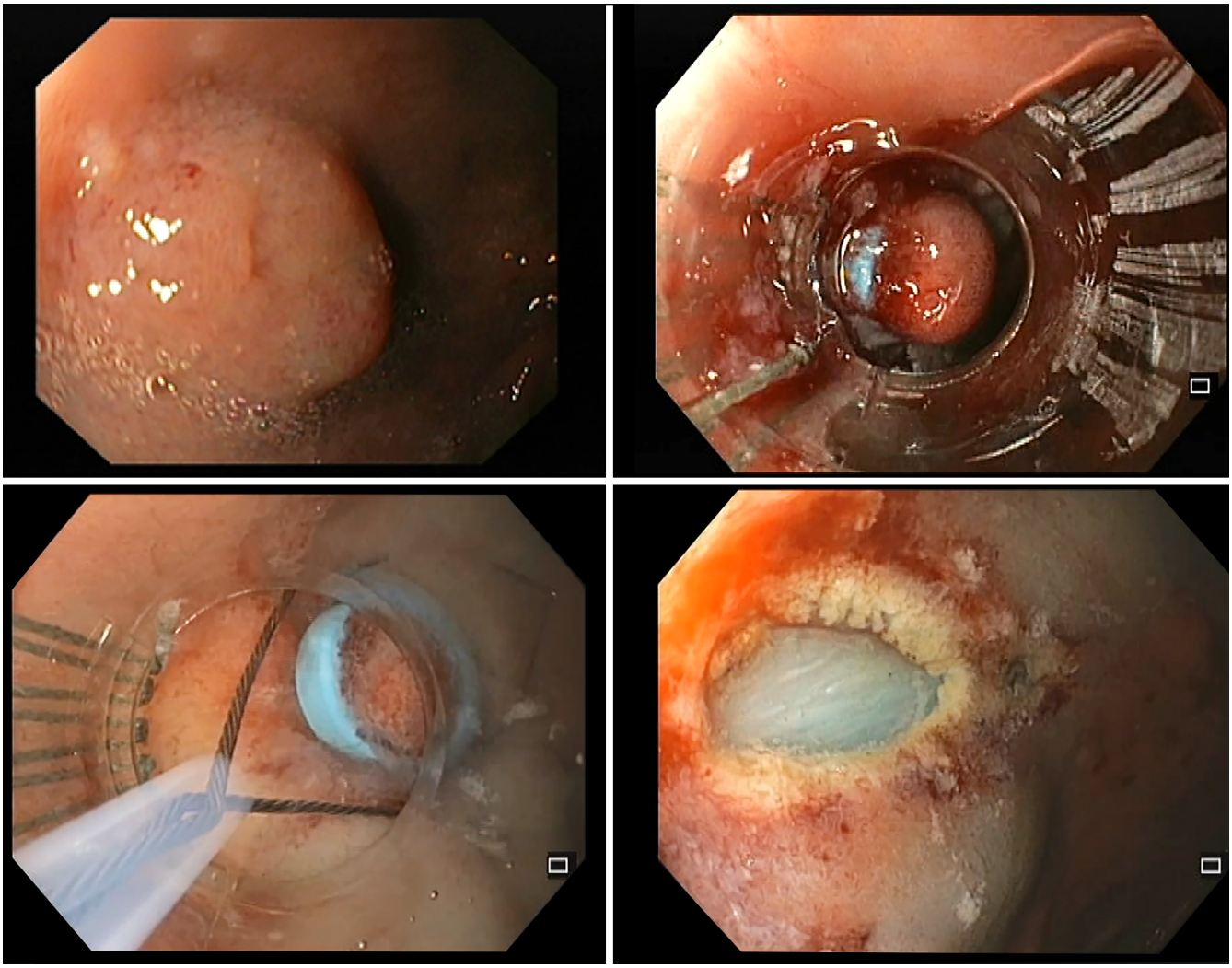
Portuguese Journal of Gastroenterology

31 | 4 | 24



Highlights in this issue:

Review article: Portuguese Pancreatic Club Perspectives on Endoscopic Ultrasound-Guided and Surgical Treatment of Pancreatic Neuroendocrine Tumors

Research article: Predictors of Outcomes in Gastric Neuroendocrine Tumors

Research article: The Journey of Patients with Metastatic Pancreatic Cancer – A Nationwide Survey

A Partner Publication by Karger

RESEARCH | OPEN ACCESS | Gastroenterology

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
ERC-No.: 117866
Editor address: Rua Abranches Ferrão, nº 10–14º, PT–1600-001 Lisbon (Portugal)

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 31 with 6 issues appears in 2024.

Karger

© 2024 S. Karger AG, Basel
www.karger.com
karger@karger.com

GE – Portuguese Journal of Gastroenterology

Vol. 31, No. 4, 2024

Contents

Cover illustration
Duodenal neuroendocrine tumor submitted to modified endoscopic mucosal resection (injection and band assisted) From Garrido et.al., pp. 296-298

Karger

GE – Portuguese Journal of Gastroenterology

Endoscopic Snapshots

Karger

GE – Portuguese Journal of Gastroenterology

Review Article

GE Port J Gastroenterol 2024;31:225–235
DOI: 10.1159/000534032

Received: June 2, 2023
Accepted: August 11, 2023
Published online: October 30, 2023

Portuguese Pancreatic Club Perspectives on Endoscopic Ultrasound-Guided and Surgical Treatment of Pancreatic Neuroendocrine Tumors

Tiago Ribeiro[a, b] Sara Castanheira-Rodrigues[c] Pedro Bastos[d]
Humberto Cristino[c] Alexandra Fernandes[e] Eduardo Rodrigues-Pinto[a, b]
Miguel Bispo[f] Ricardo Rio-Tinto[f] Filipe Vilas-Boas[a, b]

[a]Department of Gastroenterology, Centro Hospitalar Universitário de São João, Porto, Portugal; [b]Faculty of Medicine of the University of Porto, Porto, Portugal; [c]Department of General Surgery, Centro Hospitalar Universitário de São João, Porto, Portugal; [d]Department of Gastroenterology, Instituto Português de Oncologia do Porto, Porto, Portugal; [e]Gastroenterology Department, Centro Hospitalar de Leiria, Leiria, Portugal; [f]Digestive Oncology Unit, Gastroenterology Department, Champalimaud Foundation, Lisbon, Portugal

Keywords
Pancreatic neuroendocrine tumors · Endoscopic ultrasound · Tumor ablation · Radiofrequency · Surgery · Pancreatoduodenectomy

Abstract
Pancreatic neuroendocrine tumors (panNETs) are a group of neoplasms with heterogenous biological and clinical phenotypes. Although historically regarded as rare, the incidence of these tumors has been increasing, mostly owing to improvements in the detection of small, asymptomatic tumors with imaging. The heterogeneity of these lesions creates significant challenges regarding diagnosis, staging, and treatment. Endoscopic ultrasound (EUS) has improved the characterization of pancreatic lesions. Furthermore, EUS nowadays has evolved from a purely diagnostic modality to allow the performance of minimally invasive locoregional therapy for pancreatic focal lesions. The choice of treatment as well as the treatment goals depend on several factors, including tumor secretory status, grading, staging, and patient performance status. Surgery has been the mainstay for the management of these patients, particularly for localized, low-grade, large panNETs >2 cm. Over the last decade, a significant body of evidence has been accumulated evaluating the role of EUS for the ablative therapy of panNETs, namely by the use of chemoablative agents and radiofrequency. Although endoscopic techniques are not routinely recommended by international guidelines, they may be considered for the treatment of smaller lesions in patients who are unwilling or unfit for pancreatic surgery. In this review, we summarize the existing evidence on the interventional techniques for the treatment of patients with panNETs, focusing on the EUS-guided and surgical approaches.

Tiago Ribeiro and Sara Castanheira-Rodrigues contributed equally to this work.

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

Correspondence to:
Tiago Ribeiro, tiagofcribeiro@outlook.com

Perspetivas do Clube Português do Pâncreas sobre Terapêutica Guiada por Ecoendoscopia e Terapêutica Cirúrgica dos Tumores Neuroendócrinos do Pâncreas

Palavras Chave
Tumores neuroendócrinos do pâncreas · Ultrassonografia endoscópica · Ablação tumoral · Radiofrequência · Duodenopancreatectomia cefálica

Resumo
Os tumores neuroendócrinos do pâncreas (panNETs) são um grupo de neoplasias com comportamento biológico e clínico heterogéneo. Embora historicamente considerados raros, a incidência desses tumores tem aumentado, algo que se atribui principalmente à melhoria na deteção de pequenos tumores assintomáticos em exames de imagem. A heterogeneidade destas lesões cria desafios significativos no que respeita ao seu diagnóstico, estadiamento e tratamento. A ultrassonografia endoscópica melhorou a caracterização das lesões pancreáticas. Concomitantemente, a ultrassonografia endoscópica, para além da vertente diagnóstica, evoluiu no sentido do desenvolvimento de capacidades terapêuticas, permitindo a realização de terapêutica locorregional de lesões pancreáticas focais de forma minimamente invasiva. A seleção do tratamento, bem como a definição dos seus objetivos, depende de diversos fatores, incluindo a atividade secretora da neoplasia, a sua atividade mitótica, o estadiamento e o *status* funcional do doente. A cirurgia é considerada a pedra basilar do tratamento destes doentes, particularmente para panNETs localizados, de baixo grau, com >2 cm. Ao longo da última década foi gerado um conjunto significativo de evidência relativamente ao papel da ultrassonografia endoscópica na terapêutica ablativa dos panNETs, nomeadamente através da utilização de agentes quimioablativos e de radiofrequência. Embora as recomendações internacionais não recomendem a utilização rotineira destas técnicas para o tratamento dos panNETs, as mesmas podem ser consideradas no tratamento de lesões de menores dimensões em doentes que não desejem ou que sejam considerados inaptos para cirurgia pancreática. Esta revisão visa resumir a evidência existente relativa às técnicas de intervenção para o tratamento de pacientes com panNETs, com foco nas abordagens cirúrgica e guiada por ultrassonografia endoscópica.

Introduction

Pancreatic neuroendocrine tumors (panNETs) comprise a heterogenous group of neoplasms with distinct clinicopathological features and long-term prognosis, originating from the islet of Langerhans. PanNETs have been historically regarded as rare, but the reported prevalence in autopsy series (0.8–10%) is much higher than in population-based studies [1, 2]. It is likely that many individuals are affected by small and asymptomatic panNETs that will remain clinically silent for their entire lives [2]. The incidence of these lesions has increased substantially over the recent years, which can be ascribed to the widespread use of abdominal cross-sectional imaging and the increased detection of incidental findings [3]. The earlier diagnosis provided by these diagnostic techniques has been reflected on an increasing overall survival over time [4].

Clinically, panNETs are classified as functional (F-panNETs) or non-functional (NF-panNETs) according to whether they secrete hormones or not. NF-panNETs represent up to 90% of all lesions [5]. Endoscopic ultrasound (EUS) plays a major role in the characterization of these lesions, combining high-resolution morphologic evaluation with the possibility of tissue acquisition. Surgery is the standard of care for otherwise healthy subjects with larger lesions (>2 cm) or symptoms due to hormone secretion. However, the management of incidentally detected, smaller lesions (<2 cm) remains controversial [6]. EUS-guided therapy, most frequently by radiofrequency ablation (RFA) or ethanol ablation (EA), has emerged as an alternative to surgery in patients with localized disease [7]. This review summarizes the most relevant data regarding interventional therapy for panNETs, namely EUS-guided ablation techniques and surgical resection, providing a clinically oriented insight into the indications and contraindications for each approach, technical specificities, effectiveness, and safety.

Surgical Treatment of PanNETs

The surgical treatment of panNETs has evolved significantly over the last decades. A better comprehension of the biologic behavior and natural history has recently driven to reconsider surgical resection criteria.

