consistent with our results [2]. Regarding the diagnostic performance of the reverse bevel needle, our results were inferior to published findings. A subanalysis of a study comparing FNA and FNB reverse bevel needles reported a diagnostic yield of 87% for pancreatic lesions. Nevertheless, recent publications comparing different FNB needles recorded diagnostic yields of 67–81% for the FNB reverse bevel needle in pancreatic lesions in line with our results [9, 12–14]. To our knowledge, the randomized clinical trial conducted by Karsenti et al. [9] was the first study to compare the Franseen and the reverse bevel needles. However, their study used a 20-gauge reverse bevel needle, which we believe can limit tissue sampling in certain endoscopic positions. This study reported that the Franseen needle showed superior sample adequacy (100 vs. 82%) and diagnostic accuracy (87 vs. 67%). One of the observations of this analysis was that the Franseen needle provided almost twofold more tissue than the 20-gauge reverse bevel needle, which may be attributable to stiffness and poor maneuverability associated with the bigger caliber [9]. In our comparison, we included only the 22-gauge caliber and obtained similar results and thus we can conclude that the higher diagnostic yield and more adequate tissue acquisition might be exclusively associated with the design of the needle independently of the needle caliber. Young Bang et al. [15] prospectively compared sample cellularity with different 22-gauge needle designs and tissue sampling techniques including the Franseen and reverse bevel needles. Samples collected by fork-tip or Franseen needles had significantly higher cellularity than samples collected by reverse-bevel or Menghini-tip needles ($p < 0.001$). Pancreatic neoplasias were identified with greater than 90% accuracy using Franseen needles with an odds ratio of 5.18 in comparison to reverse bevel needles (95% CI = 2.53–10.6, $p < 0.001$). The reported sensitivity for pancreatic lesions sampled with suction was in accordance to our study, with a sensitivity of 73.1% (52.2–88.4) for reverse bevel needles and 92.6% (75.7–99.1) for Franseen needles ($p = 0.022$). In a subanalysis the best cellularity was achieved with a stylet retraction technique for the Franseen needles and a suction technique for the reverse bevel needles [15].

We defined two as the standard number of needle passes for the FNB procedure in our study. A retrospective cohort showed that the tissue sample adequacy rate for histological diagnosis per pass using 22-gauge Franseen needles was 89% for the first pass increasing to 99% after the second pass, without further improvement with additional passes [16]. Another retrospective study of 38 patients with pancreatic lesions biopsied using FNB Franseen needles recorded a histological diagnosis rate of 96.7% with an average of 2.1 passes [17]. Stathopoulos et al. [18] prospectively studied the quality of specimens sampled with 22-gauge Franseen needles observing a high-quality histology specimen with a Payne score of 3 in 92.5% of patients after 2 needle passes with a diagnostic accuracy of 85%. Furthermore, a subanalysis of a meta-analysis comparing the performance of FNB reverse bevel and FNA needles determined than an average of 1.3–1.4 passes was required to make a diagnosis using an FNB reverse bevel needle [19].

Twenty-two-gauge FNB needles may have the ideal size for pancreatic tissue sampling, in contrast to FNA needles, in which a smaller 25-gauge caliber may have slightly better sensitivity [20, 21]. The differences between the 22- and 25-gauge FNB needles have not been extensively studied. Two studies detailed the performance of 25-gauge FNB Franseen needles, reporting sample adequacy rates of 79 and 82%, respectively, which may be inferior to the aforementioned rates for 22-gauge needles [22, 23]. A randomized prospective study compared diagnostic yields for 25- and 22-gauge Franseen needles in patients with solid pancreatic lesions finding no significant difference in diagnostic yield (98 vs. 88%, $p = 0.105$, respectively), however finding that the 25-gauge group required additional passes to obtain an adequate cell block (1.6 ± 0.6 vs. 0.4 ± 0.7, $p = 0.001$) [24]. A second noninferiority study compared the same needles finding no statistical difference in adequate histological assessment, but with a superiority in high-quality tissue acquisition with the 22-gauge needle in 45.5 versus 25% in the 25-gauge group [25]. A prospective randomized trial compared the histological core procurement rate using the Gerke Score in patients with peripancreatic and pancreatic lesions finding histological core procurement rates of 87.1 versus

97.1% for the 25- and 22-gauge needles, respectively, with a better high-quality specimen rate in the 22-G group (70.0 vs. 28.6%, respectively; $p < 0.001$), but no difference in overall diagnostic accuracy [26].

Our study did not evaluate macroscopic on-site evaluation (MOSE) by the endoscopist. The examination of macroscopic whitish visible core or bloody tissue granules in the tissue sampled from FNB needles may further increase diagnostic accuracy. So et al. [27] found that sampling heterogenous lesions with 22-gauge Franseen needles in association with MOSE provides a high diagnostic accuracy of 97.3%. With only a median of 2 or 3 passes required to get adequate tissue in 91.2% of the patients, only 5.3% requiring 4 or more passes. Standardization of MOSE protocols are yet to be defined.

The main limitations of our study were its retrospective design and the small sample size in each group. But even with a small sample size our study was able to accurately detect a significant difference between the two needle groups, and the regression model also reached statistical significance as performed. The study strengths were that the compared groups were homogeneous and all relevant information was available for comparing outcome variables. Another advantage was that the pathologists who analyzed the samples were blinded to the needle used. Our results should be further confirmed in prospective randomized trails.

In conclusion, this study demonstrated that the 22-gauge FNB Franseen needle is more effective for EUS-guided sampling of pancreatic solid lesions than the 22-gauge FNB reverse bevel needle.

Acknowledgement

The authors would like to thank Enago (www.enago.com) for the English language review.

Statement of Ethics

This study was approved by the Instituto Nacional de Cancerologia Investigation Committee with approval No. 2020/0115. Informed consent was not required.

Conflict of Interest Statement

None of the authors declares conflicts of interest.

Funding Sources

No funding was required.

Author Contributions

Cesar Jaurrieta-Rico: conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft, project administration. Katia Picazo-Ferrera: data curation, formal analysis, investigation, methodology, writing – review and editing. Raul Aguilar-Solís: Formal analysis, software, methodology, writing – review and editing. Daniel Escobedo-Paredes: data curation, methodology, writing – review and editing. Antonio Bandala-Jacques: interpretation of data, methodology, writing – review and editing, project administration. Viridiana Chávez-Gómez: investigation, writing – review and editing, methodology. Angelica Hernández-Guerrero: conceptualization, supervision, writing – review and editing, project administration. Juan Octavio Alonso-Larraga: conceptualization, investigation, formal analysis, methodology, writing – review and editing, supervision, project administration.

Data Availability Statement

All data analyzed during this study are available at request. Enquiries can be directed to the corresponding author.

References

1 Banafea O, Mghanga FP, Zhao J, Zhao R, Zhu L. Endoscopic ultrasonography with fine-needle aspiration for histological diagnosis of solid pancreatic masses: a meta-analysis of diagnostic accuracy studies. BMC Gastroenterol. 2016 Aug;16(1):108.

2 Facciorusso A, Del Prete V, Buccino VR, Purohit P, Setia P, Muscatiello N. Diagnostic yield of Franseen and fork-tip biopsy needles for endoscopic ultrasound-guided tissue acquisition: a meta-analysis. Endosc Int Open. 2019 Oct;7(10):E1221–30.

3 El Chafic AH, Loren D, Siddiqui A, Mounzer R, Cosgrove N, Kowalski T. Comparison of FNA and fine-needle biopsy for EUS-guided sampling of suspected GI stromal tumors. Gastrointest Endosc. 2017 Sep;86(3):510–5.

4 Asokkumar R, Yung Ka C, Loh T, Ling KL, San GT, Ying H, et al. Comparison of tissue and molecular yield between fine-needle biopsy (FNB) and fine-needle aspiration (FNA): a randomized study. Endosc Int Open. 2019 Aug;7(8):E955–63.

5 Alatawi A, Beuvon F, Grabar S, Leblanc S, Chaussade S, Terris B, et al. Comparison of 22G reverse-beveled versus standard needle for endoscopic ultrasound-guided sampling of solid pancreatic lesions. United Eur Gastroenterol J. 2015 Aug;3(4):343–52.

6 Kim GH, Cho YK, Kim EY, Kim HK, Cho JW, Lee TH, et al. Comparison of 22-gauge aspiration needle with 22-gauge biopsy needle in endoscopic ultrasonography-guided subepithelial tumor sampling. Scand J Gastroenterol. 2014 Mar;49(3):347–54.

7 Khan MA, Grimm IS, Ali B, Nollan R, Tombazzi C, Ismail MK, et al. A meta-analysis of endoscopic ultrasound fine-needle aspiration compared to endoscopic ultrasound fine-needle biopsy: diagnostic yield and the value of onsite cytopathological assessment. Endosc Int Open. 2017 May;5(5):E363–75.
8 El Hajj II, Wu H, Reuss S, Randolph M, Harris A, Gromski MA, et al. Prospective assessment of the performance of a new fine needle biopsy device for EUS-guided sampling of solid lesions. Clin Endosc. 2018 Nov;51(6):576–83.
9 Karsenti D, Palazzo L, Perrot B, Zago J, Lemaistre AI, Cros J, et al. 22G Acquire vs. 20G Procore needle for endoscopic ultrasound-guided biopsy of pancreatic masses: a randomized study comparing histologic sample quantity and diagnostic accuracy. Endoscopy. 2020 Sep;52(9):747–53.
10 Pitman MB, Centeno BA, Ali SZ, Genevay M, Stelow E, Kenudson MM, et al. Standardized terminology and nomenclature for pancreatobiliary cytology: the Papanicolaou Society of Cytopathology Guidelines. Cytojournal. 2014 Jun;11(Suppl 1):3.
11 Mohan BP, Shakhatreh M, Garg R, Asokkumar R, Jayaraj M, Ponnada S, et al. Comparison of Franseen and fork-tip needles for EUS-guided fine-needle biopsy of solid mass lesions: a systematic review and meta-analysis. Endosc Ultrasound. 2019 Nov–Dec;8(6): 382–91.
12 Nayar MK, Paranandi B, Dawwas MF, Leeds JS, Darne A, Haugk B, et al. Comparison of the diagnostic performance of 2 core biopsy needles for EUS-guided tissue acquisition from solid pancreatic lesions. Gastrointest Endosc. 2017 May;85(5):1017–24.
13 Abdelfatah MM, Hamed A, Koutlas NJ, Aly FZ. The diagnostic and cellularity yield of reverse bevel versus fork-tip fine needle biopsy. Diagn Cytopathol. 2018 Aug;46(8):649–55.
14 Rahman Z, Riaz K, Hossein M, Sophia Savva SK. Comparing the diagnostic yield and safety of endosonography guided use of shark-core and pro-core needles. Gut. 2019;68:A1–269.
15 Young Bang J, Krall K, Jhala N, Singh C, Tejani M, Arnoletti JP, et al. Comparing needles and methods of endoscopic ultrasound-guided fine-needle biopsy to optimize specimen quality and diagnostic accuracy for patients with pancreatic masses in a randomized trial. Clin Gastroenterol Hepatol. 2021;19(4):825–35.e7.
16 Ishikawa T, Kawashima H, Ohno E, Tanaka H, Sakai D, Iida T, et al. Clinical impact of EUS-guided fine needle biopsy using a novel Franseen needle for histological assessment of pancreatic diseases. Can J Gastroenterol Hepatol. 2019 Feb;2019:8581743.
17 Mukai S, Itoi T, Yamaguchi H, Sofuni A, Tsuchiya T, Tanaka R, et al. A retrospective histological comparison of EUS-guided fine-needle biopsy using a novel Franseen needle and a conventional end-cut type needle. Endosc Ultrasound. 2019 Jan–Feb;8(1):50–7.
18 Stathopoulos P, Pehl A, Breitling LP, Bauer C, Grote T, Gress TM, Denkert C, Denzer UW. Endoscopic ultrasound-fine needle biopsies of pancreatic lesions: prospective study of histology quality using Franseen needle. World J Gastroenterol. 2020 Oct 7;26(37):5693–704.
19 Young Bang J, Hawes R, Varadarajulu S. A meta-analysis comparing ProCore and standard fine-needle aspiration needles for endoscopic ultrasound-guided tissue acquisition. Endoscopy. 2016;48(4):339–49.
20 Madhoun MF, Wani SB, Rastogi A, Early D, Gaddam S, Tierney WM, et al. The diagnostic accuracy of 22-gauge and 25-gauge needles in endoscopic ultrasound-guided fine needle aspiration of solid pancreatic lesions: a meta-analysis. Endoscopy. 2013 Jan;45(2):86–92.
21 Xu MM, Jia HY, Yan LL, Li SS, Zheng Y. Comparison of two different size needles in endoscopic ultrasound-guided fine-needle aspiration for diagnosing solid pancreatic lesions. Medicine. 2017 Feb;96(5):1–6.
22 Inoue T, Tsuzuki T, Takahara T, Ibusuki M, Kitano R, Kobayashi Y, et al. Prospective evaluation of 25-gauge Franseen needles for endoscopic ultrasound-guided fine-needle biopsy of solid pancreatic masses. Endosc Int Open. 2020 Apr;8(4):E566–70.
23 Sugiura R, Kuwatani M, Yane K, Taya Y, Ihara H, Onodera M, et al. Prospective, multicenter, observational study of tissue acquisition through EUS-guided fine-needle biopsy using a 25G Franseen needle. Endosc Ultrasound. 2019 Sep–Oct;8(5):321–8.
24 Siddique DA, Rahal MA, Trevino K, Wu HH, Al-Haddad MA. Endoscopic ultrasound-guided sampling of solid pancreatic lesions: a comparative analysis of 25 gauge versus 22 gauge core biopsy needles. Anticancer Res. 2020;40(10):5845–51.
25 Tomoda T, Kato H, Fujii Y, Yamazaki T, Matsumoto K, Horiguchi S, et al. Randomized trial comparing the 25G and 22G Franseen needles in endoscopic ultrasound-guided tissue acquisition from solid pancreatic masses for adequate histological assessment. Dig Endosc. Epub 2021 July 10.
26 Oh D, Kong J, Ko SW, Hong S-M, So H, Hwang JS, et al. A comparison between 25-gauge and 22-gauge Franseen needles for endoscopic ultrasound-guided sampling of pancreatic and peripancreatic masses: a randomized non-inferiority study. Endoscopy. 2021;53(11):1122–9.
27 So H, Seo DW, Hwang JS, Ko SW, Oh D, Song TJ, et al. Macroscopic on-site evaluation after EUS-guided fine needle biopsy may replace rapid on-site evaluation. Endosc Ultrasound. 2021 Mar–Apr;10(2):111–5.