Due to the considerable heterogeneity of these lesions, establishing a standard surgical strategy is difficult. It is essential to identify the primary tumor, determine disease extension, and evaluate for resectability. Tumor grading

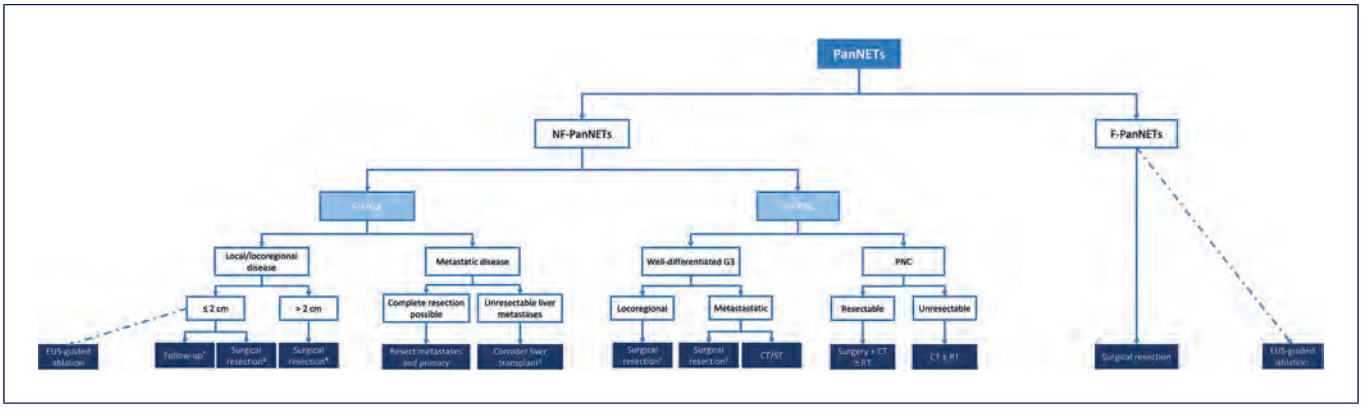


Fig. 1. Framework of the treatment of panNETs according to grading and staging. CT, chemotherapy; EUS, endoscopic ultrasound; panNETs, pancreatic neuroendocrine tumors; F-panNETs, functioning pancreatic neuroendocrine tumors; NF-panNETs, non-functioning pancreatic neuroendocrine tumors; PNC, pancreatic neuroendocrine carcinoma; RT, radiotherapy; ST, systemic therapy. *Surveillance may be the preferred option for elderly patients or with significant comorbidities. #Parenchyma-sparing surgery or standard resection ± lymphadenectomy. Consider in younger patients without significant comorbidities or in the presence of signs of local invasiveness, including main pancreatic duct dilation, jaundice, or suspected lymph node involvement. ¶Head: PD + lymphadenectomy; distal lesions: distal resection + splenectomy + lymphadenectomy. §Evaluate: absence of extrahepatic disease, histologic confirmation of a well-differentiated panNET (G1/G2, Ki-67 <10%), previous resection of the primary tumor, diffuse liver metastasis involving <50% of total liver volume, stable disease in response to therapy for at least 6 months and age <60 years old. †Resection + lymphadenectomy. Consider neoadjuvant therapy if unfavorable biology (e.g., Ki-67 >55%). ‡Primary + metastases resection.

and staging are the most important independent prognostic factors to be determined before surgery [8]. Figure 1 summarizes the approach to panNETs according to staging and grading of the disease.

The benefit from surgery must be balanced against potential post-operative morbidity, mortality, and impact on the functional status after pancreatic resection. Whenever feasible, a minimally invasive surgical approach is recommended, and patients should be referred to experienced surgeons in high-volume centers.

Low and Intermediate (G1/G2) PanNETs

Local/Locoregional Disease

Surgical resection is the treatment of choice for local/locoregional disease in panNETs G1/G2. Preoperative evaluation should account for tumor size and location, endocrine functional activity, signs of local invasiveness, and the presence of symptoms [9].

The goal of the surgical treatment of F-panNETs, irrespective of tumor size, should be to provide symptomatic control over the associated clinical syndrome, which can be significant even for small tumors. The symptoms resulting from hormone secretion should be controlled before any intervention [9]. The ultimate goal when resecting F-panNETs is to control the endocrine syndrome and treat the tumor to improve the patients' overall survival [10].

Curative resection of localized F-panNETs is generally associated with improved long-term survival and a low recurrence risk [11]. Long-term cure rates after R0-resection in localized disease depend on tumor type. For instance, resection of a localized insulinoma results in a 98% biochemical cure rate, with a 6% recurrence rate at 10 years. For sporadic gastrinoma, 60% achieve biochemical response after resection, and 30–40% have disease-free survival at 5 years [12]. For NF-panNETs, surgery should be considered in G1–G3 tumors if symptomatic, larger than 2 cm in size, and/or with atypical features, including irregular margins, heterogeneous echotexture in EUS, and upstream dilatation of the main pancreatic duct [6, 9, 13].

Small NF-panNETs (<1 cm) are often biologically indolent and remain quiescent with time. As such, clinical surveillance is reasonable for patients with asymptomatic NF-panNETs <1 cm [10]. Nevertheless, the decision on whether asymptomatic 1–2 cm NF-panNETs should be resected or kept under surveillance is not consensual, and a case-by-case decision is recommended, acknowledging the patient's functional status, comorbidities, tumor's grade, location and growth, risk of developing symptoms, extent of surgical resection, and patient's preferences [10]. The evolution of EUS-guided local ablative therapies has provided a minimally-invasive alternative to surgery for the management of low-grade, small (<2 cm) panNETs.

Currently, for incidentally discovered NF-panNETs <2 cm, surveillance is the preferred option for elderly patients with significant comorbidities and when a pancreaticoduodenectomy is required [9]. On the contrary, surgery should be proposed to younger patients without significant comorbidities or in the presence of signs of local invasiveness, including main pancreatic duct dilation, jaundice, or suspected lymph node involvement [10, 14]. If such signs are present, a standard pancreatectomy with lymphadenectomy is mandatory. A parenchyma-sparing resection can be routinely considered in patients with a long life expectancy [9]. Notwithstanding, considering the potential for morbidity, mortality, and pancreatic insufficiency after resection and the low risk of malignancy, surveillance might be a reasonable strategy for NF-panNETs <2 cm with a low proliferation index, defined as Ki-67 index <5% in EUS-guided biopsy samples (preferably acquired using an end-cutting type FNB needle) [14, 15].

For NF-panNETs >2 cm, surgical resection is recommended [10]. Either standard resection or parenchyma-sparing surgery might be considered appropriate, with or without regional lymph node removal, based on preoperative staging. NF-panNETs >2 cm are at increased risk of nodal metastasis, and some authors recommend that a standard pancreatectomy with regional lymphadenectomy be performed [9].

Advanced/Metastatic Disease

The major cause of death in patients with neuroendocrine tumors is liver failure from diffuse hepatic metastases, which is particularly frequent for panNETs. Extrahepatic disease rarely leads to a patient's death, so its presence should not contraindicate primary tumor resection and/or hepatic cytoreductive surgery [10]. Patients with metastatic disease may still have a favorable survival outcome after cytoreductive surgery [10].

The decision to resect a primary panNET in the setting of metastatic disease should be made on an individual basis, accounting for age and comorbidities, tumor functional status, location, intention to treat or potential local complications from the tumor, and the possibility to improve the response to medical therapy [10]. In fact, F-panNETs might derive more benefit, and lesions located in the tail and body of the pancreas are more favorable to resection than those in the head due to lower surgical morbidity from distal pancreatectomy compared with pancreatoduodenectomy (PD). Despite not being consensual, most experts are in favor that primary tumor resection may be beneficial in selected cases of metastatic disease [10].

Recent studies report that in panNETs, lymph node status and the number of nodes resected may have prognostic value, with a potential impact on reducing persistent disease and improving survival [6]. In the case of metastatic disease, patients with F-panNETs with a high tumor burden may benefit from cytoreductive surgery. On the other hand, the need for palliative resection in NF-panNETs is debatable, as the risk of tumor-related symptoms is low (and it is not considered in tumors with Ki-67 >10%). Nevertheless, recent evidence from retrospective series suggests that primary tumor resection can be associated with better long-term outcomes [16]. As such, for tumors with proven lymph node metastases, surgery can be recommended.

In cases of G1/G2 panNETs with liver metastasis, a favorable response with survival benefit might derive from hepatic cytoreductive surgery. Timing for recurrence or tumor progression after hepatic cytoreductive surgery has been reported to vary between 11 months and more than 3 years, depending on tumor burden, surveillance schedule, and imaging modality [10]. However, the timing of surgical cytoreduction remains debatable. Currently, no data exist favoring an observation period prior to cytoreduction surgery to allow for new metastases to develop, and both surveillance and immediate surgery (as soon as metastases become evident) are acceptable options [10].

Poorly Differentiated High-Grade Pancreatic Neuroendocrine Carcinoma

In localized poorly differentiated (always considered high-grade – G3, Ki-67 >20%) pancreatic neuroendocrine carcinoma, the role of surgical resection remains controversial as it may not have clear survival benefits as an initial approach [17]. The presence of high-risk features (large tumor size and/or high-grade poorly differentiated tumor) should discourage an upfront surgical approach. For these patients, despite the lack of evidence, neoadjuvant treatment may be considered. Nevertheless, in selected cases of resectable disease, a radical surgery followed by adjuvant chemotherapy (CT) with or without radiotherapy can be performed.

For locoregional non-resectable disease, patients should undergo neoadjuvant locoregional chemoradiation therapy. A combination of platinum-based CT with local treatment consisting of radiotherapy and/or surgery probably offers the greatest likelihood of long-term survival [10].

For patients with distant metastases or advanced non-resectable disease, CT is the preferred treatment option, provided the patient has adequate organ function and performance status [18]. Radiotherapy might be considered for lesions in selected locations, such as for brain and bone metastases, to provide symptom control. Debulking or surgical resection of metastasis is not recommended.

Well-differentiated G3 panNETs, if localized, should be evaluated for resection, in the setting of a multimodal therapeutic strategy [10]. Curative surgery is usually attempted in these cases, although retrospective series indicate that it is rarely curative as a single modality [19]. In patients with hepatic metastases, cytoreductive surgery may not be advisable due to high recurrence rates and poor survival. Thus, in this setting, CT should be considered a first line. Further studies are needed to clarify whether patients with G3 panNETs and lower Ki-67 (21–55%) may benefit from a more aggressive surgical approach [10]. Some authors propose neoadjuvant CT followed by definitive surgery, although data are scarce [20]. Most patients with pancreatic neuroendocrine carcinoma have significant extrahepatic disease or non-resectable liver metastasis (or not suitable for complete resection), thus having no benefit from undergoing surgery, owing their poor survival [10, 13].

Syndromic PanNETs

Hereditary syndromes often occur with multiple panNETs, which poses complex challenges. The goal should be the removal of the dominant lesion and, potentially, other easily accessible lesions. This should be counterbalanced with the need to preserve as much pancreatic tissue and function as possible. It should be considered to intervene prior to malignant progression while minimizing surgery-related morbidity and mortality [21].

Individual factors, such as comorbidities and the potential need for multiple surgeries to treat multifocal or metachronous tumors, should be considered when choosing optimal surgical timing and extension. Broad principles for the management include the performance of parenchyma-sparing procedures, watchful surveillance for low-risk tumors, enucleation or minimal pancreatic resection for intermediate-risk tumors (when feasible and effective), and major resections reserved for locally invasive, anatomically difficult, or high-risk lesions [10].

Which Surgery Should Be Performed for PanNETs?

Oncological outcomes for panNETs patients are widely heterogeneous depending on factors such as tumor grading, size, and staging. A recent meta-analysis reported a 5-year disease-free survival >90% in resected patients without synchronous liver metastasis [11]. If liver metastases are present and a R0-resection is performed, overall 5-year survival can be up to 85% [11].

However, despite excellent overall survival, tumor recurrences after surgery are frequent. After a R0-resection, cumulative recurrence incidence reaches 27% at 3 years and 40% at 5 years [22]. When surgery is considered, two strategies can be discussed: standard resection, with standard lymphadenectomy, and parenchyma-sparing surgery, possibly with lymph node sampling.

Standard Resection

Standard resection, distal pancreatectomy, or PD should be performed for panNETs at risk of nodal involvement or if signs of local invasion are present. It is recommended in cases of NF-panNETs >2 cm and F-panNETs other than insulinoma [13]. Regional lymphadenectomy is mandatory since lymph node involvement has significant prognostic implications. Removal of 11–15 lymph nodes should be performed for accurate nodal staging [23].

For left-sided tumors, depending on their anatomical relation with the splenic hilum and vessels, spleen-preserving distal pancreatectomy can be considered for small, presumably benign panNETs [24]. However, for large tumors or tumors invading the splenic vein and/or surrounding structures, splenic preservation is hardly possible [25].

Regarding short-term outcomes, minimally invasive distal pancreatectomy is the preferred approach to tumors confined to the distal pancreas, with no local invasion and <8 cm in size [25]. A recent meta-analysis estimated the median prevalence of exocrine pancreatic insufficiency at 22% after standard resection, most commonly after PD (median prevalence of 43%) [26]. Endocrine insufficiency, despite being less common, still affects 20% of patients submitted to standard pancreatectomy [27].

Parenchyma-Sparing Surgery

Parenchyma-sparing surgery, such as enucleation and central pancreatectomy, is seen as an alternative for small, low-grade tumors and might be an option for NF-panNETs <2 cm and insulinomas [13, 28]. Despite significant postoperative morbidity, these procedures achieve a recurrence-free 5-year survival of >95% in selected panNETs [13]. Minimally invasive approaches are technically feasible, safe, and may have potential advantages over open resection in experienced centers [10]. When limited resection is considered, the removal of suspicious nodes identified on preoperative imaging is warranted, and lymph node sampling may be considered to assess for nodal invasion if imaging is negative.

Enucleation is associated with improved pancreatic function but at a cost of a higher rate of postoperative pancreatic fistulae. Criteria for patient selection have not been defined, but expert's opinions suggest that enucleation

should be reserved for smaller tumors, those more likely to display benign behavior, and those located >2–3 mm from the main pancreatic duct [10, 13]. For instance, F-panNETs ≤2 cm represent the most appropriate lesions to be enucleated, given their safe distance from the main pancreatic duct [9].

For central pancreatectomy, the primary indication is deeply located, small, benign, or low-grade panNETs in the neck or proximal body of the pancreas that are not suitable for enucleation due to their proximity to the main duct. It is necessary to assure a pancreatic remnant long enough to maintain normal pancreatic function. A 5-cm-length segment is usually required [10]. Despite more favorable in preserving pancreatic function opposed to standard resections, this has to be balanced with a higher overall morbidity and pancreatic fistulae rate [10, 13]. Patients with larger lesions, diffuse pancreatitis, and high-grade tumors are not candidates for central pancreatectomy [10, 28].

Usually, <5% of patients develop pancreatic insufficiency [16]. These better functional outcomes in relation to standard resections have to be balanced against an increased rate of postoperative morbidity, especially pancreatic fistulae, which, in some prospective, studies reaches 45% [13, 16]. Thus, this procedure may be more appropriate for younger surgical-fit patients.

Resection Margins

There are neither randomized trials nor large series examining the impact of resection margins on local recurrence [10]. Tumor biology rather than margin status appears to impact survival [29].

Negative surgical margins should be the goal, although no conclusive data support the benefit of a more aggressive strategy. In fact, more aggressive strategies might be associated with higher morbidity, and, in selected patients, parenchyma-sparing procedures with minimal margins are reasonable options to prevent morbidity and maintain normal pancreatic function [10].

Hepatic Cytoreductive Surgery

There is no consensus regarding the role of cytoreductive hepatic surgery in patients with liver metastasis [10]. Recent studies have challenged the idea that >90% of liver metastases must be resected in order to either palliate or improve survival of patients with neuroendocrine liver metastases. It is easier to achieve higher levels of cytoreduction in patients with fewer liver metastases, but good results have been obtained even in patients with >10 lesions, and published data have shown potential survival benefits [10].

Combined Pancreatectomy and Hepatic Cytoreductive Surgery

Some patients with panNETs and liver metastases may be eligible for both primary tumor resection and hepatic cytoreductive surgery. Combining these procedures depends on the extent of planned pancreatic and liver resection and is a reasonable approach if the patient's comorbidities and functional status do not contraindicate it [8, 10]. Indeed, the morbidity of a PD ranges up to 37% and that of a hepatic resection up to 12% [30]. Nevertheless, several reports suggest that synchronous resections can be performed safely, with acceptable morbidity and mortality in selected patients, when performed by experienced surgeons. Alternatively, combining liver resection and RFA may provide the opportunity to achieve complete tumor ablation with more limited resections, thus minimizing the impact on the residual liver function [9].

Liver Transplantation

Liver transplantation may be an option in very selected patients with unresectable panNET liver metastasis [31]. Some criteria to be considered are the absence of extrahepatic disease, histologic confirmation of a well-differentiated panNET (G1/G2, Ki-67 <10%), previous resection of the primary tumor, diffuse liver metastasis involving <50% of total liver volume, stable disease in response to therapy for at least 6 months, and age <60 years old [32]. In patients that fulfilling these criteria, a 5-year overall survival of 69–97% after transplantation has been reported [32].

EUS-Guided Ablation of PanNETs

EUS allows the accurate visualization of the pancreatic parenchyma and has become a key modality for the characterization of pancreatic neoplasms, including panNETs. EUS allows for complementary diagnostic procedures, including tissue acquisition as well as lesion localization through EUS-guided fiducial placement or tattooing using sterile carbon-based ink [33, 34].

Over the last years, EUS has evolved from a purely diagnostic procedure toward an interventional modality. With the development of dedicated endoscopic devices, a lot of interest has been devoted to the possibility of delivering loco-regional treatment, avoiding the need for surgical treatment. In the case of panNETs, the treatment goals differ significantly according to their classification as F-panNETs or NF-panNETs. Indeed, as F-panNETs have a low risk of malignant transformation (particularly

insulinomas), the main goal when treating these lesions is to provide adequate control of the endocrine disturbance. On the other hand, local ablative therapies for NF-panNETs should attain complete tumor ablation [35]. Two techniques have been most extensively evaluated for EUS-guided ablation of panNETs: EUS-guided RFA (EUS-RFA) and EUS-guided EA (EUS-EA).

Patient selection is critical for the safe and effective use of this procedure. Experience with these techniques remains limited to small series, and no large prospective studies or randomized clinical trials exist on this subject [7]. Currently, the European Neuroendocrine Tumor Society (ENETS) guidelines include EUS-guided ablative therapies as an alternative to surgery in selected patients, although its routine use is not endorsed [6]. Therefore, the use of these techniques should still be considered investigational. Currently, patients with lesions up to 2 cm in size, low grade (G1) in the World Health Organization classification, as well as patients who are unfit or unwilling to undergo surgery, are included in trials on EUS-guided ablative therapy (Fig. 1) [36, 37]. Additionally, comorbidities and overall life expectancy should be considered before offering ablative therapy for any given patient. Clinical success definitions differ according to the secretory phenotype of the panNET. For F-panNETs, most studies define clinical success after ablative therapy as the complete symptomatic resolution during follow-up. The definition of clinical success after EUS-guided ablation of NF-panNETs is more variable, although most studies agree on the complete disappearance of the lesion, as determined by the absence of arterial phase contrast enhancement in computed tomography or magnetic resonance imaging [7]. Table 1 provides a summary of the studies evaluating the feasibility, performance, and safety of EUS-guided ablation of panNETs.

EUS-Guided Radiofrequency Ablation

EUS-RFA consists of the application of a high-frequency alternating current to generate thermal energy to provide local tissue destruction [57, 58]. This technique takes advantage of the thermosensitivity of the pancreatic tissue. The friction generated by the alternating current produces heat, inducing protein denaturation followed by intracellular dehydration and coagulative necrosis [59]. Additionally, there is some evidence of indirect thermal injury, including loss of membrane integrity, mitochondrial dysfunction, oxidative stress, and a delayed immune response [60, 61]. The RFA probe induces active heating of the few millimeters around the electrode and, when applied in excess (temperatures >100°C), tissue dehydration and charring occur around the probe, which act as insulators, leading to a rise in impedance and decreasing the efficiency of the procedure [62, 63].

Tissues farther from the electrode are heated by passive thermal conduction, which may not be sufficient to induce the rise in temperature required to cause necrosis [59]. Thus, one significant concern regarding this technique is the limited extent of necrosis, which may not be enough to cover all the tumor volume [59]. RFA can be applied through monopolar or bipolar probes, the latter being able to produce more rapid and focal heating, mitigating injury to adjacent tissues [62].

Ablation of panNETs by RFA is performed using conventional linear echoendoscopes. Several probes have been developed (Table 2), both coupled to a needle (needle-type) or for through-the-needle placement, in which the probe is passed into the tumor through a 19G needle. The EUSRA-RFA probe (Taewoong Medical Co., Gyeonggi-do, South Korea) has an internal cooling system to prevent tissue charring [57]. Real-time EUS control of the procedure is paramount, and doppler should be applied to mitigate the risk of vascular damage. Care should be taken to avoid extensive damage to normal parenchyma and to the wall of the gastrointestinal tract. It is recommended to start RFA at the farthest and deepest border of the lesion, since EUS-RFA induces image artifacts that can hamper the completion of the procedure. For large lesions, a fanning technique could be applied to treat the entire tumor [59]. Treatment should be withheld when hyperechoic bubbles extend beyond the lesion or when impedance increases [35].

EUS-RFA protocols vary significantly between centers (including power settings and duration of the ablation), and the existing evidence is based on studies that include a limited number of patients [7]. One of the largest prospective cohorts included 12 patients, with a total of 14 NF-panNETs [36]. This group reported a rate of significant response (decrease in diameter >50% or tumor disappearance) at 1-year follow-up of 86% [36]. These results were also observed after a longer follow-up period, as recently reported [37]. Technical success was achieved for all lesions [36]. A recent meta-analysis including 13 EUS-RFA studies (n = 113 patients) reported pooled rates of clinical and technical success of 85% and 94%, respectively [7]. Lesion size ≤18 mm and location in the head of the pancreas appear to predict higher ablation success rates [7, 64]. A recent case series including 10 patients with pancreatic insulinoma suggests that EUS-RFA presents high levels of clinical success for the treatment of

Table 1. Summary of studies evaluating EUS-guided ablative therapies for the treatment of panNETs