GE – Portuguese Journal of Gastroenterology

Clinical Case Study

GE Port J Gastroenterol 2023;30:57–60
DOI: 10.1159/000519545

Received: May 31, 2021
Accepted: August 11, 2021
Published online: October 25, 2021

Isolated Intracardiac Metastasis: The First Sign of Hepatocellular Carcinoma

Anusca Paixão Rita Silva Natália Lopes Sónia Carvalho Paulo Carrola José Presa Ramos

Serviço de Medicina Interna, Hospital de São Pedro, Vila Real, Portugal

Keywords
Acute heart failure · Isolated cardiac metastasis · Hepatocellular carcinoma

Abstract
Metastatic hepatocellular carcinoma (HCC) to the right atrium without invasion of the inferior vena cava is a very rare and difficult diagnosis, especially when the primary tumour is yet to be known. A 68-year-old man with symptoms of heart failure was admitted to the emergency department; his transthoracic echocardiogram showed a mass comprehending almost the totality of the right atrium, obliterating its entrance nearly completely and impeding the normal auricular–ventricular flux, described as a possible auricular myxoma. The patient was promptly transferred to cardiothoracic surgery and submitted to an urgent surgery to completely remove the mass, which was macroscopically described as suspected of malignancy. Further investigation demonstrated a single nodule in the liver with malignant imaging characteristics, and the histology confirmed the diagnosis of metastatic HCC of the right atrium, without metastatic disease elsewhere. He was then submitted to radiofrequency ablation and medicated with sorafenib. The disease progressed slowly but subsequently involved the inferior vena cava and portal vein, culminating in his death 4 years and 3 months after the diagnosis. Although the prognosis for metastatic HCC may be poor, especially with intracavitary heart metastasis, this case shows that an aggressive initial approach with surgical metastasectomy may prolong the median survival of the patients.

Metástase intracardíaca isolada: O primeiro sinal de carcinoma hepatocelular

Palavras Chave
Insuficiência cardíaca aguda · Metástase cardíaca isolada · Carcinoma hepatocelular

Resumo
A metastização intracardíaca de um carcinoma hepatocelular sem invasão da veia cava inferior é um diagnóstico raro e difícil, especialmente quando o tumor primário não foi ainda diagnosticado. Um homem de 68 anos foi admitido no Serviço de Urgência com sintomas de insuficiência cardíaca aguda. O ecocardiograma transtorácico mostrou uma massa que atingia quase a totalidade da aurícula direita, praticamente obliterando a sua entrada e impedindo o normal fluxo auriculoventricular, descrita como possível mixoma auricular. O doente foi imediatamente transferido para cirurgia cardiotorácica e submetido a cirurgia urgente para resseção da massa que foi mac-

karger@karger.com
www.karger.com/pjg

Correspondence to:
Anusca Paixão, aksuna16@gmail.com

roscopicamente descrita como suspeita de malignidade. A investigação subsequente demonstrou um nódulo isolado hepático com características imagiológicas de malignidade, e a histologia da massa auricular confirmou o diagnóstico de metastização auricular de carcinoma hepatocelular. O doente foi posteriormente submetido a ablação por radiofrequência e medicado com sorafenib, com progressão lenta mas contínua da doença e subsequente atingimento metastático da veia cava inferior e veia porta, que culminou na sua morte quatro anos e três meses após o diagnóstico. Apesar do prognóstico ser reservado para o carcinoma hepatocelular metastático, especialmente na presença de metástases intracardíacas, este caso clínico mostra que uma abordagem inicial mais agressiva com metastasectomia pode prolongar a sobrevida média dos doentes.

Introduction

Hepatocellular carcinoma (HCC) is the number one malignancy of the liver, the fifth most common tumour worldwide and the third most common cause of death related to cancer [1]. Chronic liver disease and cirrhosis remain the most important risk factors to develop HCC [2]. Most cases of HCC are diagnosed at an advanced stage, and the tumour spreads most frequently to the lungs, peritoneum, adrenal glands, and bones [3]. Intracavitary cardiac metastases are very unusual in HCC, and when they occur, they usually invade the heart as an extension of intravascular metastasis or infiltration through nearby organs [4]. The prognosis is poor for metastatic HCC, but surgical treatment, especially in symptomatic intracardiac metastasis, may improve not only quality of life but also survival [5].

Herein, we present a case of an isolated metastasis of HCC to the heart, in which symptoms led to the diagnosis of the primary neoplasm. Informed consent was obtained from the patient's relatives.

Case Report/Case Presentation

We present the case of a 68-year-old male with reported history of systemic arterial hypertension, hypercholesterolemia, benign prostatic hyperplasia, and alcoholic liver cirrhosis of Child-Pugh A with no recent follow-up, medicated with lisinopril, simvastatin and dutasteride + tamsulosin. He was a non-smoker but had sustained alcoholic habits, had no known allergies and his family history was irrelevant. He presented to the emergency department with dyspnoea, orthopnoea and lower limbs oedema of 4 months duration and acute aggravation. He was initially diagnosed with acute heart failure and medicated with furosemide. A transthoracic echocardiogram was scheduled to evaluate the cardiac function, which showed a mass comprehending almost the totality of the right atrium, obliterating its entrance nearly completely and impeding the normal auricular–ventricular flux, described as an auricular myxoma (Fig. 1). The patient was promptly transferred to cardiothoracic surgery and submitted to an urgent intervention to remove the mass completely. Macroscopically, it was not compatible with a myxoma, but rather with malignant metastatic tissue, which was why the patient was then transferred to internal medicine to investigate the location of the primary tumour, while waiting for the histological results. A multiphasic contrast-enhanced computed tomography (CT) scan evidenced a 3.5-cm nodule in the IV segment of the liver, with arterial enhancement and subsequent washout on the portal phase, with no evidence of malignant disease elsewhere (Fig. 2).

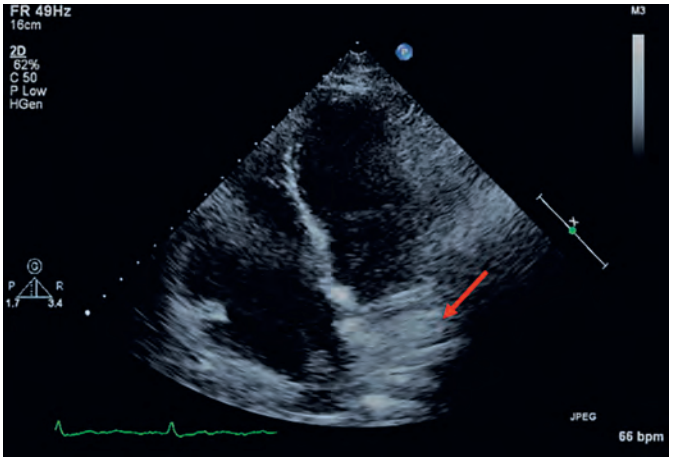


Fig. 1. Echocardiography showing right atrial mass (red arrow).

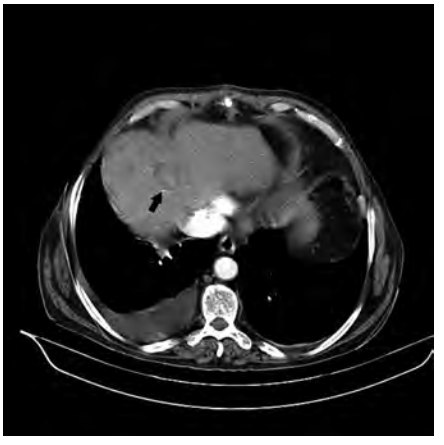


Fig. 2. Initial CT scan showing 3.5-cm nodule in the IV segment of the liver (black arrow).

GE Port J Gastroenterol 2023;30:57–60
DOI: 10.1159/000519545

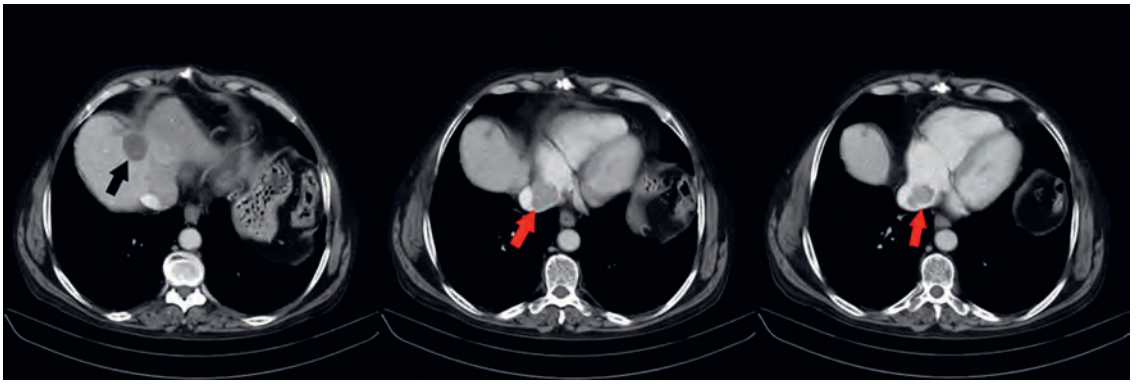


Fig. 3. CT scan showing invasion of the inferior vena cava by the tumoral mass with extension to the right atrium (red arrows) and an extensive lesion of the liver comprehending the IV and II segments (black arrow).

The diagnosis of HCC with single heart metastasis was established with the aid of the histopathological result of the atrial mass, which showed an epithelioid neoplasm of solid and trabecular pattern with areas of necrosis, constituted of bulky cells of granular eosinophilic cytoplasm with round nuclei and with a prominent eosinophilic nucleolus. The immunohistochemical study showed diffuse and intense immunoreactivity of the neoplastic cells for HepPar-1, in the absence of expression of S100, vimentin, CD34, factor VIII, alpha fetoprotein and AE1AE3, compatible with metastatic hepatocarcinoma.

Considering that the single metastasis had been removed with no evidence of portal invasion or any other metastatic disease, it was decided that the patient should undergo radiofrequency ablation (RFA) followed by sorafenib 400 mg/day. During this period, the patient stopped consuming alcohol, having been medicated with oxazepam and baclofen without relapsing. One month after the RFA, the CT scan showed signs of complete response. Nevertheless, 1 year later, the patient recurred with a new liver lesion of 14 mm in the IV segment and was again submitted to RFA with complete response. One year later, on a control CT scan, the patient presented an invasion of the inferior vena cava by a tumoral mass with extension to the right atrium and an extensive lesion of the liver comprehending the IV and II segments (Fig. 3), after which referral to palliative care was decided.

He maintained sorafenib for another 2 years with progressive vascular invasion, that is, with portal vein thrombosis and extension to the medial and right hepatic veins. Progressive hepatic encephalopathy and increasing oedema led to his hospitalization and death. The survival time of this patient, from the date of diagnosis, was 4 years and 3 months.

Discussion/Conclusion

This unique case shows the development of single metastatic disease of the heart in a patient with previous alcoholic liver cirrhosis who missed the follow-up. Although HCC may metastasize to various extrahepatic organs, metastases with cardiac involvement are rare [6], generally occurring in advanced stages of the disease with invasion of the portal vein and evidence of portal thrombosis [4], which were both absent at diagnosis in this particular case report.

The prognosis of HCC with cardiac involvement is poor, and the median survival time at diagnosis is 102 days [7]. Our patient survived for 4 years and 3 months, most of them with good quality of life and autonomy, with a total of only 33 days of hospitalization in that period. This may be due to the initial and early surgical approach to metastatic disease.

Although we were initially optimistic about the patient's evolution after the initial removal of the atrial mass and RAF of the first liver injury, the recurrence of HCC and metastatic disease in the inferior vena cava may indicate that haematogenous spread of the previous disease to the atrial implant had occurred, even in the absence of macroscopic invasion of the portal vein at the time of diagnosis.

Statement of Ethics

This case report was written in accordance with the World Medical Association Declaration of Helsinki. Informed consent was obtained from the patient's relatives.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding or sponsors were used in the preparation of this manuscript.

Author Contributions

Anusca Paixão: First author. Interpreted and organized the data. Wrote the case report. Rita Silva: Conception, organization and design of the work/case report. Natália Lopes: Revised the work for intellectual content. Sónia Carvalho: Revised the work for intellectual content. Paulo Carrola: Final approval of the version to be published. José Presa Ramos: Revised the work for intellectual content.