Author	EUS-guided treatment	Patients (male), *n*	Lesions, *n*	Mean size, mm	Non-functioning panNETs, *n*	Sessions, *n*	Technical success, %	Clinical success, %	Adverse events (pancreatitis), *n*
Levy et al. [38] (2012)	EA	5 (1)	5	15.0±4.2	0	11	100	60.0	0
Park et al. [39] (2015)	EA	11 (5)	14	12.3±3.2	10	18	100	61.5	5 (3)
Yang et al. [40] (2015)	EA	4 (NR)	4	NR	0	5	100	75.0	0
Paik et al. [41] (2016)	EA	6 (4)	6	11.3±3.7	2	6	100	83.3	3 (1)
Choi et al. [42, 43] (2018)	EA	33 (10)	40	11.0 (8–13)	39	63	100	60	2 (2)
Matsumoto et al. [44] (2020)	EA	5 (2)	5	10.2±2.5	5	8	100	80	0
So et al. [45] (2022)	EA	97 (50)	97	12.1±3.7	97	158	100	87	NR (23)
Pai et al. [46] (2015)	RFA	2 (0)	2	27.5±17.7	NR	3	100	100	0
Lakhtakia et al. [47] (2016)	RFA	3 (3)	3	13.0±5.5	0	3	100	100	0
Choi et al. [43] (2018)	RFA	8(4)	8	19.3±6.7	7	14	100	75	2 (1)
De La Serna et al. [48] (2018)	RFA	3 (3)	3	16.1±6.3	NR	6	100	33	0
Oleinikov et al. [49] (2019)	RFA	18 (10)	27	14.3±7.3	19	18	96	93	2 (2)
Dancour et al. [49] (2019)	RFA	8 (4)	8	15.3±1.9	0	8	87.5	100	0
Barthet et al. [36] (2019)	RFA	12 (7)	14	13.1 (10–20)	14	14	100	86	2 (1)
Malikowsky et al. [50] (2019)	RFA	8 (3)	8	21.9±15.5	5	9	100	89	1 (0)
De Nucci et al. [51] (2020)	RFA	10 (5)	11	14.5 (9–20)	5	10	100	100	2 (0)
Ferreira et al. [52] (2022)	RFA	23 (NR)	24	NR	10	NR	100	82	NR
Marx et al. [53] (2022)	RFA	27 (14)	27	14.0±4.6	27	29	100	85	7 (3)
Younis et al. [54] (2022)	RFA	7 (4)	7	8.9 (6–18)	6	7	100	57	0
Andreis et al. [55] (2023)	RFA	10 (3)	10	11.9±3.3	0	11	100	100	3 (0)
Crinò et al. [56] (2023)	RFA	89 (27)	89	13.4±3.9	0	89	100	96	16 (9)

EA, ethanol ablation; EUS, endoscopic ultrasound; panNETs, pancreatic neuroendocrine tumors; NR, not reported; RFA, radiofrequency ablation.

Table 2. EUS-guided radiofrequency probes

	EUS-RFA probe			
	Radionics, Inc. (MA, USA)	Cryotherm™ probe ERBE GmbH (Tübingen, Germany)	EUSRA™ EUS-guided RFA TaeWoong Medical (Gyeonggi-do, South Korea)	Habib EUS-RFA Boston Scientific (MA, USA)
Type	"Needle-type"	"Needle-type"	"Needle-type"	"Through-the-needle"
Caliber	19G	14G	18G/19G	1F
Polarity	Monopolar	Bipolar	Monopolar	Monopolar
Active length	10–15 mm	26 mm	5–20 mm	20 mm
Internal cooling	No	Yes	Yes	No

Adapted from Lakhtakia et al. [13].

F-panNETs. In this series, technical success was achieved in all patients, with 90% requiring one EUS-RFA session. All patients remained free of hypoglycemia events [55].

Globally, EUS-guided RFA of panNETs appears to be a relatively safe procedure. Only 12 adverse events were reported in the previously cited meta-analysis (pooled rate of 14%), most commonly acute pancreatitis (pooled rate of 8%) and abdominal pain [7].

EUS-Guided Ethanol Ablation

Chemoablation with ethanol has been widely used for the treatment of a wide range of cystic and solid lesions, including renal cysts and hepatocarcinoma [62, 65]. EUS-EA is inexpensive and induces coagulation necrosis, cell lysis, protein denaturation, and vascular thrombosis, subsequently leading to fibrosis [66, 67].

Regarding the technical aspects of this technique, the ablation agent is delivered by a small gauge EUS-FNA needle (22G or 25G), and small volumes of ethanol are injected within the tumor, which can be repeated until a hyperechoic blush is observed. The first-ever application of EUS-EA for a solid pancreatic lesion was reported in 2006 for the treatment of a symptomatic insulinoma [68]. A 95% ethanol solution was used, with complete symptom disappearance and endosonographic resolution of the lesion being achieved.

In general terms, this technique appears to be effective and safe. Indeed, one of the largest cohorts including 33 patients with a total of 40 tumors, reported a complete ablation rate of 60% after injection with 99% ethanol, with no recurrence during follow-up and an adverse event rate of 3.2% [42]. Nevertheless, the technique is not standardized, and there is currently no recommended protocol for the application of this ablative therapy. This is particularly evident for ethanol concentration, which varies largely between 40% and 99% in different reports. A recent systematic review with meta-analysis of 7 studies on EUS-EA, including a total of 91 patients, reported a pooled rate of technical and clinical success of 97% and 82%, respectively [7].

One of the main concerns regarding this technique is the injection of ethanol intra- or retroperitoneally or at the adjacent normal pancreatic parenchyma. The rate of adverse events after EUS-EA is reported to be around 12%, with a pooled rate of pancreatitis of 8% [7].

The efficiency and long-term effects of EUS-EA are still not completely understood as current evidence is based on case reports and small case series. At this point, this technique is not included in formal treatment and follow-up guidelines on panNETs but should be considered for patients requiring treatment and who are unfit for surgery. Future studies should provide evidence regarding the influence of different ethanol concentrations, needle sizes, and follow-up protocol.

Conflict of Interest Statement

The authors have no conflict of interest to disclose.

Funding Sources

No funding sources to be declared.

Author Contributions

Tiago Ribeiro and Sara Castanheira-Rodrigues had equal contribution on bibliographical review, study design, drafting of the manuscript, and critical revision of the manuscript. Pedro Bastos, Humberto Cristino, and Filipe Vilas-Boas had equal contribution to study design and drafting and critical revision of the manuscript. Alexandra Fernandes, Eduardo Rodrigues-Pinto, and Ricardo Rio-Tinto provided critical revision of the manuscript. Results were discussed in two meetings of Clube Português do Pâncreas and approved by all members. All authors critically reviewed and approved the final manuscript.

References

1 Lawrence B, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM. The epidemiology of gastroenteropancreatic neuroendocrine tumors. Endocrinol Metab Clin North Am. 2011;40(1):1–18, vii.
2 Andreasi V, Partelli S, Muffatti F, Manzoni MF, Capurso G, Falconi M. Update on gastroenteropancreatic neuroendocrine tumors. Dig Liver Dis. 2021;53(2):171–82.
3 Hallet J, Law CH, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. Cancer. 2015;121(4):589–97.
4 Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol. 2017;3(10):1335–42.
5 Gorelik M, Ahmad M, Grossman D, Grossman M, Cooperman AM. Nonfunctioning incidental pancreatic neuroendocrine tumors: who, when, and how to treat? Surg Clin North Am. 2018;98(1):157–67.
6 Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, et al. ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. Neuroendocrinology. 2016;103(2):153–71.
7 Garg R, Mohammed A, Singh A, Harnegie MP, Rustagi T, Stevens T, et al. EUS-guided radiofrequency and ethanol ablation for pancreatic neuroendocrine tumors: a systematic review and meta-analysis. Endosc Ultrasound. 2022;11(3):170–85.
8 Kulke MH, Anthony LB, Bushnell DL, de Herder WW, Goldsmith SJ, Klimstra DS, et al. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. Pancreas. 2010;39(6):735–52.
9 Pavel M, Öberg K, Falconi M, Krenning EP, Sundin A, Perren A, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31(7):844–60.
10 Howe JR, Merchant NB, Conrad C, Keutgen XM, Hallet J, Drebin JA, et al. The North American neuroendocrine tumor society consensus paper on the surgical management of pancreatic neuroendocrine tumors. Pancreas. 2020;49(1):1–33.
11 Jilesen AP, van Eijck CH, in't Hof KH, van Dieren S, Gouma DJ, van Dijkum EJ. Postoperative complications, in-hospital mortality and 5-year survival after surgical resection for patients with a pancreatic neuroendocrine tumor: a systematic review. World J Surg. 2016;40(3):729–48.
12 Mehrabi A, Fischer L, Hafezi M, Dirlewanger A, Grenacher L, Diener MK, et al. A systematic review of localization, surgical treatment options, and outcome of insulinoma. Pancreas. 2014;43(5):675–86.
13 Jeune F, Taibi A, Gaujoux S. Update on the surgical treatment of pancreatic neuroendocrine tumors. Scand J Surg. 2020;109(1):42–52.
14 Sallinen VJ, Le Large TYS, Tieftrunk E, Galeev S, Kovalenko Z, Haugvik SP, et al. Prognosis of sporadic resected small (≤2 cm) nonfunctional pancreatic neuroendocrine tumors: a multi-institutional study. HPB. 2018;20(3):251–9.
15 Bettini R, Partelli S, Boninsegna L, Capelli P, Crippa S, Pederzoli P, et al. Tumor size correlates with malignancy in nonfunctioning pancreatic endocrine tumor. Surgery. 2011;150(1):75–82.
16 Falconi M, Mantovani W, Crippa S, Mascetta G, Salvia R, Pederzoli P. Pancreatic insufficiency after different resections for benign tumours. Br J Surg. 2008;95(1):85–91.
17 Yoshida T, Hijioka S, Hosoda W, Ueno M, Furukawa M, Kobayashi N, et al. Surgery for pancreatic neuroendocrine tumor G3 and carcinoma G3 should be considered separately. Ann Surg Oncol. 2019;26(5):1385–93.
18 Garcia-Carbonero R, Sorbye H, Baudin E, Raymond E, Wiedenmann B, Niederle B, et al. ENETS consensus guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. Neuroendocrinology. 2016;103(2):186–94.
19 Brenner B, Tang LH, Shia J, Klimstra DS, Kelsen DP. Small cell carcinomas of the gastrointestinal tract: clinicopathological features and treatment approach. Semin Oncol. 2007;34(1):43–50.
20 Sørbye H, Westre B, Horn A. Curative surgery after neoadjuvant chemotherapy in metastatic poorly differentiated neuroendocrine carcinoma. Eur J Surg Oncol. 2007;33(10):1209–10.
21 Lairmore TC, Chen VY, DeBenedetti MK, Gillanders WE, Norton JA, Doherty GM. Duodenopancreatic resections in patients with multiple endocrine neoplasia type 1. Ann Surg. 2000;231(6):909–18.
22 Singh S, Chan DL, Moody L, Liu N, Fischer HD, Austin PC, et al. Recurrence in resected gastroenteropancreatic neuroendocrine tumors. JAMA Oncol. 2018;4(4):583–5.
23 Hashim YM, Trinkaus KM, Linehan DC, Strasberg SS, Fields RC, Cao D, et al. Regional lymphadenectomy is indicated in the surgical treatment of pancreatic neuroendocrine tumors (PNETs). Ann Surg. 2014;259(2):197–203.
24 Conrad C, Schwarz L, Perrier N, Fleming JB, Katz MH, Aloia TA, et al. Spleen and splenic vessel preserving distal pancreatectomy for bifocal PNET in a young patient with MEN1. Surg Endosc. 2016;30(10):4619.
25 Kang CM, Lee SH, Lee WJ. Minimally invasive radical pancreatectomy for left-sided pancreatic cancer: current status and future perspectives. World J Gastroenterol. 2014;20(9):2343–51.
26 Moore JV, Tom S, Scoggins CR, Philips P, Egger ME, Martin RCG 2nd. Exocrine pancreatic insufficiency after pancreatectomy for malignancy: systematic review and optimal management recommendations. J Gastrointest Surg. 2021;25(9):2317–27.
27 Kusakabe J, Anderson B, Liu J, Williams GA, Chapman WC, Doyle MMB, et al. Long-term endocrine and exocrine insufficiency after pancreatectomy. J Gastrointest Surg. 2019;23(8):1604–13.
28 Iacono C, Bortolasi L, Facci E, Nifosì F, Pachera S, Ruzzenente A, et al. The Dagradi-Serio-Iacono operation central pancreatectomy. J Gastrointest Surg. 2007;11(3):364–76.
29 Zhang XF, Wu Z, Cloyd J, Lopez-Aguiar AG, Poultsides G, Makris E, et al. Margin status and long-term prognosis of primary pancreatic neuroendocrine tumor after curative resection: results from the US Neuroendocrine Tumor Study Group. Surgery. 2019;165(3):548–56.
30 Brooke-Smith M, Figueras J, Ullah S, Rees M, Vauthey JN, Hugh TJ, et al. Prospective evaluation of the International Study Group for Liver Surgery definition of bile leak after a liver resection and the role of routine operative drainage: an international multicentre study. HPB. 2015;17(1):46–51.
31 Máthé Z, Tagkalos E, Paul A, Molmenti EP, Kóbori L, Fouzas I, et al. Liver transplantation for hepatic metastases of neuroendocrine pancreatic tumors: a survival-based analysis. Transplantation. 2011;91(5):575–82.