References

1 Raza A, Sood GK. Hepatocellular carcinoma review: current treatment, and evidence-based medicine. World J Gastroenterol. 2014 Apr;20(15):4115–27.
2 Balogh J, Victor D 3rd, Asham EH, Gordon Burroughs S, Boktour M, Saharia A, et al. Hepatocellular carcinoma: a review. J Hepatocell Carcinoma. 2016;3:41–53.
3 Masci G, Magagnoli M, Grimaldi A, Covini G, Carnaghi C, Rimassa L, et al. Metastasis of hepatocellular carcinoma to the heart: a case report and review of the literature. Tumori. 2004 May-Jun; 90(3):345–7.
4 Tastekin E, Usta U, Ege T, Kazindir G, Kutlu AK. Cardiac metastasis of hepatocellular carcinoma in a young non-cirrhotic patient, to the left ventricle. Ann Hepatol. 2012 May-Jun;11(3):392–4.
5 Kim SB, Shin YC, Kwon SU. Isolated metastasis of hepatocellular carcinoma in the right ventricle: A case report. Medicine (Baltimore). 2016 Dec;95(51):e5544.
6 Fukuoka K, Masachika E, Honda M, Tsukamoto Y, Nakano T. Isolated metastases of hepatocellular carcinoma in the left atrium, unresponsive to treatment with sorafenib. Mol Clin Oncol. 2015 Mar;3(2):397–9.
7 Albackr HB. A large Right atrial mass in a patient with hepatocellular carcinoma: case report and literature review. J Saudi Heart Assoc. 2014 Jul;26(3):174–8.

GE – Portuguese Journal of Gastroenterology

Clinical Case Study

GE Port J Gastroenterol 2023;30:61–67
DOI: 10.1159/000519926

Received: May 9, 2021
Accepted: August 9, 2021
Published online: November 23, 2021

Percutaneous Endoscopic Gastrostomy Placement under NIV in Amyotrophic Lateral Sclerosis with Severe Ventilatory Dysfunction: A Safe and Effective Procedure

Rui Gaspar[a, f] Rosa Ramalho[a, f] Rosa Coelho[a, f] Patrícia Andrade[a, f]
Miguel R. Goncalves[b, c, d, e, f] Guilherme Macedo[a, f]

[a]Gastroenterology Department, Centro Hospitalar São João, Faculty of Medicine of the University of Porto, Porto, Portugal; [b]Noninvasive Ventilatory Support Unit, Pulmonology Department, Centro Hospitalar São João, Faculty of Medicine of the University of Porto, Porto, Portugal; [c]Emergency and Intensive Care Medicine Department, Centro Hospitalar São João, Faculty of Medicine of the University of Porto, Porto, Portugal; [d]UNiC – Cardiovascular R&D Unit, Faculty of Medicine of the University of Porto, Porto, Portugal; [e]CAI_Vent – Home Mechanical Ventilation Program, Centro Hospitalar São João, Porto, Portugal; [f]Faculty of Medicine, University of Porto, Porto, Portugal

Keywords

Percutaneous endoscopic gastrostomy · Amyotrophic lateral sclerosis · Severe ventilatory impairment

Abstract

Introduction: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder with an inexorably progressive course which leads to a progressive neuromuscular weakness. Weight loss is one of the major bad prognostic factors in ALS. The placement of percutaneous endoscopic gastrostomy (PEG) is of paramount importance in patients with dysphagia to improve the disease outcomes, although some fear exists regarding the possible ventilatory complications during the procedure. The aim of this study was to evaluate the safety and effectiveness of PEG tube insertion under non-invasive ventilation (NIV) in patients with ALS and severe ventilatory impairment. ***Methods:*** A retrospective study of all consecutive PEGs placed in our department from May 2011 to January 2018 in patients with ALS was performed. The procedure was performed under non-invasive positive-pressure ventilation for ventilatory support. ***Results:*** We included 59 patients with ALS with severe ventilatory impairment, 58% were female, with a mean age of 67.2 ± 10.1 years and a median follow-up of 6 [2–15] months. The main indication for PEG placement was dysphagia (98%). The median time for PEG tube insertion since the established diagnosis of ALS was 12 [6–25] months and 4 [2–18] months since the beginning of bulbar symptoms. The majority of the patients had placed a 20-Fr PEG (63%) and under mild sedation with midazolam (80%), all under NIV. There were no immediate complications during and after the procedure (no episodes of aspiration or orotracheal intubation) and mortality. ***Conclusion:*** The placement of PEG is a very important procedure in patients with ALS and severe ventilatory impairment. The interdisciplinary department collaboration permitted the placement of PEG under NIV, in a safe and effective procedure in this special population.

karger@karger.com
www.karger.com/pjg

Correspondence to:
Rui Gaspar, ruilopesgaspar@gmail.com

Colocação de gastrostomia endoscópica percutânea sob ventilação não invasiva em doentes com esclerose lateral amiotrófica com disfunção ventilatória grave: um procedimento seguro e eficaz

Palavras Chave
Gastrostomia endoscópica percutânea · Esclerose lateral amiotrófica · Disfunção ventilatória grave

Resumo
Introdução: A esclerose lateral amiotrófica (ELA) é uma doença neurodegenerativa com um curso inexorável que leva a fraqueza neuromuscular progressiva. A perda de peso é um dos principais fatores de mau prognóstico na ELA. Apesar do receio de complicações ventilatórias durante o procedimento, a colocação de gastrostomia percutânea endoscópica em doentes com disfagia é extremamente importante para melhorar o prognóstico. O objetivo deste estudo é avaliar a segurança e eficácia da colocação de gastrostomia percutânea endoscópica (GEP) sob ventilação não invasiva (VNI) em doentes com ELA e disfunção ventilatória grave. ***Métodos:*** Estudo retrospetivo de todas as gastrostomias percutâneas endoscópicas colocadas em doentes com ELA no nosso departamento entre Maio 2011 e Janeiro 2018. O procedimento foi realizado sob VNI para suporte ventilatório. ***Resultados:*** Foram incluídos 59 doentes com ELA e disfunção ventilatória grave, 58% do sexo feminino, com uma idade média de 67.2 ± 10.1 anos e um follow-up mediano de 6 [2–15] meses. A principal indicação para colocação de gastrostomia percutânea endoscópica foi disfagia (98%). O tempo mediano para a colocação de GEP desde o diagnóstico de ELA foi 12 [6–25] meses e 4 [2–18] meses desde o início dos sintomas bulbares. A maioria dos doentes colocaram uma GEP de 20 Fr (63%) e sob sedação com midazolam (80%), todos sob VNI. Não se verificaram complicações imediatas durante e após o procedimento (sem episódios de aspiração ou entubação orotraqueal) e mortalidade. ***Conclusão:*** A colocação de GEP é um procedimento muito importante em doentes com ELA e disfunção ventilatória grave. A colaboração interdisciplinar permitiu a colocação de GEP sob ventilação não invasiva, tornando-o um procedimento seguro e eficaz nesta população especial.

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with progressive loss of the upper and lower motor neurons at the spinal or bulbar levels.

It is known that the course of this disorder is heterogeneous and the survival relies on several factors: clinical presentation (limb onset vs. bulbar onset), age of symptom onset, rate of disease progression, development of respiratory muscle weakness with consequent respiratory failure and nutritional status [1–4]. Since there is no therapy that offers a substantial clinical benefit for patients with ALS, it presents a very poor prognosis. Generally, death occurs due to respiratory failure, aspiration pneumonia, malnutrition, and dehydration [1, 5, 6].

The clinical presentation of ALS is heterogeneous but typically begins with muscle weakness, twitching, and cramping in the limbs. The disease can eventually progress to bulbar involvement, presenting with dysphagia and dysarthria [3, 7].

Nutritional assessment is a major issue to address in patients with ALS, as it has been clearly demonstrated that weight loss is an independent poor prognostic factor. Malnutrition in ALS patients can be explained in part by poor food intake, which might be due to dysphagia, severe upper-limb disability and high ventilatory dependence in patients under continuous non-invasive positive-pressure ventilation (NIV). Dysphagia develops in the majority of ALS patients during the course of the disease and, besides being inevitably associated with weight loss and malnutrition, it also entails an increased risk of respiratory infections due to aspiration, features that are associated with a poor prognosis [2, 3, 8].

Dietary changes are of paramount importance to preserve nutrition and can postpone the need for percutaneous endoscopic gastrostomy (PEG). However, with the progression of the disease, oral feeding will become insufficient and nutrition can only be guaranteed through PEG placement [2, 8, 9].

Respiratory dysfunction is an established indicator of ALS severity and progression. Furthermore, vital capacity (VC) is a good indicator of respiratory function, and its decline is associated with a poor prognosis in ALS patients, especially when VC decreases to less than 50% of predicted. Thus, this parameter is most commonly used as a criterion for initiating ventilatory support. Respiratory complications are common in ALS, and NIV and, less frequently, invasive mechanical ventilation are used to alleviate symptoms of respiratory insufficiency. In fact, NIV significantly prolongs survival, preserves respiratory

function and improves or maintains quality of life in ALS patients [10].

The American Academy of Neurological Societies and the European Federation of Neurological Societies guidelines for the management of ALS recommend PEG placement before the occurrence of respiratory insufficiency (FVC ≤50%) as it reduces procedure risks and improves survival and quality of life [10, 11].

PEG placement is an invasive and high-risk endoscopic procedure especially in very vulnerable patients, such as ALS patients. The procedure usually requires mild sedation and is more dangerous in patients with ventilatory impairment, particularly severe respiratory impairment, and/or at an advanced stage of the disease. In this subset of patients, NIV during the PEG procedure may be feasible [10].

Our department has a dedicated team of gastroenterologists working in cooperation with the Pneumology Department that permits the insertion of a PEG tube under NIV in these high-risk patients with ALS and severe ventilatory impairment.

The aim of this study was to evaluate the PEG tube insertion under NIV in patients with ALS and severe ventilatory impairment.

Methods

Study Design, Inclusion and Exclusion Criteria

A retrospective study including all consecutive PEGs under NIV placed in the Gastroenterology Department from May 2011 to January 2018 in patients with ALS under pneumology support was performed in a tertiary centre in Porto.

All patients were actively followed at the neuromuscular outpatient clinic of the Pulmonology Department, with nutritional status and swallowing status always evaluated. Severe ventilatory dysfunction was characterized by a VC below 50% of predicted.

The criteria considered to placement of PEG were: insufficient oral feeding due to dysphagia or inability of having an entire meal without the use of NIV, weight loss >10% and suspicion of aspiration pneumonia.

At the time of referral, all patients were evaluated by a pulmonologist and a specialized respiratory physiotherapist, as well as by the gastroenterologist in charge of patients who were candidates for PEG placement. The procedure was explained to the patient and the family, and all the periprocedure risks and implications to the future of the patient were considered. A patient or family informed consent was obtained before the procedure.

Procedure

A 12-h fasting prior to the examination was recommended to the patient and anticoagulation therapy stopped for 1 week (warfarin was substituted by enoxaparin that was stopped 24 h before the procedure).

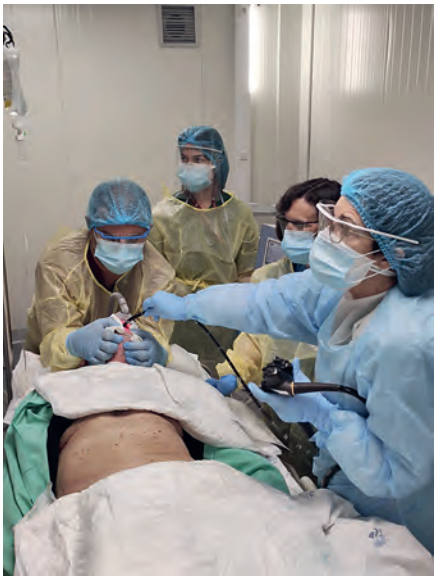


Fig. 1. Esophagogastroduodenoscopy with a standard upper endoscope for PEG placement in a patient with ALS and severe ventilatory impairment under nasal non-invasive ventilatory support.

All patients received prophylactic antibiotic treatment with 1 g cephazolin 1 h before PEG placement.

The procedure was done with an upper endoscope (Olympus® GIF-Q160, GIF-Q165 and GIF-Q180 models), and a PEG kit was used (PEG US Endoscopy® Pull Silicone (20–24 Fr).

PEG placement was performed by three operators in strict collaboration: one experienced endoscopist, one gastroenterologist responsible for the percutaneous component of the procedure and a specialized respiratory physiotherapist responsible for adjusting NIV parameters whenever it was necessary. This team was also responsible for sedation and its control (with midazolam).

An upper endoscopy was performed to exclude malignancy or gastric outlet obstruction and determine the optimal site for PEG placement. After lidocaine injection, a 2-cm-deep horizontal incision was made and the PEG placed by the through pull method. This procedure was performed without general anaesthesia or profound sedation and under nasal NIV (Fig. 1) in spontaneous timed bilevel mode. When needed, a conscious sedation with midazolam was applied. Those patients who had not been using NIV, were adapted and trained in nasal NIV usage previously by the specialized respiratory physiotherapist to prepare them for the procedure. Estimated tidal volumes, airleaks through the mouth, SpO_2, heart rate and respiratory rate were monitored continuously. Due to the increase in mouth air leaks during the PEG placement, home ventilator parameters were readjusted to achieve patient comfort. Low flow oxygen was only employed with NIV to obtain an SpO_2 ≥92%, despite NIV optimization. If SpO_2 ≥92% could not be reached with nasal NIV plus low flow O_2 (≤2 L/min), then PEG placement was cancelled. All patients maintained NIV with their home interface for at least 3 h after the procedure.

Data Collection

Patient data were collected from electronic medical records.

Age, gender, presence of dysphagia, previous episodes of aspiration pneumonias, date of established diagnosis of ALS and time of the beginning of bulbar symptoms and presence of comorbidities (diabetes mellitus, liver disease, malignancy, AIDS, moderate to severe chronic kidney disease, heart failure, previous myocardial infarction, chronic obstructive pulmonary disease, peripheral vascular disease, previous cerebral vascular accident or transitory ischaemic accident, dementia, hemiplegia, connective tissue disease and peptic ulcer disease) were obtained, and the Charlson comorbidity index was calculated.

Data regarding the procedure such as type of PEG, need of sedation and dose of midazolam and periprocedure complications were also obtained, as well as postmortality and postprocedure complications (more than 1 month after PEG tube placement).

We used our non-ALS PEG patient database to compare the rate of complications of PEG tube insertion in ALS patients.

Statistical Analysis

Continuous variables are expressed as medians (standard deviation). Categorical variables are reported as absolute (n) or relative frequencies (%).

p values <0.05 were considered significant. Data were analysed using SPSS 21.0 (IBM Corp., Armonk, NY, USA).

Ethical Considerations

This study was conducted according to the Declaration of Helsinki.

Informed consent to participate in the study was obtained from each patient.

Results

We included 59 patients, 34 females (58%) and 25 males (42%), with a mean age of 67.2 ± 10.1 years, and the median follow-up was 6 [range 2–15] months.

The median Charlson index was 3 [2–4], and 24 patients had arterial hypertension, 13 had dyslipidaemia, 5 patients had type 2 diabetes, 3 previous episodes of cerebral vascular accident or transitory ischaemic accident and 2 previous episodes of acute myocardial infarction.

Nine patients had suspicion of previous episodes of aspiration (15.3%), and 11 patients had previous admissions for pneumonia (10 patients 1 single episode and 1 patient with 2 admissions due to pneumonia).

The main reason for referral for PEG placement was dysphagia with associated weight loss (98.3%).

The clinical characterization is listed in Table 1.

The median time for PEG tube insertion since the established diagnosis of ALS was 12 [6–25] months and 4 [2–18] months since the beginning of bulbar symptoms.

The majority of the patients had placed a 20-Fr PEG tube (62.7%) and 47 needed midazolam sedation (92% up to 2 mg of midazolam). There were no immediate complications during and after the procedure (no episodes of aspiration or orotracheal intubation), need for admission or mortality. In addition, regarding minor complications, there were no episodes of apnoea/hypoventilation, aspiration pneumonia or peristomal infection in the postprocedure period.

Eleven patients developed long-term complications after PEG tube placement. Six patients needed to substitute the PEG because of 5 accidental exteriorizations and

Table 1. Clinical characterization

Clinical characterization	*n* (%)
Dysphagia	58 (98.3)
Arterial hypertension	24 (40.7)
Dyslipidaemia	13 (22.0)
Type 2 diabetes	5 (8.5)
Previous cerebral vascular accident or transitory ischaemic accident	3 (5.1%)
Previous acute myocardial infarction	2 (3.4)
Heart failure	1 (1.7)
Dementia	1 (1.7)
Charlson index ≤3	43 (72.9)
Charlson index >3 and <8	16 (27.1)
Patients with previous admission due to pneumonia	11 (18.6)
Number of previous admissions considering all causes	
0	19 (32.2)
1	31(52.5)
2	4 (6.8)
3	4 (6.8)
4	1 (1.7)

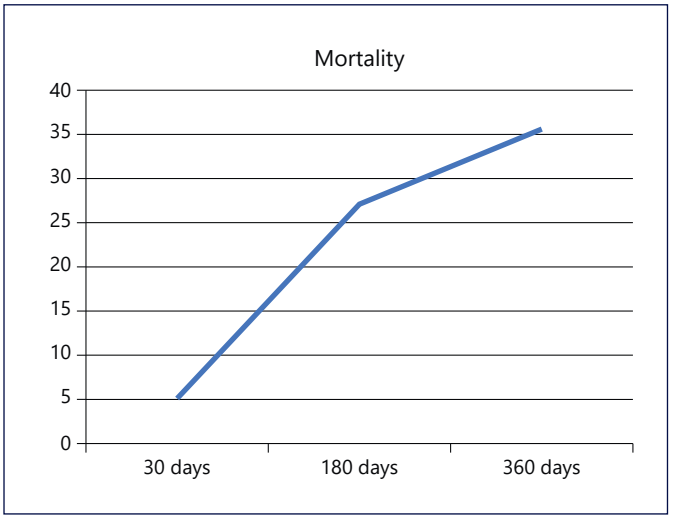


Fig. 2. 30-, 180- and 360-day mortality after PEG placement.

Table 2. Postprocedure complications

Long-term complications of PEG placement	ALS patients (n = 59)	Non-ALS patients (n = 402)
Exteriorization	5 (8.5%)	44 (10.9%)
Pain	4 (6.8%)	30 (7.5%)
Bleeding	1 (1.7%)	2 (0.5%)
Degradation of PEG tube	1 (1.7%)	29 (7.2%)
Number of admissions for all causes after PEG placement	18 (30.5%)	128 (31.8%)
Number of admissions due to pneumonia after PEG placement	9 (15.3%)	100 (24.9%)

1 PEG tube degradation, 4 patients developed pain at the site of the PEG tube due to skin erythema (these cases were totally solved after topic fusidic acid use) and 1 patient had self-limited bleeding for the site of the PEG.

In the period of follow-up, there were 18 admissions after PEG placement, with 9 admissions due to pneumonia.

The 30-day mortality after PEG placement was 5.1%, the 180-day mortality was 27.1% and the 360-day mortality was 35.6% (Fig. 2).

Discussion

In this study, we showed that placement of PEG under NIV in ALS patients with severe ventilatory impairment through a strict cooperation between the Gastroenterology and Pneumology Departments is a safe and effective procedure. No respiratory distress or infection, or any other pulmonary complication, was observed in this cohort of patients. No death after the procedure could be imputable to PEG placement.

Malnutrition is undoubtedly one of the main prognostic factors with some studies showing a linear decline in muscle strength. In addition, severe malnutrition is associated with muscle atrophy, muscle weakness, increase in fatigue and decrease in respiratory capacity, leading to the development of depression and decreasing quality of life [1, 8, 12]. Therefore, it is essential to provide effective nutritional care to ALS patients. Several studies have evaluated the efficacy of gastrostomies to solve this problem and linked PEG placement to decreased morbidity and improved survival rates (mainly by decreasing pneumonia and cachexia), being a successful and safe procedure in highly disabled ALS patients with respiratory compromise and advanced neurological disease [9, 13, 14]. In our opinion, it should be noted that the proposal of this procedure should not be conditioned by the severity of the respiratory functional impairment of the patient. Otherwise, many patients would have to undergo PEG placement too early in the course of the disease and would have been unnecessarily exposed to the constraints that PEG implies. In fact, a patient with a functional and preserved deglutition and capable of autonomous breathing should not undergo PEG placement uniquely because VC is decreasing and reaching the threshold of 50% of predicted. Thus, we think that the recommendation of the American Academy of Neurology – that, for optimal management of ALS, PEG should be placed when VC is above 50% of predicted [10] – might be exaggerated and contribute to needlessly diminishing the quality of life of ALS patients. This recommendation is mainly based on the argument that it would minimize the risk of respiratory complications [10, 15, 16]. However, in a centre with an experienced and multidisciplinary team, ALS patients with severe ventilatory impairment can be addressed safely and undergo PEG placement under nasal NIV support, as we show with our results. Accordingly, an individualized approach should be undertaken to each patient, taking into account the overall condition of the patient, as well as the severity of dysphagia symptoms and the degree of malnutrition. Recently, an interesting risk-stratifying tool for the approach of PEG placement in late-stage ALS patients was proposed, considering also the NIV support during the procedure in high-risk patients [17–24].

Conscious sedation is another point of discussion in ALS patients, being carefully considered by the European guidelines, as there are only scarce data. In our study, almost 80% received conscious sedation with midazolam with simultaneous NIV and there were no changes in blood pressure, anaesthetic or respiratory complications [3, 10]. We did not find any disadvantage of conscious sedation (in the majority of cases with 2 mg of midazolam) compared with general anaesthesia with propofol,

and the procedure with conscious sedation was performed without affecting technical success.

Another interesting fact is that we found fewer long-term complications of PEG placement when we compared our cohorts of PEG in our department (18.6% in ALS patients vs. 33.8% in general patients; Table 2). This difference is even higher if we look to exteriorization and degradation of PEG. This fact might be explained because ALS patients are a population that maintain their cognitive functions preserved till very advanced phases of the disease, which will lead to careful management of the PEG tube. When we also compared the number of admissions due to pneumonia during the period of follow-up, it was also reduced even with the progressive character of the disease.

The impact of PEG on survival cannot be directly extrapolated in our group of patients, since no control group without PEG placement was enrolled. However, it is difficult to evaluate the real impact of PEG on survival, since other factors such as NIV usage, bulbar muscle impairment, timing of PEG placement and patient comorbidities might have also a significant impact on mortality. Besides that, we can assume that PEG placement is mainly a symptomatic treatment, deemed to be a quality of life measure. By reducing the risk of weight loss, malnourishment and respiratory infections due to aspiration, PEG placement might have a positive impact on the survival of ALS patients. As an additional remark, in our study population, there was a high proportion of patients under NIV. It is well known that NIV improves survival in ALS patients, a fact that was also demonstrated in our analyses, since patients under continuous non-invasive ventilatory support, despite the severity of respiratory function impairment, had a tendency for a higher median survival.

Conclusion

The placement of PEG is a very important procedure in patients with ALS and severe ventilatory impairment.

The interdisciplinary department collaboration permitted the placement of PEG under NIV, in a safe and effective procedure in this special population.

Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study protocol was reviewed and approved by the Ethics committee of Centro Hospitalar de São João. Written informed consent to participate in the study was obtained from each patient. Written informed consent was obtained from the individuals (participant and practitioners) to publish Figure 1 as well as the medical details of the case.

Disclosure Statement

The authors disclose no possible conflicts of interest.

Funding Sources

There were no funding sources to this research.

Author Contributions

Rui Gaspar was responsible for the study design, acquisition and interpretation of data, drafting the manuscript and statistical analysis. Miguel Gonçalves was responsible for acquisition and interpretation of data, and critical revision of the manuscript for important intellectual content. Rosa Ramalho, Rosa Coelho and Patrícia Andrade were responsible for acquisition and interpretation of data. Guilherme Macedo was responsible for critical revision of the manuscript for important intellectual content. All the authors approved the final version of the paper.

References

1 Cui F, Sun L, Xiong J, Li J, Zhao Y, Huang X. Therapeutic effects of percutaneous endoscopic gastrostomy on survival in patients with amyotrophic lateral sclerosis: a meta-analysis. PLoS One. 2018 Feb;13(2):e0192243.

2 Onesti E, Schettino I, Gori MC, Frasca V, Ceccanti M, Cambieri C, et al. Dysphagia in amyotrophic lateral sclerosis: impact on patient behavior, diet adaptation, and riluzole management. Front Neurol. 2017 Mar;8:94.

3 Strijbos D, Hofstede J, Keszthelyi D, Masclee AA, Gilissen LP. Percutaneous endoscopic gastrostomy under conscious sedation in patients with amyotrophic lateral sclerosis is safe: an observational study. Eur J Gastroenterol Hepatol. 2017 Nov;29(11):1303–8.

4 Carbo Perseguer J, Madejon Seiz A, Romero Portales M, Martinez Hernandez J, Mora Pardina JS, Garcia-Samaniego J. Percutaneous endoscopic gastrostomy in patients with amyotrophic lateral sclerosis: mortality and complications. Neurologia. 2019;34(9):582–8.

5 Brown RH Jr, Al-Chalabi A. Amyotrophic Lateral Sclerosis. N Engl J Med. 2017 Oct;377(16):1602.

6 Czaplinski A, Yen AA, Simpson EP, Appel SH. Predictability of disease progression in amyotrophic lateral sclerosis. Muscle Nerve. 2006 Dec;34(6):702–8.

7 Zarei S, Carr K, Reiley L, Diaz K, Guerra O, Altamirano PF, et al. A comprehensive review of amyotrophic lateral sclerosis. Surg Neurol Int. 2015 Nov;6(1):171.