32 Mazzaferro V, Sposito C, Coppa J, Miceli R, Bhoori S, Bongini M, et al. The long-term benefit of liver transplantation for hepatic metastases from neuroendocrine tumors. Am J Transplant. 2016;16(10):2892–902.
33 Wang AY, Yachimski PS. Endoscopic management of pancreatobiliary neoplasms. Gastroenterology. 2018;154(7):1947–63.
34 Rodriguez A, Canto MI, Makary MA. Endoscopic localization and tattooing of a proinsulinoma for minimally invasive resection. Pancreas. 2011;40(3):474–7.
35 Rimbaş M, Horumbă M, Rizzatti G, Crinò SF, Gasbarrini A, Costamagna G, et al. Interventional endoscopic ultrasound for pancreatic neuroendocrine neoplasms. Dig Endosc. 2020;32(7):1031–41.
36 Barthet M, Giovannini M, Lesavre N, Boustiere C, Napoleon B, Koch S, et al. Endoscopic ultrasound-guided radiofrequency ablation for pancreatic neuroendocrine tumors and pancreatic cystic neoplasms: a prospective multicenter study. Endoscopy. 2019;51(9):836–42.
37 Barthet M, Giovannini M, Gasmi M, Lesavre N, Boustière C, Napoleon B, et al. Long-term outcome after EUS-guided radiofrequency ablation: prospective results in pancreatic neuroendocrine tumors and pancreatic cystic neoplasms. Endosc Int Open. 2021;9(8):E1178–85.
38 Levy MJ, Thompson GB, Topazian MD, Callstrom MR, Grant CS, Vella A. US-guided ethanol ablation of insulinomas: a new treatment option. Gastrointest Endosc. 2012;75(1):200–6.
39 Park DH, Choi JH, Oh D, Lee SS, Seo DW, Lee SK, et al. Endoscopic ultrasonography-guided ethanol ablation for small pancreatic neuroendocrine tumors: results of a pilot study. Clin Endosc. 2015;48(2):158–64.
40 Yang D, Inabnet WB 3rd, Sarpel U, DiMaio CJ. EUS-guided ethanol ablation of symptomatic pancreatic insulinomas. Gastrointest Endosc. 2015;82(6):1127.
41 Choi JH, Paik WH, Lee SH, Lee MW, Cho IR, Ryu JK, et al. Efficacy and predictive factors of endoscopic ultrasound-guided ethanol ablation in benign solid pancreatic tumors. Surg Endosc. 2023;37(8):5960–8.
42 Choi JH, Park DH, Kim MH, Hwang HS, Hong SM, Song TJ, et al. Outcomes after endoscopic ultrasound-guided ethanol-lipiodol ablation of small pancreatic neuroendocrine tumors. Dig Endosc. 2018;30(5):652–8.
43 Choi JH, Seo DW, Song TJ, Park DH, Lee SS, Lee SK, et al. Endoscopic ultrasound-guided radiofrequency ablation for management of benign solid pancreatic tumors. Endoscopy. 2018;50(11):1099–104.
44 Matsumoto K, Kato H, Kawano S, Fujiwara H, Nishida K, Harada R, et al. Efficacy and safety of scheduled early endoscopic ultrasonography-guided ethanol reinjection for patients with pancreatic neuroendocrine tumors: prospective pilot study. Dig Endosc. 2020;32(3):425–30.
45 So H, Ko SW, Shin SH, Kim EH, Son J, Ha S, et al. Comparison of EUS-guided ablation and surgical resection for nonfunctioning small pancreatic neuroendocrine tumors: a propensity score-matching study. Gastrointest Endosc. 2023;97(4):741–51.e1.
46 Pai M, Habib N, Senturk H, Lakhtakia S, Reddy N, Cicinnati VR, et al. Endoscopic ultrasound guided radiofrequency ablation, for pancreatic cystic neoplasms and neuroendocrine tumors. World J Gastrointest Surg. 2015;7(4):52–9.
47 Lakhtakia S, Ramchandani M, Galasso D, Gupta R, Venugopal S, Kalpala R, et al. EUS-guided radiofrequency ablation for management of pancreatic insulinoma by using a novel needle electrode (with videos). Gastrointest Endosc. 2016;83(1):234–9.
48 De la Serna C, Cimavilla M, Madrigal B, Sanchez-Ocana R, Nuñez H, Garcia-Alonso FJ, et al. Su1384 eus-guided radiofrequency ablation (eus-rfa) for pancreatic neuroendocrine tumors and cystic mucinous neoplasms: a pilot study of safety, feasibility and efficacy. Gastrointest Endosc. 2018;87(6):AB332–3.
49 Oleinikov K, Dancour A, Epshtein J, Benson A, Mazeh H, Tal I, et al. Endoscopic ultrasound-guided radiofrequency ablation: a new therapeutic approach for pancreatic neuroendocrine tumors. J Clin Endocrinol Metab. 2019;104(7):2637–47.
50 Malikowski T, Ganda T, Agarunov E, Sharaiha RZ, Gleeson FC, Abu Dayyeh BK, et al. Sa1410 prospective assessment of the efficacy and safety of a newly designed endoscopic ultrasound guided radiofrequency ablation (eus-rfa) device for treating pancreatic neuroendocrine tumors and secondary pancreatic metastasis. Gastrointest Endosc. 2020;91(6):AB177–8.
51 de Nucci G, Mandelli ED, Redaelli D, Morganti D, Imperatore N, Reati R, et al. Endoscopic ultrasound guided radiofrequency ablation for neuroendocrine tumors: a single center case series. Endoscopy. 2019;51(4):OP163.
52 Figueiredo Ferreira M, Garces-Duran R, Eisendrath P, Devière J, Deprez P, Monino L, et al. EUS-guided radiofrequency ablation of pancreatic/peripancreatic tumors and oligometastatic disease: an observational prospective multicenter study. Endosc Int Open. 2022;10(10):E1380–5.
53 Marx M, Godat S, Caillol F, Poizat F, Ratone J-P, Pesenti C, et al. Management of non-functional pancreatic neuroendocrine tumors by endoscopic ultrasound-guided radiofrequency ablation: retrospective study in two tertiary centers. Dig Endosc. 2022;34(6):1207–13.
54 Younis F, Ben-Ami Shor D, Lubezky N, Geva R, Osher E, Shibolet O, et al. Endoscopic ultrasound-guided radiofrequency ablation of premalignant pancreatic-cystic neoplasms and neuroendocrine tumors: prospective study. Eur J Gastroenterol Hepatol. 2022;34(11):1111–5.
55 Borrelli de Andreis F, Boškoski I, Mascagni P, Schepis T, Bianchi A, Schinzari G, et al. Safety and efficacy of endoscopic ultrasound-guided radiofrequency ablation for pancreatic insulinoma: a single-center experience. Pancreatology. 2023;23(5):543–9.
56 Crinò SF, Napoleon B, Facciorusso A, Lakhtakia S, Borbath I, Caillol F, et al. Endoscopic ultrasound-guided radiofrequency ablation versus surgical resection for treatment of pancreatic insulinoma. Clin Gastroenterol Hepatol. 2023;21(11):2834–43.e2.
57 Lakhtakia S, Seo DW. Endoscopic ultrasonography-guided tumor ablation. Dig Endosc. 2017;29(4):486–94.
58 Chaudhary S, Sun SY. Endoscopic ultrasound-guided radiofrequency ablation in gastroenterology: new horizons in search. World J Gastroenterol. 2017;23(27):4892–6.
59 Alvarez-Sánchez MV, Napoléon B. Review of endoscopic radiofrequency in biliopancreatic tumours with emphasis on clinical benefits, controversies and safety. World J Gastroenterol. 2016;22(37):8257–70.
60 Chu KF, Dupuy DE. Thermal ablation of tumours: biological mechanisms and advances in therapy. Nat Rev Cancer. 2014;14(3):199–208.
61 Zerbini A, Pilli M, Penna A, Pelosi G, Schianchi C, Molinari A, et al. Radiofrequency thermal ablation of hepatocellular carcinoma liver nodules can activate and enhance tumor-specific T-cell responses. Cancer Res. 2006;66(2):1139–46.
62 Signoretti M, Valente R, Repici A, Delle Fave G, Capurso G, Carrara S. Endoscopy-guided ablation of pancreatic lesions: technical possibilities and clinical outlook. World J Gastrointest Endosc. 2017;9(2):41–54.
63 Gazelle GS, Goldberg SN, Solbiati L, Livraghi T. Tumor ablation with radio-frequency energy. Radiology. 2000;217(3):633–46.
64 Imperatore N, de Nucci G, Mandelli ED, de Leone A, Zito FP, Lombardi G, et al. Endoscopic ultrasound-guided radiofrequency ablation of pancreatic neuroendocrine tumors: a systematic review of the literature. Endosc Int Open. 2020;8(12):E1759–64.
65 Melita G, Pallio S, Tortora A, Crinò SF, Macrì A, Dionigi G. Diagnostic and interventional role of endoscopic ultrasonography for the management of pancreatic neuroendocrine neoplasms. J Clin Med. 2021;10(12):2638.
66 Canakis A, Law R, Baron T. An updated review on ablative treatment of pancreatic cystic lesions. Gastrointest Endosc. 2020;91(3):520–6.
67 Arshad HM, Bharmal S, Duman DG, Liangpunsakul S, Turner BG. Advanced endoscopic ultrasound management techniques for preneoplastic pancreatic cystic lesions. J Investig Med. 2017;65(1):7–14.
68 Jürgensen C, Schuppan D, Neser F, Ernstberger J, Junghans U, Stölzel U. EUS-guided alcohol ablation of an insulinoma. Gastrointest Endosc. 2006;63(7):1059–62.