8 Banfi P, Volpato E, Valota C, D'Ascenzo S, Alunno CB, Lax A, et al. Use of Noninvasive Ventilation During Feeding Tube Placement. Respir Care. 2017 Nov;62(11):1474–84.
9 Spataro R, Ficano L, Piccoli F, La Bella V. Percutaneous endoscopic gastrostomy in amyotrophic lateral sclerosis: effect on survival. J Neurol Sci. 2011 May;304(1-2):44–8.
10 Andersen PM, Abrahams S, Borasio GD, de Carvalho M, Chio A, Van Damme P, et al; EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS) – revised report of an EFNS task force. Eur J Neurol. 2012 Mar;19(3):360–75.
11 Miller RG, Jackson CE, Kasarskis EJ, England JD, Forshew D, Johnston W, et al.; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2009 Oct;73(15):1227–33.
12 Desport JC, Preux PM, Truong CT, Courat L, Vallat JM, Couratier P. Nutritional assessment and survival in ALS patients. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000 Mar;1(2):91–6.
13 Shaw AS, Ampong MA, Rio A, Al-Chalabi A, Sellars ME, Ellis C, et al. Survival of patients with ALS following institution of enteral feeding is related to pre-procedure oximetry: a retrospective review of 98 patients in a single centre. Amyotroph Lateral Scler. 2006 Mar;7(1):16–21.
14 Mathus-Vliegen LM, Louwerse LS, Merkus MP, Tytgat GN, Vianney de Jong JM. Percutaneous endoscopic gastrostomy in patients with amyotrophic lateral sclerosis and impaired pulmonary function. Gastrointest Endosc. 1994 Jul-Aug;40(4):463–9.
15 Miller RG, Rosenberg JA, Gelinas DF, Mitsumoto H, Newman D, Sufit R, et al. Practice parameter: the care of the patient with amyotrophic lateral sclerosis (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology: ALS Practice Parameters Task Force. Neurology. 1999 Apr;52(7):1311–23.
16 Kasarskis EJ, Scarlata D, Hill R, Fuller C, Stambler N, Cedarbaum JM. A retrospective study of percutaneous endoscopic gastrostomy in ALS patients during the BDNF and CNTF trials. J Neurol Sci. 1999 Oct;169(1-2):118–25.
17 Thompson AG, Blackwell V, Marsden R, Millard E, Lawson C, Nickol AH, et al. A risk stratifying tool to facilitate safe late-stage percutaneous endoscopic gastrostomy in ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2017 May;18(3-4):243–8.
18 Blondet A, Lebigot J, Nicolas G, Boursier J, Person B, Laccoureye L, et al. Radiologic versus endoscopic placement of percutaneous gastrostomy in amyotrophic lateral sclerosis: multivariate analysis of tolerance, efficacy, and survival. J Vasc Interv Radiol. 2010 Apr;21(4):527–33.
19 Allen JA, Chen R, Ajroud-Driss S, Sufit RL, Heller S, Siddique T, et al. Gastrostomy tube placement by endoscopy versus radiologic methods in patients with ALS: a retrospective study of complications and outcome. Amyotroph Lateral Scler Frontotemporal Degener. 2013 May;14(4):308–14.
20 Sato Y, Goshi S, Kawauchi Y, Nishigaki Y, Mizuno KI, Hashimoto S, et al. Safety of unsedated PEG placement using transoral ultrathin endoscopy in patients with amyotrophic lateral sclerosis. Nutr Neurosci. 2017 Jan;20(1):71–5.
21 ProGas Study Group. Gastrostomy in patients with amyotrophic lateral sclerosis (ProGas): a prospective cohort study. Lancet Neurol. 2015 Jul;14(7):702–9.
22 Boitano LJ, Jordan T, Benditt JO. Noninvasive ventilation allows gastrostomy tube placement in patients with advanced ALS. Neurology. 2001 Feb;56(3):413–4.
23 Sancho J, Servera E, Chiner E, Bañuls P, Gómez-Merino E, Sancho-Chust JN, et al. Noninvasive respiratory muscle aids during PEG placement in ALS patients with severe ventilatory impairment. J Neurol Sci. 2010 Oct;297(1-2):55–9.
24 Bach JR. Amyotrophic lateral sclerosis: prolongation of life by noninvasive respiratory AIDS. Chest. 2002 Jul;122(1):92–8.

GE – Portuguese Journal of Gastroenterology

Clinical Case Study

GE Port J Gastroenterol 2023;30:68–72
DOI: 10.1159/000520271

Received: April 30, 2021
Accepted: September 10, 2021
Published online: November 29, 2021

IgG4-Related Esophageal Disease Presenting as Esophagitis with Chronic Strictures

Catarina Correia[a] Hélder Moreira[b] Nuno Almeida[a, c] Marta Soares[a, c]
Augusta Cipriano[b] Pedro Figueiredo[a, c]

[a]Gastroenterology Department, Coimbra University Hospital Centre, Coimbra, Portugal; [b]Department of Pathology, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; [c]Faculty of Medicine, University of Coimbra, Coimbra, Portugal

Keywords
IgG4 · Doença relacionada com IgG4 · Estenose crónica

Abstract
IgG4-related disease is a recently recognized autoimmune systemic disorder that has been described in various organs. The disease is characterized histologically by a dense lymphoplasmacytic infiltrate with IgG4-positive cells, storiform fibrosis, obliterative phlebitis, and can be associated with space-occupying lesions. IgG4-related disease involving the upper gastrointestinal tract is rare. We report the case of a 30-year-old female patient with a long-standing history of severe dysphagia and odynophagia. Symptoms persisted despite anti-acid therapy, and control esophagogastroduodenoscopy revealed endoscopic images consistent with a nontransposable stenosis in the proximal esophagus. An underlying autoimmune process was suspected, and topical immunosuppressants were tried to control her disease. The patient maintained disabling dysphagia secondary to chronic esophageal strictures. A diagnosis of probable IgG4-related disease was made after esophageal biopsies. Treatment attempts with topical corticosteroids was not associated with a significant improvement of the symptoms of dysphagia and odynophagia, possibly because of the chronic nature of the disease associated with a high fibrotic component. This report describes a case of IgG4-related esophageal disease presenting as chronic esophagitis with strictures. We also briefly review the main histopathological features and treatment options in IgG4-related disease.

Doença esofágica relacionada com IgG4 – Apresentação sob a forma de esofagite com estenoses crónicas

Palavras Chave
IgG4 · Doença relacionada com IgG4 · Estenose crónica

Resumo
A doença relacionada com IgG4 é uma doença sistémica, autoimune, que pode acometer vários órgãos. Caracteriza-se histologicamente por um denso infiltrado linfoplas-

karger@karger.com
www.karger.com/pjg

Correspondence to:
Catarina Correia, catarina-jac@hotmail.com

mocítico com células IgG4-positivas, fibrose e flebite obliterante, podendo estar associada a lesões ocupantes de espaço. A doença relacionada com IgG4 envolvendo o trato gastrointestinal superior é rara. Relatamos o caso de uma paciente de 30 anos com história de disfagia e odinofagia com vários anos de evolução, em que apesar da instituição de terapêutica antiácida, os sintomas persistiram. A endoscopia digestiva alta revelou imagens endoscópicas consistentes com uma estenose não transponível no esófago proximal. Suspeitou-se de um processo autoimune subjacente sendo tentada terapêutica imunossupressora tópica para controlo da doença. A paciente manteve disfagia incapacitante secundária a estenose esofágica crónica. O diagnóstico de provável doença relacionada com IgG4 foi feito após biópsias esofágicas. As tentativas de tratamento com corticosteroides tópicos não foram associadas a uma melhora significativa dos sintomas de disfagia e odinofagia, possivelmente devido à natureza crónica da doença associada a um elevado componente fibrótico. Este caso pretende ilustrar uma situação de doença esofágica relacionada com IgG4 apresentando-se como esofagite crónica estenosante. Apresentamos ainda, uma breve revisão das principais características histopatológicas e opções de tratamento em doenças relacionadas com IgG4.

Introduction

IgG4-related disease (IgG4-RD) has recently been recognized as an autoimmune systemic disorder [1]. The first reports of the disease came from Japan where it was thought that autoimmune pancreatitis associated with high serum concentration of IgG4 and extra-pancreatic manifestations might be part of a more systemic autoimmune disorder [2].

IgG4-RD is diagnosed histologically as a dense lymphoplasmacytic infiltrate with IgG4-positive cells, fibrosis organized in a storiform pattern and obliterative phlebitis [3]. Many organs can be involved in the disease such as the pancreas, biliary tract, salivary glands, lymph nodes, thyroid, kidneys, lung, skin, prostate, and aorta. Involvement of the upper gastrointestinal tract is rare, and there have only been few case reports describing IgG4-related esophageal disease [3]. We report a case of IgG4-related esophageal disease presenting as chronic esophagitis with strictures.

Case Report

A young Caucasian woman was evaluated for a very long history (years of evolution) of progressive odynophagia and dysphagia. Her medical history was positive for hypothyroidism. This patient was initially followed in primary care for symptoms of heartburn and dyspepsia. The presumed diagnosis was gastroesophageal reflux disease and she was treated with a proton pump inhibitor (PPI), at a standard daily dose. The patient maintained complaints despite treatment with PPI, and an esophagogastroduodenoscopy (EGD) was then requested. This endoscopic examination revealed a fibrous ring/membrane, just below the upper esophageal sphincter (UES) that was not amenable to be transposed by the endoscope. After this, a cervical CT scan was performed and revealed circumferential thickening of the upper cervical esophagus, not determining obstructive phenomena to the normal progression of the administered oral contrast. Given these findings, she was then referred to the Gastroenterology Department. A new EGD with possible endoscopic dilation was proposed, and it was accepted by the patient. This examination confirmed a circumferential membranous ring just below the UES. Dilation was performed with a through-the-scope (TTS) balloon up to 10 mm, with deep laceration after the procedure. It was then possible to further advance the endoscope, and other mucosal rings were seen distally. Biopsies were performed, and histopathology revealed a probable IgG4-associated esophagitis due to lymphoplasmacytic infiltrate with large numbers of positive IgG4 plasma cells (>200/high power field), IgG:IgG4 ratio greater than 50%, nonobliterative phlebitis, and mild fibrosis, without storiform pattern (Fig. 1). Serum IgG4 value was within the normal range (0.52 g/L).

Two months later, she maintained complaints of dysphagia, with only transient improvement after endoscopic dilation. Considering the histological diagnosis and the possibility of a systemic disease, the following examinations were requested: blood tests to exclude autoimmune disease (immunoglobulins: IgG, IgA, IgE, IgM; antinuclear antibodies; antineutrophil cytoplasmic antibodies; tissue transglutaminase antibodies; serum protein electrophoresis; thyroid hormones) and immunoallergology evaluation to exclude possible association with food or other allergies. No changes were found in the requested exams. Liver enzymology was also normal, and there were no complaints of sialadenitis. In order to exclude the involvement of other organs, namely the pancreas, an MRI was carried out which did not reveal alterations.

Topical corticosteroids were started – oral puffs of fluticasone (220 μg/spray, four sprays daily in divided doses – twice daily) for 8 weeks.

Since there was no apparent symptomatic response, a new EGD was then proposed. There were two stenotic rings just below the UES and another one at the distal esophagus. Endoscopic dilation with a TTS balloon up to 10 mm was performed at both locations, and superficial lacerations were visible after treatment. It was then possible to advance the endoscope to the stomach. However, shortly after this endoscopic maneuver, the patient developed chest and cervical pain with subcutaneous emphysema. A CT scan confirmed an esophageal perforation, but since there were no signs of systemic toxicity, a conservative treatment was implemented after surgical consultation. The patient tolerated parenteral nutrition and antibiotics. A later water-soluble contrast showed a slight decrease in distensibility of the distal esophagus, with slow and

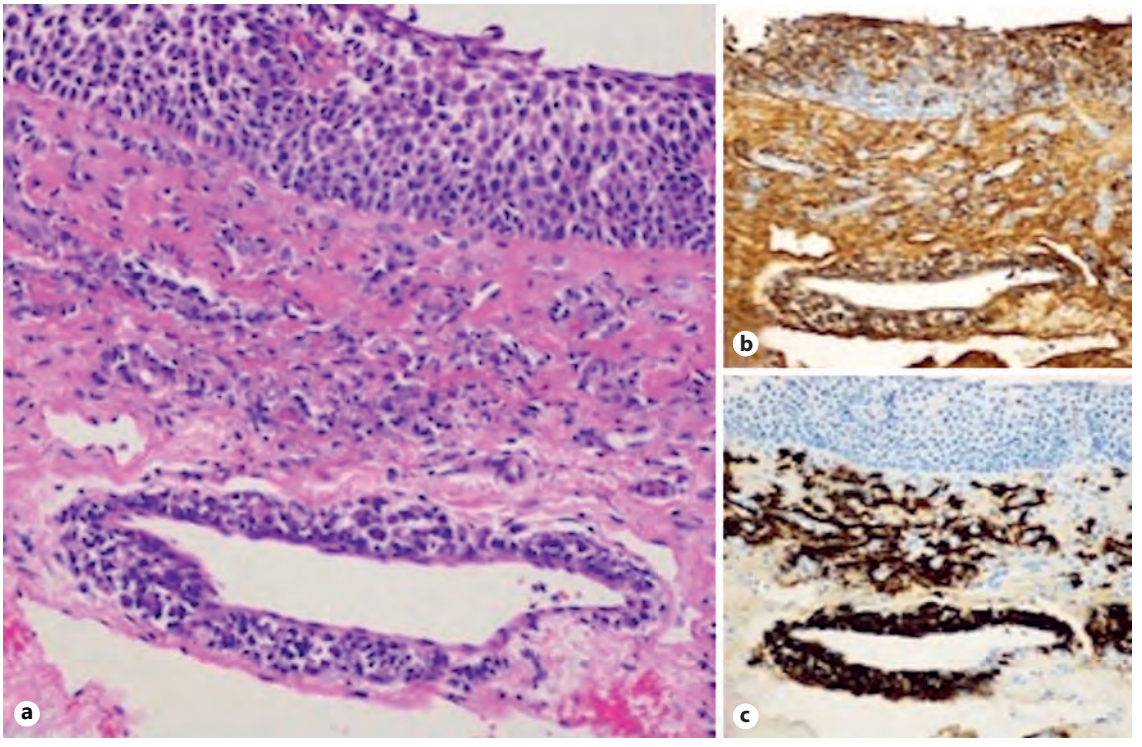


Fig. 1. a Esophageal biopsy showing a dense lymphoplasmacytic infiltrate with perivascular disposition and fibrosis. HE. ×200. Immunohistochemical staining with IgG (**b**, ×200) and IgG4 (**c**, ×200), with an IgG4/IgG ratio >40%.

intermittent passage of contrast to the stomach, but without extravasation or retention of contrast.