GE – Portuguese Journal of Gastroenterology

Research Article

GE Port J Gastroenterol 2024;31:236–245
DOI: 10.1159/000530684

Received: September 30, 2022
Accepted: February 2, 2023
Published online: July 14, 2023

Predictors of Outcomes in Gastric Neuroendocrine Tumors: A Retrospective Cohort

Raquel Ortigão[a] Luís Pedro Afonso[b] Pedro Pimentel-Nunes[c, d, e]
Mário Dinis-Ribeiro[a, f] Diogo Libânio[a, f]

[a]Gastroenterology Department, Portuguese Oncology Institute of Porto, Porto, Portugal; [b]Department of Pathology, Portuguese Oncology Institute of Porto, Porto, Portugal; [c]Department of Surgery and Physiology, Faculty of Medicine, University of Porto (FMUP), Porto, Portugal; [d]RISE@CI-IPOP (Health Research Network, IPO Porto), Porto Comprehensive Cancer Center (Porto.CCC), Porto, Portugal; [e]Unilabs Portugal, Porto, Portugal; [f]MEDCIDS, Faculty of Medicine, University of Porto, Porto, Portugal

Keywords
Gastric neuroendocrine tumors · Endoscopic resection · Chromogranin A

Abstract

Introduction/Aim: Gastric neuroendocrine tumors (GNETs) frequently have an indolent clinical course, despite their metastatic potential. The aim of the study was to identify prognostic factors associated with overall survival and risk of metastases and to evaluate the impact of serial measurements of chromogranin A (CgA). ***Methods:*** The authors performed a retrospective cohort study including consecutive patients with GNET diagnosed between 2010 and 2019, with a minimum follow-up of 1 year. Univariate and multivariate analyses were performed. ***Results:*** We included 132 patients with GNET (type I, 113 patients; type II, 1 patient; type III, 14 patients; type IV, 2 patients; not classifiable, 2 patients), with 61% being female and a mean age at diagnosis of 66 years. During the follow-up period (median 66 months), 3 (2.3%) patients died due to metastatic disease (1 patient with type III and 2 patients with type IV). Male gender ($p = 0.030$), type III/IV ($p < 0.001$), Ki-67 index >20% ($p < 0.001$), grade 2/3 ($p < 0.001$), invasion beyond the submucosa ($p < 0.001$), and presence of metastases ($p < 0.001$) were identified as risk factors for mortality in the univariate analysis. Metastasis developed in 7 patients (5.3%). Multivariable analysis revealed that Ki-67 >20% ($p = 0.016$) was an independent risk factor for metastasis. Overall, CgA showed a sensitivity of 20% for detection of recurrence and a specificity of 79% (sensitivity of 8% and specificity of 71% in type I GNETs). ***Conclusion:*** Identification of risk factors for the presence of metastases and for mortality in these groups of patients can help in individualizing the therapeutic strategy. CgA seems to be a weak marker for monitoring patients with GNET.

Preditores de prognóstico nos Tumores Neuroendócrinos Gástricos: um estudo retrospetivo

Palavras Chave
Tumores neuroendócrinos gástricos · Resseção endoscópica · Cromogranina A

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

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

Resumo

Introdução/Objetivo: Os tumores neuroendócrinos gástricos (TNEs-G) têm frequentemente um curso indolente, apesar do seu potencial metastático. O objetivo deste trabalho foi identificar fatores de prognóstico associados à sobrevida global e à metastização nos doentes com TNEs-G e avaliar o impacto da análise seriada de cromogranina A (CgA). ***Methods:*** Estudo retrospectivo incluindo doentes consecutivos admitidos por TNE-G entre 2010 e 2019, com um follow-up mínimo de 1 ano. Foi realizada análise univariada e multivariada. ***Results:*** Foram incluídos 132 doentes com TNE-G (Tipo I, 113 doentes; Tipo II, 1 doente; Tipo III, 14 doentes; Tipo IV, 2 doentes; Não classificável, 2 doentes), sendo 61% mulheres, com idade média de 66 anos. Durante o periodo de follow-up (mediana 66 meses), 3 (2.3%) doentes faleceram por doença metastática (1 doente com Tipo III e 2 com Tipo IV). O sexo masculino (p = 0,030), tipo III/IV (p < 0,001), Ki-67 index >20% (p < 0,001), Grau 2/3 (p < 0,001), invasão além da submucosa (p < 0,001) e presença de metástases (p < 0,001) foram identificados como fatores de risco para mortalidade na análise univariada. Sete doentes desenvolveram metástases (5,3%). A análise multivariáda revelou que o Ki-67 >20% (p = 0,016) era um factor de risco independente para metastização. Globalmente, a CgA mostrou uma sensibilidade de detecção de recorrência de 20% e uma especificidade de 79% (sensibilidade de 8% e especificidade de 71% em em TNEs-G do Tipo I). ***Conclusão:*** A identificação dos fatores de risco para a presença de metástases e para a mortalidade neste grupo de pacientes pode ajudar a individualizar a estratégia terapêutica. A CgA parece ser um marcador fraco para a monitorização de doentes com TNEs-G.

Introduction

Gastrointestinal neuroendocrine tumors (NET) arise from diffuse neuroendocrine system and account for only 0.5% of all malignancies and 2% of gastrointestinal malignancies. Gastric NETs (GNETs) are the most frequent of all digestive NETs, representing up to 23% of the cases [1, 2]. The incidence and prevalence have been increasing, probably due to the widespread use of endoscopic and radiological examinations and increased recognition by pathologists. Thus, GNETs are now often found by chance during endoscopy that was done for another reason.

In 2019, the World Health Organization (WHO) categorized these neoplasms as grade 1–3 NET, neuroendocrine carcinoma (NEC), and mixed neuroendocrine-nonneuroendocrine neoplasm based on histological classification, Ki-67 index, and mitotic activity [3]. Formal TNM staging classifications have been introduced for gastrointestinal NETs by the American Joint Committee on Cancer (AJCC), and the European Neuroendocrine Tumor Society (ENETS). In addition to grade and TNM, GNETs should be further subclassified into 4 subtypes according to clinicopathological characteristics since this classification has management implications. GNETs arising in the context of hypergastrinemia are classified into type I if associated with corpus atrophic gastritis/autoimmune gastritis and type II if associated with noncompensatory hypergastrinemia (produced by a gastrinoma) and Zollinger-Ellison syndrome. Types III and IV are considered sporadic, not being associated with hypergastrinemia nor any background pathology. They are distinguished by histological grade, with type IV being grade 3 (mitotic index >20% and Ki-67% >20%) [4]. This classification is useful in predicting prognosis as well as in therapeutic decision-making.

Despite the increasing incidence of these types of lesions, it is not yet certain which factors are predictors of worse prognosis and whether these should alter the therapeutic strategy. Moreover, with the current use of advanced endoscopic techniques, these now play a role in the treatment of these patients, particularly in patients with type I GNET. However, evidence regarding the different therapeutic strategies in these patients is limited and optimal management is still not well established. The strategy adopted depends on the preference and experience of the endoscopist, while others propose a size threshold for endoscopic resection.

The aim of the study was to analyze the clinical and pathological characteristics of GNETs, identify prognostic factors associated with overall survival and metastasis, specifically in type I NETs, and evaluate the impact of serial measurements of chromogranin A (CgA) in these patients. We also assessed the clinical outcomes of patients with type I GNET treated with different strategies (polypectomy/surveillance, mucosectomy [EMR], endoscopic submucosal dissection [ESD], surgery, and somatostatin analogues).

Materials and Methods

Patients and Methods

A retrospective cohort study was performed. The Pathological database of the Portuguese Oncology Institute of Porto was searched for GNETs diagnosed between January 2010 and

December 2019 and consecutive patients were included. Patients with less than 12 months of follow-up and patients submitted to surgery for gastric adenocarcinoma were excluded.

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: sex, age, presence of symptoms at diagnosis, chronic use of proton pump inhibitors (PPIs) (>2 years), hemoglobin, vitamin B12, gastrin and CgA levels at diagnosis, presence of antiparietal cell and anti-intrinsic factor antibody, number and size of lesions, histological characteristics of the biopsy or the specimen (Ki-67 index and mitotic activity, submucosal invasion, lymphovascular infiltration and perineural permeation, resection margins), presence of gastric premalignant conditions (atrophy and intestinal metaplasia [IM]) in the antrum and body of the stomach, NET type, treatment, local and metastatic recurrence, metastasis, and overall survival.

At our center, there is a multidisciplinary meeting where the most complex patients are discussed. Endoscopies were performed by 6 experienced endoscopists who perform >500 endoscopies/year.

This study was approved by the Ethical Committee of the Portuguese Oncology Institute of Porto in 2020 (CES 44/021). Patients signed informed consent for the endoscopic procedures.

Definitions

En bloc resection was defined as the removal of a lesion in a single piece regardless of the depth of invasion and lymphovascular invasion. Complete resection (R0) was defined as en bloc resection with no involvement of the lateral and vertical margins, and no lymphovascular invasion.

Local recurrence referred to the recurrence of tumor at the previous endoscopic resection site, and synchronous lesions was defined as the recurrence of tumor at a different site in the stomach within 1 year of the initial endoscopic resection. Metachronous recurrence was defined as tumor detected more than 1 year later, distant from the site of initial resection. The follow-up period was defined as the interval from the initial diagnosis of gastric NETs to the last outpatient clinic visit.

The Ki-67 proliferation index is a scoring system that measures proliferation and growth of cells. A Ki-67 index of 3% or lower means that fewer than 3 in every 100 cells (3%) are dividing – grade 1 NET (NET G1). Ki-67 index of more than 20% corresponds to a grade 3 [3]. Serial measurements of CgA (at least 3 measurements during the follow-up) were performed and an elevation of 200 ng/mL above a baseline value was considered as increased.

Management on Type I GNETs

The endoscopic characteristics were examined during esophagogastroduodenoscopy, focusing on the size, number, morphology, and location of the lesions. A simultaneous assessment of the gastric mucosa was performed and biopsies of antrum and corpus were regularly taken according to the modified Sydney-Houston protocol. Depending on the characteristics found and factors such as the presence of metastases, different strategies were carried out and patients were divided into 5 groups: surveillance/polypectomy, endoscopic mucosal resection (EMR), ESD, surgery, and somatostatin analogues.

The surveillance/polypectomy group included patients diagnosed through biopsy who had no lesions removed during endoscopic follow-up and patients who had one or more polyps removed by polypectomy with biopsy forceps or cold snare (lesions <5–10 mm) and no other strategy was performed.

Beyond this size, the definitive choice for selecting the type of endoscopic resection was made mainly by the endoscopist (EMR vs. ESD) taking into account lesion size, morphology, and endosonographic/radiological findings. The surgery group includes patients undergoing atypical gastrectomy, subtotal gastrectomy, or antrectomy. Subtotal/atypical gastrectomy was performed in patients with larger lesions (not amenable to endoscopic resection) or with the presence of concomitant lymph node metastasis. Antrectomy was selected only in 1 patient with type I GNET who had multiple lesions as a way to reduce the acid-producing stimulus. Somatostatin analogues were the therapy of choice for patients with type I GNET with multiple lesions (>10) or in the presence of metastases.

Statistical Analysis

All statistical analysis was performed using IBM SPSS version 26. Data are presented as the number and percentages for categorical variables. Continuous variables are presented as mean and standard deviation or as median and interquartile range (IQR) (Q25–Q75). Univariable analysis was performed using the χ^2 test or Fisher's exact test, while continuous variables were compared using Student's *t* test or Mann-Whitney test if nonparametric data. Multivariable model included variables with $p < 0.2$ in the univariable analysis. A p value <0.005 was considered statistically significant.

Results

Patients

A total of 137 patients with GNET were identified in the Pathological database, of which 4 patients submitted to surgery due to carcinoma with the presence of GNET on the surgical specimen and 1 patient with less than 1 year of follow-up were excluded. We included 132 patients with GNET (type I, 113 patients; type II, 1 patient; type III, 14 patients; type IV, 2 patients; not classifiable, 2 patients), with 61% being female (n = 80) and a mean age at the diagnosis of 65.5 years (±12.2) (Table 1). Two patients were not classified since no data were available in these patients on serum gastrin, antiparietal cell, or intrinsic factor antibodies or histology of the gastric mucosa.