After full recovery, the patient was still symptomatic concerning dysphagia, and systemic corticoid therapy was proposed. However, the patient refused this medical option and decided to maintain the current status until her condition worsens.

Discussion

We report a 30-year-old woman with IgG4-related esophageal disease presenting as esophagitis with chronic strictures. Little is known about IgG4-RD-associated dysphagia.

In 2011, Lee et al. [4] described the first case of IgG4-related sclerosing esophagitis. Their patient had progressive dysphagia and weight loss, and the diagnosis was made by the histological study of the esophagectomy specimen.

The presentation of IgG4-RD is nonspecific because the symptoms depend on the affected organ. The reported symptoms of esophageal involvement include dysphagia, odynophagia, and weight loss. Endoscopy can reveal simple esophagitis, ulceration, stricture formation, submucosal tumors, or even evidence of malignancy. The duration from the 1st symptom to diagnosis ranges from 11 months to 10 years [1, 4, 5].

The microscopic diagnosis of IgG4-RD requires both the typical histological appearance and increased numbers of IgG4 plasma cells or an elevated IgG4/IgG ratio. The three major histopathological features are: dense lymphoplasmacytic infiltrate; fibrosis, at least focally with a storiform pattern; and obliterative phlebitis. As the last two features are difficult to access in biopsy specimens, and a reliable pathological diagnosis requires the presence of two of the three major histopathological features, the diagnosis rendered was of probability. Other two histopathological features are phlebitis without obliteration of the lumen, as seen in our case, and increased numbers of eosinophils. However, none of these findings, on their own, are either sensitive or specific for the diagnosis [6].

Corticosteroids are used as initial therapy for IgG4-related disease. Initial dosage of 0.6 mg/kg has been suggested in a 2012 Japanese consensus for treatment of symptomatic autoimmune pancreatitis, which included patients with symptomatic extra-pancreatic manifesta-

tions [7]. After 2–4 weeks, the dose is gradually tapered every 1–2 weeks until a maintenance dose of 2.5–5 mg of prednisolone is achieved. Corticosteroids can be stopped completely after a few months if the patient does not have residual active disease, but there is a high rate of relapse.

Immunomodulators such as azathioprine, methotrexate, and mycophenolate mofetil can be used as maintenance therapy and as a steroid-sparing strategy in patients refractory to or dependent on corticosteroid therapy. Rituximab, a monoclonal antibody directed at CD20 antigen on B-lymphocytes, has recently been used in a few patients with disease refractory to standard treatment [8, 9].

In the present case, we had no opportunity to ascertain whether oral corticosteroid therapy could result in resolution of symptoms due to patient refusal. However, it is noticeable that topical corticosteroids, unlike in most cases of eosinophilic esophagitis, do not allow reversal of the symptoms, perhaps due to the high fibrotic component involved [10]. It is also clear that repeated dilation is not a therapeutic option to be taken into account in these patients with high fibrotic component and friable mucosa because of the complications that may be associated with it.

There are only two cases described in the literature that have undergone endoscopic dilation (prior to treatment with corticosteroids), with no mention of complications associated with the procedure. Until now, this is the first reported case in which an endoscopic dilation was performed in an IgG4-RD patient with associated complications.

Complications include pulmonary aspiration, bleeding, perforation, risks of sedation, and chest pain; the last of these being more common in patients with eosinophilic esophagitis [11]. According to the currently available literature, factors associated with a higher risk of perforation include complex stricture, stricture from eosinophilic esophagitis, malignancy-associated stricture, radiation-induced stricture, and limited experience of the practitioner performing the endoscopic procedure [12]. Strictures can be simple or complex. Simple strictures are short (<2 cm), concentric, straight, and allow the passage of a normal diameter endoscope. Complex strictures are usually longer (≥2 cm), angulated, irregular or have a severely narrowed diameter. These are more difficult to treat and have a tendency to be refractory or to recur despite dilatation [11].

There is nothing in the literature saying that patients with IgG4-RD have a higher risk of complications when performing endoscopic dilation. However, due to diffuse mucosal friability and ulceration with fibrotic changes, often ending up in complex strictures, these patients may be more predisposed to complications associated with endoscopic dilations. Therefore, medical therapy should be the first line of treatment to reduce the need for multiple esophageal dilations which can carry associated risks.

In conclusion, although IgG4-related sclerosing disease rarely manifests in the esophagus, clinicians and pathologists should consider this condition in the differential diagnosis of unexplained esophagitis with strictures in order to avoid unwarranted esophagectomies and failed medical treatment due to lack of recognition of this rare entity.

Statement of Ethics

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no financial support.

Author Contributions

The authors contributed equally to the writing of this paper.

References

1 Dumas-Campagna M, Bouchard S, Soucy G, Bouin M. IgG4-related esophageal disease presenting as esophagitis dissecans superficialis with chronic strictures. J Clin Med Res. 2014 Aug;6(4):295–8.
2 Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, et al. A new clinicopathological entity of IgG4-related autoimmune disease. J Gastroenterol. 2003;38(10):982–4.
3 Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med. 2012 Feb;366(6):539–51.
4 Lee H, Joo M, Song TJ, Chang SH, Kim H, Kim YS, et al. IgG4-related sclerosing esophagitis: a case report. Gastrointest Endosc. 2011 Apr;73(4):834–7.
5 Lopes J, Hochwald SN, Lancia N, Dixon LR, Ben-David K. Autoimmune esophagitis: IgG4-related tumors of the esophagus. J Gastrointest Surg. 2010 Jun;14(6):1031–4.

6 Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol. 2012 Sep;25(9):1181–92.
7 Okazaki K, Kawa S, Kamisawa T, Shimosegawa T, Tanaka M; Research Committee for Intractable Pancreatic Disease and Japan Pancreas Society. Japanese consensus guidelines for management of autoimmune pancreatitis: I. Concept and diagnosis of autoimmune pancreatitis. J Gastroenterol. 2010 Mar;45(3):249–65.
8 Khosroshahi A, Carruthers MN, Deshpande V, Unizony S, Bloch DB, Stone JH. Rituximab for the treatment of IgG4-related disease: lessons from 10 consecutive patients. Medicine (Baltimore). 2012 Jan;91(1):57–66.
9 Khosroshahi A, Bloch DB, Deshpande V, Stone JH. Rituximab therapy leads to rapid decline of serum IgG4 levels and prompt clinical improvement in IgG4-related systemic disease. Arthritis Rheum. 2010 Jun;62(6):1755–62.
10 Gomez Torrijos E, Gonzalez-Mendiola R, Alvarado M, Avila R, Prieto-Garcia A, Valbuena T, et al. Eosinophilic esophagitis: review and update. Front Med (Lausanne). 2018 Oct;5:247.
11 Sami SS, Haboubi HN, Ang Y, Boger P, Bhandari P, de Caestecker J, et al. UK guidelines on oesophageal dilatation in clinical practice. Gut. 2018 Jun;67(6):1000–23.
12 Benites Goñi HE, Arcana López R, Bustamante Robles KY, Burgos García A, Cervera Caballero L, Vera Calderón A, et al. Factors associated with complications during endoscopic esophageal dilation. Rev Esp Enferm Dig. 2018 Jul;110(7):440–5.

GE – Portuguese Journal of Gastroenterology

Endoscopic Snapshot

GE Port J Gastroenterol 2023;30:73–75
DOI: 10.1159/000518000

Received: February 12, 2021
Accepted: May 5, 2021
Published online: August 24, 2021

Gastrointestinal Metastatic Melanoma: The Key for Diagnosis

Daniela Filipa Soares Santos Marta Costa Patrícia Carvalho Rui M. Santos Armando Carvalho

Internal Medicine, Centro Hospitalar e Universitário de Coimbra and University Clinic of Internal Medicine, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

Keywords
Melanoma · Gastric metastasis · Duodenal metastasis

Melanoma metastático gastrointestinal: a chave para o diagnóstico

Palavras Chave
Melanoma · Metástase gástrica · Metástase duodenal

An 80-year-old Caucasian woman was hospitalized with a 2-month course of intermittent fever (max. 38 °C), asthenia, weight loss (12%), anorexia and nausea. Her medical history includes breast cancer submitted to radical mastectomy and axillary lymph node dissection, papillary thyroid carcinoma and pulmonary and ocular tuberculosis that had been treated more than 5 years previously. She had heart failure, arterial hypertension, dyslipidaemia and obesity under treatment.

Physical examination showed obesity and left upper limb lymphedema. Abdominal and rectal examinations were unremarkable. A laboratory study revealed iron deficiency anaemia with haemoglobin 10 g/dL and ferritin 10 ng/mL (normal = 10–120 ng/mL), elevated lactate dehydrogenase 1,379 U/L (normal <247 U/L), aspartate transaminase 59 U/L (normal <31 U/L), alkaline phosphatase 185 U/L (normal = 30–120 U/L), C-reactive protein 21.9 mg/dL (normal = 0–0.5 mg/dL) and a normal procalcitonin value. A bacterial, mycobacterial, viral or fungal infectious disease was excluded by blood, urine and sputum cultures. A thoracic abdominal and pelvic computerized tomography (CT) scan was negative for malignant disease.

During hospital stay she presented with intense nausea and vomiting during most meals. A red blood cell transfusion was necessary due to progressive decrease in haemoglobin. Upper endoscopy was performed showing multiple black nodular lesions in the stomach and duodenum (Fig. 1). Narrow-band imaging revealed the presence of black patches on the top of these nodular lesions (Fig. 2). Histopathological examination showed an epithelioid malignant injury with intense and diffuse HMB45 expression suggestive of pigmented melanoma (Fig. 3). The diagnosis of gastrointestinal

karger@karger.com
www.karger.com/pjg

Correspondence to:
Daniela Filipa Soares Santos, danielafssantos@gmail.com

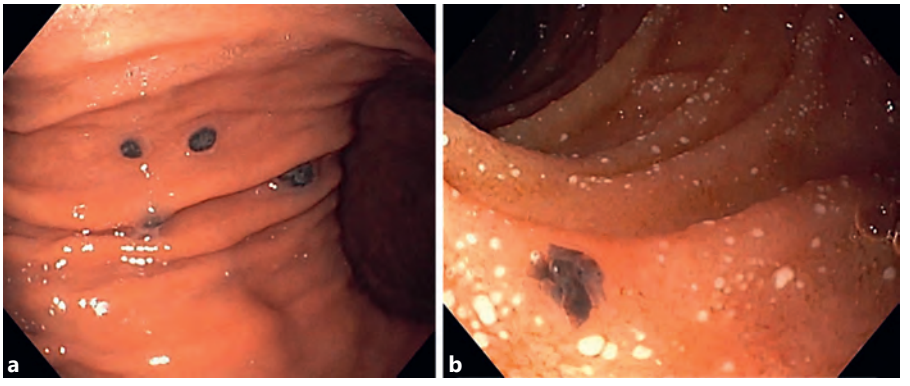


Fig. 1. a In gastric mucosa, multiple black nodular lesions were identified with white light. The two largest lesions of 5 mm were present on the distal body. These lesions were suggestive of melanoma metastasis. **b** Similar black nodular lesion of 3 mm on the duodenum.

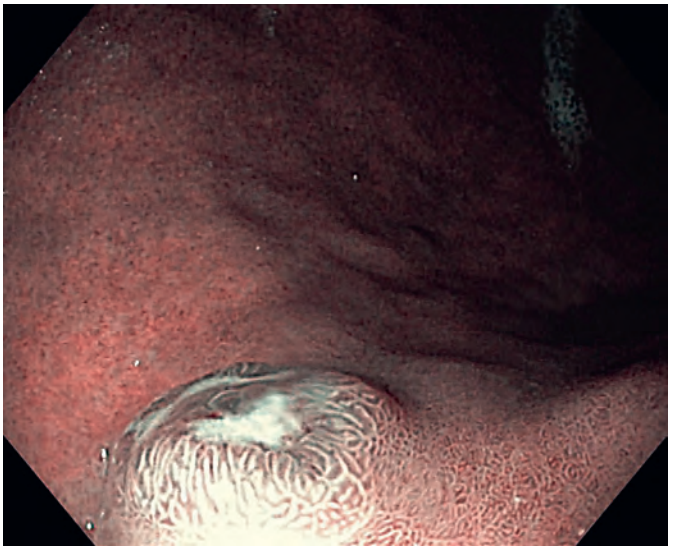


Fig. 2. Narrow-band imaging: black patches present on the summit of elevated lesions. The lesions' base showed an enlarged regularly placed oval and elongated pit pattern in contrast to a small pit pattern of the surrounding normal gastric mucosa.

metastatic melanoma was made. A positron emission tomography/CT scan revealed the presence of bone, cervical and mediastinal lymph node metastases. *BRAF* gene mutation was not present. The primary tumour was not found. Due to the patient's limited functional status no treatment was initiated, and death occurred 4 months after diagnosis.

We present a metastatic gastric melanoma in an elderly woman without any history of melanoma with a very rare presentation. Melanoma gastrointestinal metastases are rare and represent a late stage of malignant disease. Its incidence in clinical and autopsy series varies between 0.2 and 0.7%, and it has been reported that only 7% of gastric metastases are due to malignant melanoma [1]. Primary tumours commonly occur in the skin but can also develop from other tissues containing melanocytes such as the meninges, gastrointestinal tract and eyes. Primary or metastatic malignant melanoma of the gastrointestinal tract is an uncommon entity, and more than 90% of cases are identified only during autopsy. The most common gastrointestinal metastatic sites are the jejunum and ileum, followed by the colon, rectum and stomach [2]. The diagnosis is difficult due to non-specific symptoms. Symptoms are present in only 1–4% of patients, and they are related to complications such as haemorrhage, obstruction and perforation [3]. Imaging studies have low sensitivity for diagnosing, and CT sensitivity is only 60–70% in detecting metastases [4]. Gastrointestinal endoscopy allows the diagnosis [3]. Depending on the patient's functional status, treatment includes surgical resection, immunotherapy, targeted and radiation therapy. The average life expectancy following diagnosis is 4–6 months [5].

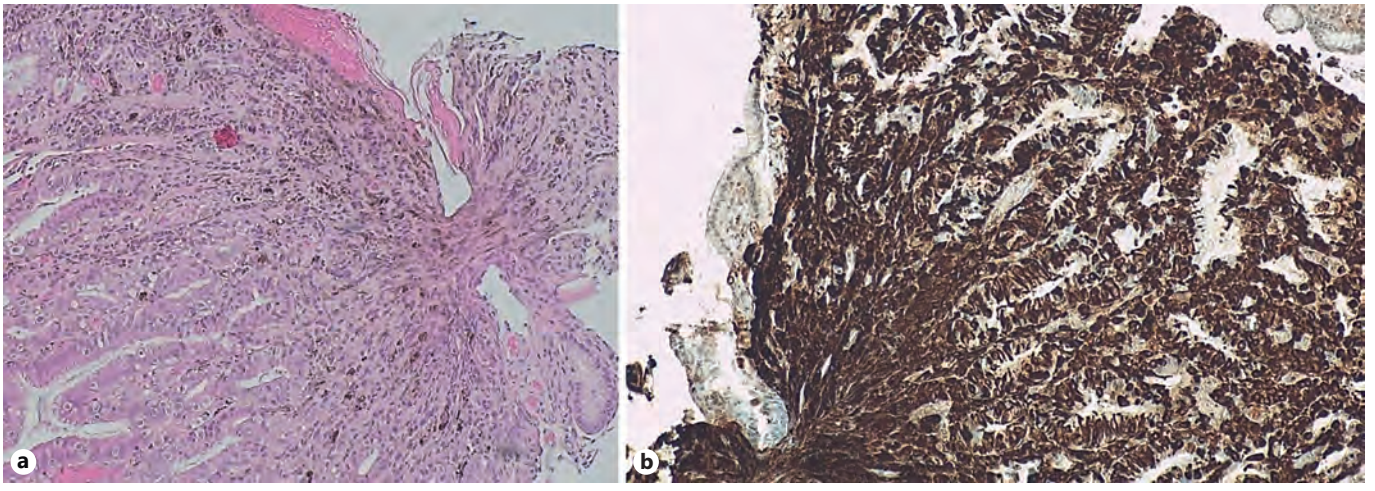


Fig. 3. a Lamina propria diffuse infiltration by epithelioid malignant neoplasia. Haematoxylin-eosin staining. ×40. **b** Tumoural cells show intense and diffuse expression for HMB45. HMB45. ×40.

Statement of Ethics

This study did not require review or approval by the appropriate ethics committee. Written informed consent was obtained from the patient's next of kin.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

None declared.

Author Contributions

Daniela Soares Santos drafted the manuscript. Marta Costa helped writing the manuscript. Patrícia Carvalho, Rui M. Santos and Armando Carvalho revised the manuscript critically. All authors commented on drafts of the paper. All authors approved the final draft of the article.

References

1 Kobayashi O, Murakami H, Yoshida T, Cho H, Yoshikawa T, Tsuburaya A, et al. Clinical diagnosis of metastatic gastric tumors: clinicopathologic findings and prognosis of nine patients in a single cancer center. World J Surg. 2004 Jun;28(6):548–51.

2 Dasgupta T, Brasfield R. Metastatic melanoma. A clinicopathological study. Cancer. 1964 Oct;17(10):1323–39.

3 Ercolino GR, Guglielmi G, Pazienza L, Urbano F, Palladino D, Simeone A. Gallbladder and small bowel metastasis of regressive melanoma: a case report. BJR Case Rep. 2018 Aug;5(1):20180032.

4 Wong K, Serafi SW, Bhatia AS, Ibarra I, Allen EA. Melanoma with gastric metastases. J Community Hosp Intern Med Perspect. 2016 Sep;6(4):31972.

5 Farshad S, Keeney S, Halalau A, Ghaith G. A case of gastric metastatic melanoma 15 years after the initial diagnosis of cutaneous melanoma. Case Rep Gastrointest Med. 2018 Jul;2018:7684964.

GE – Portuguese Journal of Gastroenterology

Endoscopic Snapshot

GE Port J Gastroenterol 2023;30:76–78
DOI: 10.1159/000519546

Received: May 7, 2021
Accepted: July 21, 2021
Published online: October 5, 2021

Band Ligation-Assisted Forceps Scissor Transection of a Unique Pedunculated Colorectal Lesion with Stalk Varices

Vincent Zimmer[a, b] Christoph Heinrich[c]

[a]Department of Medicine, Marienhausklinik St. Josef Kohlhof, Neunkirchen, Germany; [b]Department of Medicine II, Saarland University Medical Center, Saarland University Homburg, Homburg, Germany; [c]Institute of Pathology Saarbrücken-Rastpfuhl, Saarbrücken, Germany

Keywords
Ileocolonoscopy · Endoluminal resection · Band ligation · Colon polyp · Polypectomy · Advanced endoscopy

Exérese assistida por banda com pinça de tesoura de uma lesão pediculada colorretal única com varizes no pedículo

Palavras Chave
Ileocolonoscopia · Exérese endoluminal · Laqueação por banda · Pólipo do cólon · Polipectomia · Endoscopia avançada

An 81-year-old male patient presented for ileocolonoscopy for anemia workup. While smaller polypoid lesions in the remaining colon were resected without complications, an estimated 50-mm, complex pedunculated (Paris Ip) lesion with a unique multinodular, uneven surface was observed in the sigmoid (Fig. 1a). However, dedicated optical assessment of large areas of the lesion indicated adenoma-typical vessel and surface pattern, albeit full optical assessment of the large and floppy lesion was not feasible (EC760R-V/I; Fuji, Düsseldorf, Germany) (Fig. 1b). More intriguingly, the 25-mm-long and 10-mm-wide stalk demonstrated marked varices originating from adjacent flat sigmoid mucosa (Fig. 1c). Given concerns as to whether adequate placement of a snare and/or prophylactic loop would be feasible in consideration of the large head and markedly uneven surface, in this unique setting we opted for an individual approach, implementing stalk transection after endoscopic band ligation. To this end, we provided the insertion point at 35 cm with two rubber bands as per standard procedure (Fig. 1d, e). Alternatively, clip application at the stalk base might have been discussed for prophylactic hemostasis. However, this was decided against due to, among others, concerns for thermal injury. Cap-fitted gastroscope reinsertion exposed the edematous stalk with the ligations at 6 o'clock and the polyp head at 12 o'clock (Fig. 1f). Next, we completed an uncomplicated forceps scissor transection of the highly fibrotic stalk, using a scissor-type knife device, only at the first cut resulting in self-limited bleeding from ligated varices (Fig. 2a, b). Electrosurgical settings were as follows: transection (mucosa and submucosa): Endocut Q, effect 2, duration 3,

karger@karger.com
www.karger.com/pjg

Correspondence to:
Vincent Zimmer, vincent.zimmer@gmx.de

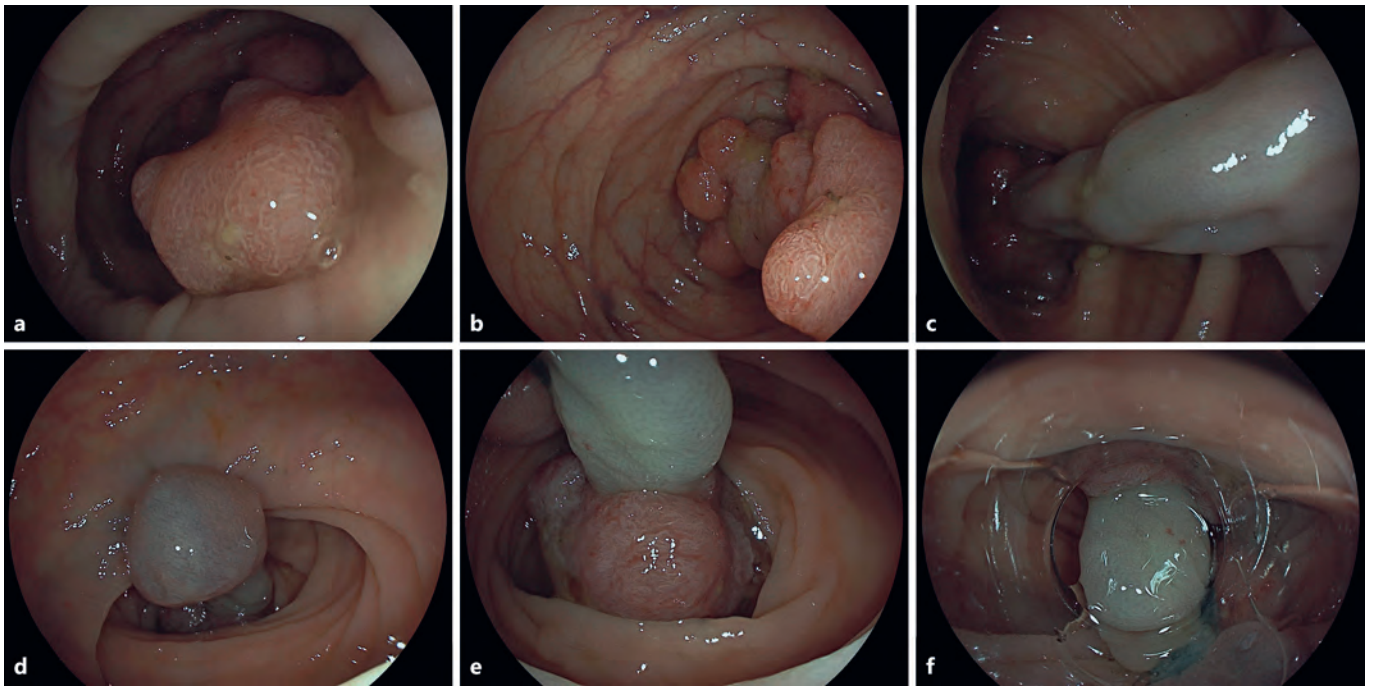


Fig. 1. a, **b** Endoscopic illustration of a large pedunculated Paris Ip lesion estimated at 50 mm in the sigmoid colon with an uneven, multinodular surface. Limited optical assessment suggested adenoma-typical regular surface and vessel pattern. **c** Of note, the estimated 25-mm stalk exhibited prominent stalk varices. **d**, **e** Visualization of the first anal side endoscopic band ligation (**d**) and the second one at upper left (**e**) (note marked traction-related stalk shortening). **f** Cap-fitted visualization of the operative situs with the two ligations at 6 o'clock and the polyp head at 12 o'clock.

interval 1; hemostasis (not needed): soft coagulation, effect 5, 100 W (VIO 200D; Erbe Elektromedizin, Tübingen, Germany) Postinterventional assessment of the resection site excluded hemorrhage with the two bands still in situ (Fig. 2c). The specimen was retrieved by a Roth net. Final pathology confirmed R0 resection of low-grade intraepithelial neoplasia (Fig. 2d).

While stalk transection of large pedunculated lesions has been well documented in the literature, a combinatorial approach involving band ligation of associated stalk varices is altogether novel [1, 2]. A literature review identified a similar case involving band ligation of adjacent cirrhosis-related varices in a unique patient undergoing rectal endoscopic submucosal dissection [3]. In addition, a recent pilot study has pioneered endoscopic band ligation of longer stalks combined with standard snare-based polypectomy [4]. In the absence of portal hypertension and more widespread dilated veins throughout the colon, stalk varices were considered to be directly related to the giant head of this pedunculated lesion.

Statement of Ethics

The patient provided written informed consent for publication (including publication of images).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This work received no funding.

Author Contributions

V. Zimmer: clinical care, drafting and finalization of the manuscript. C. Heinrich: pathology care, revision and final approval of the manuscript.