At diagnosis, 52% of patients had symptoms (36 patients had dyspeptic symptoms, 18 abdominal pain, 14 symptoms related to gastroesophageal reflux and 1 diarrhea), 18% anemia, and 15% vitamin B12 deficiency. The median gastrin value was 689 pg/mL (IQR 184–1,141) and CgA 186 ng/mL (100–288). One-third of the patients (33/99) had used PPIs for more than

Table 1. Characteristics of NET patients

	Type I	Type II	Type III	Type IV
Mean age±SD, years	59.6±12.6	NA (1 patient, 53 years)	55.8±9.2	61.0±2.8
Male sex, *n* (%)	43/113 (38.1)	0/1 (0)	6/14 (42.9)	2/2 (100)
Symptoms at diagnosis, *n* (%)	54/105 (51.4)	1/1 (100)	7/12 (58.3)	2/2 (100)
PPI >2 years, *n* (%)	26/85 (30.6)	1/1 (100)	5/13 (38.5)	1/1 (100)
Anemia, *n* (%)	20/109 (18.3)	0/1 (0)	2/14 (14.3)	0/2 (0)
Vitamin B12 deficiency, *n* (%)	16/99 (16.2)	NA	1/11 (9.1)	0/1 (0)
Antiparietal cell antibody, *n* (%)	75/99 (75.8)	NA	0/10 (0)	NA
Intrinsic factor antibody, *n* (%)	4/99 (4.0)	NA	0/10 (0)	NA
Solitary lesions, *n* (%)	84/113 (74.3)	1/1 (100)	14/14 (100)	2/2 (100)
Median size±IQR, mm	5 (3–8.8)	NA	10 (4.8–17)	31 (NA)
Hp positive, *n* (%)	25/101 (24.8)	1/1 (100)	2/12 (16.7)	1/1(100)
Antrum atrophy, *n* (%)	66/94 (70.2)	1/1 (100)	6/12 (50.0)	NA
Corpus atrophy, *n* (%)	84/97 (86.6)	1/1 (100)	7/13 (53.8)	NA
Antrum IM, *n* (%)	30/95 (31.6)	1/1 (100)	3/12 (25.0)	NA
Corpus IM, *n* (%)	70/99 (70.7)	1/1 (100)	7/13 (53.8)	NA

NA, not applicable/not available; SD, standard deviation; IQR, interquartile range; PPI, proton pump inhibitors; IM, intestinal metaplasia.

2 years. Antiparietal cell antibody and intrinsic factor assays were performed in 109 patients and were positive in 75 and 4 patients, respectively.

Most lesions were solitary (79%, n = 104), with a median size of 5 mm (IQR 3–10). Thirty-five patients had a lesion larger than 10 mm. In the evaluation of gastric mucosa, 68.5% and 83.0% had atrophy of the antrum and atrophy of the body, respectively. IM of the antrum and body was present in 32.1% and 69.3%, respectively. Hp was present in 29 patients (25%).

Prognostic Factors

During the follow-up period (median 66 months), 3 patients died due to metastatic disease (1 patient with type III GNET and 2 patients with type IV GNET) and there were no deaths due to other causes. Overall, disease–specific survival was 100% for type I and type II gastric NETs, 92.9% for type III, and 0% for type IV (mean follow-up 69 months).

Male gender (p = 0.030), lesion size >10 mm (p = 0.004), type III/IV versus I/II (p < 0.001), Ki-67 ≥3% versus <3% (p = 0.025), intermediate/high grade versus low grade (p = 0.025), WHO Classification G2 or more versus G1 (p = 0.007), invasion beyond the submucosa (p < 0.001), and presence of metastases (p < 0.001) were identified as risk factors for mortality (Table 2). Age, anemia, vitamin B12 deficit, chronic use of PPIs, and presence of gastric premalignant conditions were not related to mortality. Multivariate analysis did not identify any independent factors for mortality.

Seven patients presented metastatic disease, 4 at diagnosis and 3 during follow-up (5.3%, 3 patients with type I GNET, 2 patients type III, and 2 with type IV), diagnosed with Gallium-68-Dota-NOC-PET. Four patients presented distant metastases and 3 lymphatic metastases. The most common distant metastatic site was the liver (n = 4), followed by bone (n = 2) and peritoneum (n = 1). Lesion size >10 mm (p = 0.001), Ki-67 > 20% (p < 0.001), high grade (p < 0.001), NET G3/NEC (p = 0.003), invasion beyond submucosa (p < 0.001), and lower gastrin value (p = 0.003) were associated with metastasis on univariate analysis. Multivariable analysis revealed that Ki-67 >20% (p = 0.016) was an independent risk factor for metastasis (Table 3). In our cohort, patients with type I and III GNETs, <10 mm, and confined to the mucosa did not develop metastasis or died due to GNET.

Evaluation of Chromogranin A

Serial measurements of CgA were performed in 73 patients. Overall, CgA showed a sensitivity for detection of recurrence (recurrence of disease requiring a change in therapeutic strategy) of 20% and a specificity of 79%. In type I GNET patients, CgA demonstrated a sensitivity of 8% and a specificity of 71%.

Management of Patients with Type I GNET

Overall, 113 patients with type I GNET were included, 62% were women, with a mean age of 60 years. At diagnosis, 18% of patients had anemia and 16% vitamin B12 deficiency.

Table 2. Risk factors for mortality in patients with GNETs

Factors	All	Mortality (n = 3)	Univariate analysis, p value	Multivariable analysis, p value
Male sex, *n* (%)	52/132 (39.4%)	3 (100%)	**0.030**	0.609
Age (mean, years)	65.5	79.8	0.541	
Size, *n* (%)				
>10 mm	36/131 (27.5)	3 (100)	**0.004**	0.077
<10 mm	95/131 (72.5)	0 (0)		
Symptoms at diagnosis, *n* (%)	64/122 (52.5)	3 (100)	0.095	0.777
Chronic use of PPI, *n* (%)	33/99 (33.3)	1 (33.3)	0.598	
Anemia, *n* (%)	23/128 (17.9)	1 (33.3)	0.483	
B12 deficiency, *n* (%)	17/112 (15.2)	0 (0)	0.671	
NET type, *n* (%)				
I	113/132 (85.6)	0 (0)	<**0.001***	0.541
II	1/132 (0.8)	0 (0)		
III	14/132 (10.6)	1 (33.3)		
IV	2/132 (1.5)	2 (100)		
CgA value (median, ng/mL)	59.0	51.8	0.881	
Gastrin value (median, pg/mL)	689.0	7.67	**0.009**	0.169
Antrum atrophy, *n* (%)	74/108 (68.5)	1 (33.3)	0.496	
Corpus atrophy, *n* (%)	93/112 (83.0)	1 (33.3)	0.650	
Antrum IM, *n* (%)	35/109 (32.1)	1 (33.3)	0.144	0.733
Corpus IM, *n* (%)	79/115 (68.7)	1 (33.3)	0.504	
Helicobacter pylori +, *n* (%)	29/116 (25.0)	1 (33.3)	0.082	0.956
Ki-67 index, *n* (%)				
<3%	92/131 (70.2)	0 (0)	<**0.001****	0.407
3–20%	36/131 (27.5)	1 (33.3)		
>20%	3/131 (2.3)	2 (66.7)		
Grade, *n* (%)				
Low	92/131 (70.2)	0 (0)	<**0.001****	
Intermediate	36/131 (27.5)	1 (33.3)		
High	3/131 (2.3)	2 (66.7)		
WHO Classification, *n* (%)				
NET, G1	93/132 (70.5)	0 (0)	<**0.001**[a]	
NET, G2	36/132 (27.3)	1 (33.3)		
NET, G3	2/132 (1.5)	1 (33.3)		
NEC	1/132 (0.8)	1 (33.3)		
Invasion depth, *n* (%)				
Mucosa	57/99 (57.6)	0 (0)[b]	<**0.001**[c]	0.319
Submucosa	35/99 (35.4)	0 (0)		
Muscularis propria	7/99 (7.1)	2 (100)		
Presence of metastasis, *n* (%)	7/127 (5.5)	3 (100)	<**0.001**	0.925

PPI, proton pump inhibitor; NET, neuroendocrine tumor; CgA, chromogranin A; IM, intestinal metaplasia; NEC, neuroendocrine carcinoma. *$p < 0.001$ for type I/II versus III/IV and I/II/III versus IV; **$p = 0.025$ for Ki-67 ≥3% versus <3% and grade low versus intermediate/high. [a]$p = 0.007$ for G2/G3/NEC versus G1. [b]Data available for 2 of the 3 patients who had died. [c]$p = 0.004$ for invasion beyond submucosa versus invasion of mucosa/submucosa and $p = 0.096$ for invasion beyond mucosa versus invasion of mucosa.

In the evaluation of gastric mucosa, 70% and 87% had atrophy of the antrum and atrophy of the body, respectively. IM of the antrum and body was present in 32% and 71%, respectively. Hp was present in 25 patients (24.8%). Antiparietal cell and intrinsic factor antibodies were present in 76% and 4% of patients with autoimmune gastritis, respectively.

At diagnosis, the surveillance/polypectomy strategy was adopted in 77 patients. Twenty-four patients underwent EMR, 6 underwent ESD, 3 underwent surgery (2 for evidence of lymph node metastases), and 3 started somatostatin analogues.

Patients undergoing EMR and ESD had no statistically significant differences in maximum lesion

Table 3. Risk factors for metastasis in patients with GNETs

Factors	All	Metastasis (n = 7)	Univariate analysis, p value	Multivariable analysis, p value
Male sex, *n* (%)	50/127 (39.4)	4 (57.1)	0.322	
Age (mean, years)	59.6	63.1	0.949	
Size, *n* (%)				
>10 mm	33/127 (25.9)	7 (100.0)	<**0.001**	0.560
<10 mm	94/127 (74.0)	0 (0.0)	<**0.001**	
Symptoms at diagnosis, *n* (%)	61/118 (51.7)	5 (71.4)	0.111	0.253
Chronic use of PPI, *n* (%)	33/95 (34.7)	1 (33.3)[a]	0.959	
Anemia, *n* (%)	22/125 (17.6)	2 (28.6)	0.433	
B12 deficiency, *n* (%)	16/109 (14.7)	0 (0.0)	0.398	
NET type, *n* (%)				
I	108/125 (86.4)	3 (42.9)	<**0.001***	0.130
II	1/125 (0.8)	0 (0.0)		
III	14/125 (11.2)	2 (28.6)		
IV	2/125 (1.6)	2 (28.6)		
CgA value (median, ng/mL)	59.0	63.4	0.348	
Gastrin value (median, pg/mL)	689.0	20.1	**0.003**	0.485
Antrum atrophy, *n* (%)	72/106 (67.9)	4 (57.1)	0.161	0.335
Corpus atrophy, *n* (%)	91/110 (82.7)	3 (42.9)	0.677	
Antrum IM, *n* (%)	35/107 (32.7)	2 (28.6)	0.453	
Corpus IM, *n* (%)	77/113 (68.1)	3 (42.9)	0.945	
Helicobacter pylori+, *n* (%)	28/114 (24.6)	2 (50.0)[b]	0.229	
Ki-67 index, *n* (%)				
<3%	88/126 (69.8)	3 (42.9)	<**0.001****	**0.016**
3–20%	35/126 (27.7)	2 (28.6)	<**0.001****	
>20%	3/126 (2.4)	2 (28.6)	<**0.001****	
Grade, *n* (%)				
Low	88/126 (69.8)	3 (42.9)	<**0.001****	
Intermediate	35/126 (27.7)	2 (28.6)		
High	3/126 (2.4)	2 (28.6)		
WHO Classification, *n* (%)				
NET, G1	89/127 (70.1)	3 (42.9)	<**0.001*****	
NET, G2	35/127 (27.6)	2 (28.6)		
NET, G3	2/127 (1.6)	1 (14.3)		
NEC	1/127 (7.9)	1 (14.3)		
Invasion depth, *n* (%)				
Mucosa	56/95 (58.9)	0 (0%)[c]	<**0.001**[d]	0.055
Submucosa	32/95 (33.7)	3 (50.0)		
Muscularis propria	7/95 (7.4)	3 (50.0)		

PPI, proton pump inhibitor; NET, neuroendocrine tumor; CgA, chromogranin A; IM; intestinal metaplasia; NEC, neuroendocrine carcinoma; WHO, World Health Organization. [a]Data available for 3 patients with metastasis. [b]Data available for 4 patients with metastasis. [c]Data available for 6 patients with metastasis. [d]$p < 0.001$ for invasion beyond submucosa (vs. invasion of mucosa or submucosa). *$p < 0.001$ for type I/II versus III/IV and I/II/III versus IV. **$p < 0.001$ for Ki-67 ≥20% versus <20% and for high grade versus low/intermediate grade. ***$p = 0.003$ for NET G3/NEC Versus NET G1/G2.

diameter (16 vs. 13 mm, $p = 0.515$), Ki-67 index ($p = 0.745$), and grade ($p = 0.855$). The rate of complete histological resection (78 vs. 60%, $p = 0.255$) and the presence of negative horizontal and vertical margins (89 vs. 100%, $p = 0.597$; 77 vs. 60%, $p = 0.470$, respectively) were similar in both groups. The presence of positive horizontal or vertical margins had no impact on the development of metastases during the follow-up ($p = 0.917$ and $p = 0.790$, respectively) (Table 4).