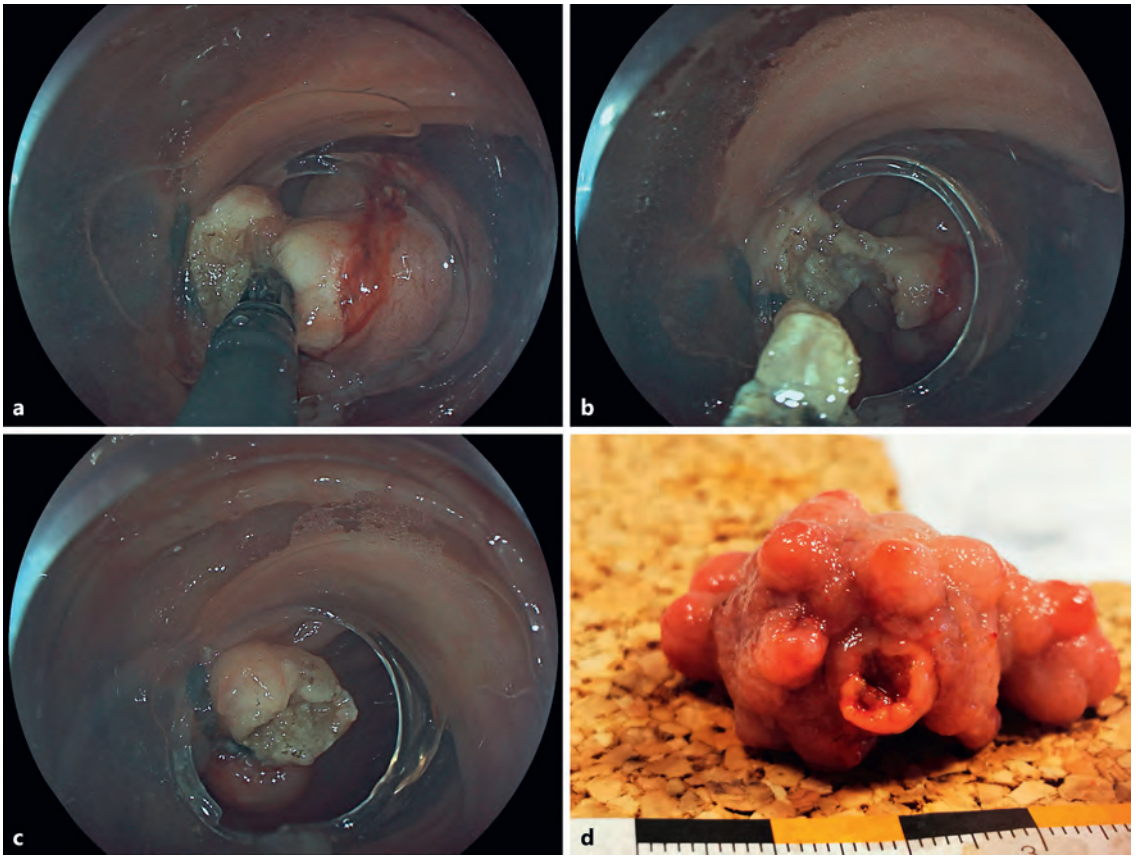


Fig. 2. a Stalk transection using a scissor-type knife (3.5-mm ClutchCutter, Fuji) utilizing an 18.1-mm large-diameter oblique transparent cap (D-206-5; Olympus, Hamburg, Germany) for improved intracap device rotation. **b** Progression of transection prior to the final cut; note lack of hemorrhage during the procedure. **c** Final endoscopic result with the two ligations still in situ and lack of bleeding. **d** Ex vivo representation of the specimen after Roth net retrieval.

References

1 Gravito-Soares E, Gravito-Soares M, Fraga J, Figueiredo P. Large pedunculated lipoma of the colon: endoscopic resection using "loop-and-let-go" technique. GE Port J Gastroenterol. 2018 Sep;25(5):268–70.

2 Miwa T, Ibuka T, Ozawa N, Sugiyama T, Kubota M, Imai K, et al. Idiopathic ileocolonic varices coexisting with a colon polyp treated successfully by endoscopy: a case report and literature review. Intern Med. 2019 Dec;58(23):3401–7.

3 Rodrigues J, Barreiro P, Herculano R, Carvalho L, Marques S, Chagas C. Endoscopic submucosal dissection for curative resection of a superficial rectal lesion over a varix in a patient with cirrhosis. Endoscopy. 2015;47(Suppl 1):E633–4.

4 Choi HH, Kim CW, Kim HK, Kim SW, Han SW, Seo KJ, et al. A novel technique using endoscopic band ligation for removal of long-stalked (>10 mm) pedunculated colon polyps: a prospective pilot study. Saudi J Gastroenterol. 2021 doi: 10.4103/sjg.sjg_625_20. Online ahead of print.

GE – Portuguese Journal of Gastroenterology

Images in Gastroenterology and Hepatology

GE Port J Gastroenterol 2023;30:79–81
DOI: 10.1159/000520211

Received: March 2, 2021
Accepted: April 21, 2021
Published online: December 6, 2021

Gastric Metastatic Melanoma Mimicking a Hyperplastic Lesion

Cláudia Martins Marques Pinto[a] Marta Rodriguez[a] Madalena Souto Moura[b] Mariana Afonso[b] Pedro Bastos[a] Mário Dinis Ribeiro[a, c]

[a]Gastroenterology Department, Portuguese Oncology Institute of Porto, Porto, Portugal; [b]Pathology Department, Portuguese Oncology Institute of Porto, Porto, Portugal; [c]MEDCIDS, Faculty of Medicine, University of Porto, Porto, Portugal

Keywords
Endoscopy · Gastric lesion · Metastasis

Metástase gástrica de melanoma a mimetizar lesão hiperplásica

Palavras Chave
Endoscopia · Lesão gástrica · Metástase

A 56-year-old woman was submitted to an upper gastrointestinal endoscopy due to a recent history of epigastric pain. Endoscopic examination revealed a 20-mm 0-IIa type lesion in the great curvature of the proximal corpus with a hyperplastic appearance and a dark coloration area in one of the edges (Fig. 1, 2). Biopsy of the lesion was suggestive of mesenchymal proliferation and some cells with moderate cytologic atypia. The patient was then referred to our Endoscopy Department to undergo endoscopic resection. Due to the previous histological result, we decided to perform an endoscopic ultrasonography that showed thickening of the superficial layers of the mucosa. Endoscopic biopsies were repeated, and pathological evaluation revealed diffuse involvement of the lamina propria by a malignant neoplasm, composed of cells with nuclear pleomorphism and high mitotic rate, entrapping benign gastric glands. Immunohistochemistry showed diffuse positivity for melanocytic markers (PS100, SOX10 and MelanA) and negativity for cytokeratins, DOG-1 and CD45 (Fig. 3, 4). Given the clinical history of a malignant melanoma of the third left hand finger submitted to amputation 5 years before, a diagnosis of gastric metastasis of malignant melanoma was made. Thoraco-abdomino-pelvic computed tomography and PET scan showed no other metastasis. After multidisciplinary discussion, total gastrectomy was proposed to the patient given the location of the lesion (proximal corpus). During surgery, it was decided to perform an atypical gastrectomy following endoscopic tattoo. The histological specimen confirmed the diagnosis of malignant melanoma with free surgical margins. The patient is currently under clinical and imagiological (PET scan) surveillance.

Malignant melanoma is a frequent source of metastases in the gastrointestinal tract [1]. The most frequent location is the small bowel followed by the colon and rectum; gastric metastases are rare [1, 2]. Metastatic disease is usually diagnosed within the first 3 years, but metasta-

karger@karger.com
www.karger.com/pjg

Correspondence to:
Cláudia Martins Marques Pinto, claudia.marquespinto@gmail.com

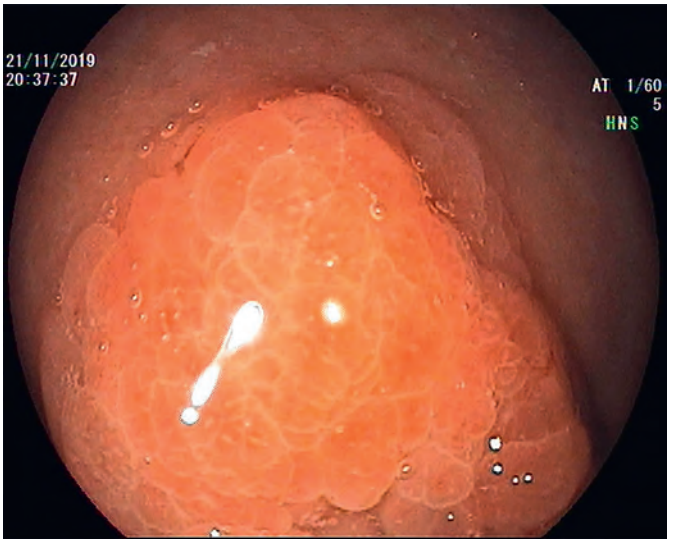


Fig. 1. Endoscopic image of a gastric lesion 0-IIa with hyperplastic appearance of the mucosa.

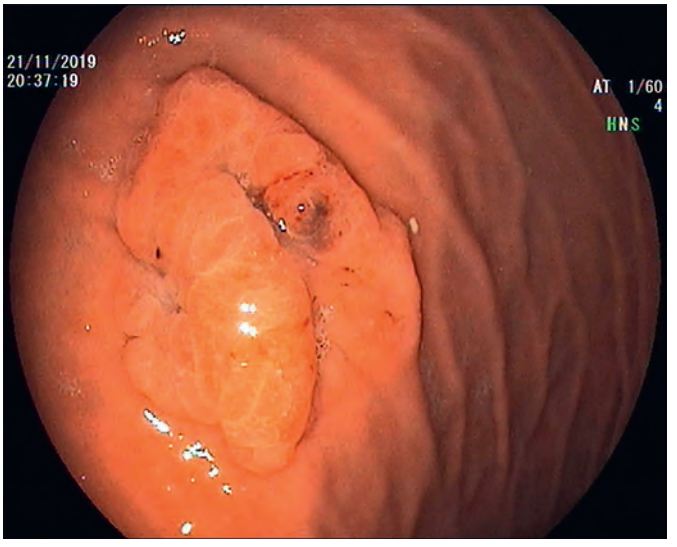


Fig. 2. Endoscopic image of the lesion with a dark coloration area of 5 mm in one of the edges.

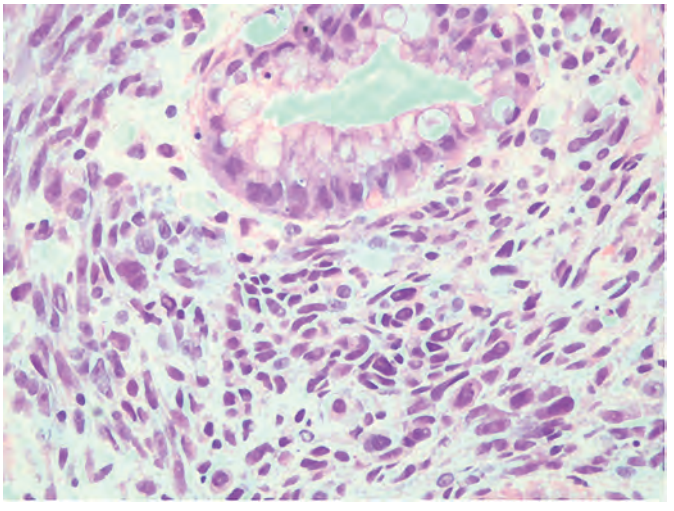


Fig. 3. Gastric body mucosa with normal epithelial cells and a diffuse infiltration of the lamina propria by sheets of malignant neoplastic cells. HE staining, ×40.

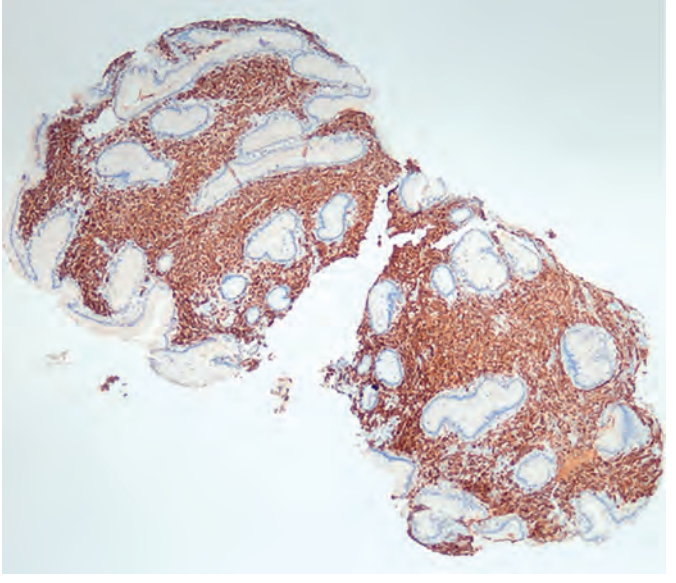


Fig. 4. Diffuse positivity for MelanA and PS100.

ses after 15 years have also been reported [3]. Lesions mimicking submucosal or primary gastric ulcerated tumours are the most frequent presentation, although endoscopic findings are variable [2, 4].

It is important to keep in mind the different possible endoscopic appearances of metastatic lesions to avoid further delay in diagnosis and treatment. Immunohistochemistry is an imperative tool for making a correct diagnosis in these circumstances.

Statement of Ethics

Patient consent was obtained for publication of the case (including publication of images).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have no funding source to declare.

Author Contributions

C.M.M. Pinto wrote the manuscript. M. Rodriguez, M. Souto Moura, M. Afonso, P. Bastos and M. Dinis-Ribeiro wrote and revised the manuscript. M. Souto Moura and M. Afonso collected the pathology images. All authors approved the final version. C. Pinto is the article guarantor.

References

1 Blecker D, Abraham S, Furth EE, Kochman ML. Melanoma in the gastrointestinal tract. Am J Gastroenterol. 1999 Dec;94(12):3427–33.
2 El-Sourani N, Troja A, Raab HR, Antolovic D. Gastric Metastasis of Malignant Melanoma: Report of a Case and Review of Available Literature. Viszeralmedizin. 2014 Aug;30(4):273–5.
3 Farshad S, Keeney S, Halalau A, Ghaith G. A Case of Gastric Metastatic Melanoma 15 Years after the Initial Diagnosis of Cutaneous Melanoma. Case Rep Gastrointest Med. 2018 Jul;2018:7684964.
4 Rastrelli M, Tropea S, Rossi CR, Alaibac M. Melanoma: epidemiology, risk factors, pathogenesis, diagnosis and classification. In Vivo. 2014 Nov-Dec;28(6):1005–11.