Lesions removed by ESD had more frequently lymphovascular invasion, without significant difference (40 vs. 6%, $p = 0.120$). All patients had at least one surveillance endoscopy. The development of metachronous lesions and local

Table 4. Outcomes of EMR and ESD in type I GNET patients

	EMR (n = 24)	ESD (n = 6)	p value
Characteristics of the lesion			
Endoscopic tumor size (mean, mm)	16.02	13.42	0.515
Ki-67 index, *n* (%)			
<3%	11 (45.8)	3 (50)	0.855
3–20%	13 (54.2)	3 (50)	
Grade, *n* (%)			
G1	11 (45.8)	3 (50)	0.855
G2	13 (54.2)	3 (50)	
Resection analysis			
Histological complete resection,* *n* (%)			
Horizontal margins	16 (88.9)	5 (100)	0.737
Vertical margins	14 (77.9)	3 (60)	0.490
Lymphovascular invasion, *n* (%)	16 (88.9)	3 (60)	0.120
Curative resection, *n* (%)	14 (77.9)	3 (60)	0.490
Follow-up analysis			
Local recurrence, *n* (%)	5 (21.7)	1 (20)	0.923
Metachronous lesions, *n* (%)	9 (37.5)	2 (40)	0.914
Metastasis, *n* (%)	0 (0)	1 (20)	**0.029**

*Histological complete resection implies both vertical and horizontal margins negative.

recurrence was similar in EMR and ESD groups (38 vs. 40%, $p = 0.914$ and 22 vs. 20%, $p = 0.932$, respectively). In the ESD group, 1 patient developed lymph node metastasis ($p = 0.029$) during surveillance – a patient with a type I GNET, with 12 mm (Ki-67 3–20%, G2) with vertical and lymphovascular invasion on the endoscopic dissection specimen.

Three patients were submitted to surgery. One of the patients had multiple lesions and underwent antrectomy in 2010 to reduce hypergastrinemia. The other 2 patients underwent subtotal gastrectomy since at diagnosis they presented lesions 16 and 26 mm in size with lymph node metastasis on preoperative CT. Three patients started somatostatin analogues since they had multiple gastric lesions that were considered not amenable to surveillance/endoscopic resection.

Management of Patients with Type III/IV Gastric NETs

Overall, 14 patients were treated for type III GNET in our center: 5 underwent polypectomy at diagnostic endoscopy (lesions <10 mm), 5 underwent EMR, 1 underwent ESD, and 3 underwent surgery. In the group of patients submitted to polypectomy, there was no local recurrence or evidence of metastases during the follow-up. The complete resection rate after EMR was 40% and 1 patient developed lymph node metastasis (20% of the patients submitted to EMR). In 1 patient, ESD was curative and without local or distant recurrence during a follow-up of 10.6 years. Also, surgery was curative for the 3 patients, but 1 patient developed liver metastasis and died during follow-up. Of the 2 patients with type IV GNET, 1 underwent surgery and chemotherapy after the diagnosis of metastatic disease and the other started chemotherapy at diagnosis.

Discussion

The incidence of GNETs has increased over the past few decades and type I GNETs represent 70–80% [5]. In our study, type I GNETs accounted for 86% of the patients, type III, 11%, type IV, 2%, and only 1 patient had type II. The lack of a standard staging system for GNETs substantially hinders the prediction of the risk of recurrence and prognosis of patients suffering from GNETs. The AJCC, ENETS, and WHO staging classifications provide a better stratification of gastric NETs and they are routinely employed [3, 6]. Our retrospective cohort with a long follow-up confirms that type I GNETs have an excellent prognosis, and that endoscopic resection is effective and safe for the treatment of type I and small type III gastric NETs (selected lesions in the latter). We also identified risk factors for metastasis and mortality that should dictate a more intensive surveillance in these cases. Our findings of low sensitivity and specificity

of sequential CgA for tumor recurrence show that it is not useful neither as diagnostic nor as tumor biomarker for surveillance of these patients.

Most GNETs are diagnosed incidentally during screening endoscopy and classifying them is crucial in deciding the proper treatment as they can be either indolent or aggressive. In our study, as expected, we found type of GNET as a prognostic factor, with no deaths in the group of patients with type I GNET, even though 3 patients presented lymph node metastasis. Type III and IV GNETs have a more malignant biological behavior with a metastasis rate in our study of 8.7 and 100%, which was different to that reported in the literature (40%), probably due to the low number of patients [7, 8].

In our cohort, we found male sex as a mortality predictor, which is in line with previous studies [9, 10]. The protective effect of female gender observed in various studies is still unclear.

All patients with metastases or who died during the follow-up period had lesions larger than 10 mm in size. In a Korean study, a tumor size was significantly associated with survival and a tumor size of ≥2 cm was a risk factor for metastasis [11]. We also demonstrated that patients with Ki-67 >20%, an intermediate/high grade (vs. low), and invasion beyond submucosa had a poor prognosis, with a high risk of metastasis and mortality. According to Nadler et al. [12], Ki-67 is a very reliable marker for NETs when used to stage tumors with ENETS and WHO staging methods. GNETs with poor differentiation (G3) are more aggressive tumors and have poorer prognosis than well-differentiated (G1-G2) [13]. Tian et al. [14] found a 5-year survival of patients with well-differentiated tumors of 80.4%, which was nearly 4 times the overall survival of patients with G3 tumors. In our study, there was only 1 patient with NEC and two with G3 lesions, and the mortality was 100 and 50%, respectively. In multivariate analysis, we did not identify any independent factor for mortality probably due to the low number of deaths (n = 3). For metastasis, Ki-67 was identified as an independent risk factor. According to our results, patients with prognostic factors such as lesions >10 mm, Ki-67 >20%, intermediate/high grade, and invasion beyond the submucosa should be monitored with PET-DOTANOC initially every 6 months and after 2 years annually.

According to ENETS guidelines, published in 2016, GNETs should be treated according to their classification and size. Type I and II small tumors should be monitored or treated with minimal endoscopic or laparoscopic surgery and type III tumors require radical gastrectomy. However, some studies showed that endoscopic resection is possible for larger lesions (>10 mm) and even for smaller type III GNETs [15–17].

In our cohort, we had 113 patients with type I GNET. The strategy adopted depended on the characteristics of the lesions (morphology and size), but also on endoscopist experience and preferences. In a recent study by Chin et al. [18], the rate of disease progression during surveillance was 29.5%, suggesting that simple surveillance may not be safe in these patients. However, Esposito et al. [15] demonstrated that a noninterventional approach might be justified for small lesions (<5 mm), since none of the patients underwent disease progression after a median follow-up of almost 4 years. Also, the authors agree that endoscopic resection remains the preferred approach for larger tumors, owing the risk of disease progression, although low, as suggested by European guidelines [19]. There are a few studies with a limited number of patients comparing endoscopic resection by EMR and ESD for type I GNETs. A retrospective study (n = 87) has compared both techniques for <10 mm lesions and ESD showed a trend to a better pathologically complete resection rate (95% vs. 83%, p = 0.17) and a trend to a higher adverse event rate (perforation 2.6% vs. 0%, delayed bleeding 5.1% vs. 4.2%), but with no statistically significant differences [20]. Sato et al. [16] analyzed 13 patients and showed a better complete resection with ESD versus conventional EMR. In our study, the characteristics of the lesions submitted to ESD and EMR were comparable and the rate of complete histological resection was similar in both groups (78 vs. 60%), but lymphovascular invasion was more frequent in the ESD group (40 vs. 6%). Besides, the recurrence rate was also similar in both groups. Of note, the presence of positive vertical or horizontal margins after EMR or ESD had no impact on prognosis. There is no evidence of clear superiority of one technique over another, and the choice of technique should take into account not only size but also morphology and lifting, and the technique with a high likelihood of en bloc/R0 resection should be chosen.

For type III GNETs, ENETs recommend surgery and endoscopic resection is still not debated [6]. However, there is now evidence to support endoscopic resection. Kwon et al. [17] analyzed 50 patients with type III GNETs treated with endoscopic resection (EMR in 41 and ESD in 9 cases). Pathological incomplete resection was observed in 10 cases (no differences between the two techniques), and during the follow-up period (43 months), there was no evidence of tumor recurrence). In our cohort, polypectomy was performed in 5 patients at diagnosis because these lesions were small (5–10 mm) and were not

suspected to be NETs. Endoscopic resection was performed in 6 patients (5 EMR and 1 ESD). A complete resection rate after EMR was 40% and 100% after ESD. In the authors opinion, in selected patients with lesions <15–20 mm, Ki-67 <3% (consider up to 3–20%), without evidence of lymph node metastasis, endoscopic resection should be attempted (with ESD being the preferred technique for lesions >10 mm).

CgA level has been shown to be elevated in various diseases, including benign and malignant diseases and associated with acid-suppressive medications [21, 22]. The specificity of CgA for the diagnosis or prognosis of NETs is compromised by the nononcological and non-NET oncological situations, but is the most common circulating biomarker used for the follow-up of NETs. Tsai et al. [23] suggested that baseline CgA level is associated with overall survival of gastroenteropancreatic NET (GEP-NET) patients (HR = 13.52, $p = 0.045$). A 40% or greater increase of change of CgA level may predict tumor progression or recurrence during treatment or surveillance of gastroenteropancreatic NETs. In our study, CgA showed a low sensitivity for detection of recurrence (20%) but a specificity of 79%. The sensitivity was even lower in type I GNET patients (8%). Routine determination of serum CgA in all patients with GNET does not seem to be beneficial. However, it may be helpful in patients with distant disease to assess response to therapy.

This study has some potential limitations. The retrospective nature of our cohort presented limitations mainly in the selection of patients for each therapeutic group and in the collection of patients' data. Also, this unicenter design can limit the generalizability of findings. Furthermore, an important limitation in our work was that, although a significant number of patients were included, due to the reduced rate of recurrence and mortality of most GNETs, only 3 patients died and 7 patients had metastasis making it difficult to identify prognostic factors.

In conclusion, type I GNET is the most frequent in our series. Identification of risk factors for the presence of metastases and for mortality in these groups of patients can help in individualizing the therapeutic strategy and possibly reducing the burdensome surveillance for patients and hospital endoscopy resources as, even after endoscopic resection, lifelong endoscopic surveillance is required due to the multifocal nature of this tumor. Regardless of disease stage, the overall survival of our patients with type I GNET is excellent. ESD and EMR achieved similar short- and long-term results in this group of patients.

Statement of Ethics

This study was approved by the Ethical Committee of the Portuguese Oncology Institute of Porto in 2020.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There are no funding sources to declare.

Author Contributions

Raquel Ortigão performed research, collected and analyzed data, and wrote the paper; Luís Pedro Afonso performed the pathological evaluation of all lesions; Pedro Pimentel-Nunes and Mário Dinis-Ribeiro critically revised the article; and Diogo Libânio participated in the design of the study, critically revised the paper, and approved the final version for submission.

Data Availability Statement

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

References

1 Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol. 2017;3(10):1335–42.

2 Oberg K, Knigge U, Kwekkeboom D, Perren A; ESMO Guidelines Working Group. Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23(Suppl 7):vii124–130.

3 Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020;76(2):182–8.

4 Carvao J, Dinis-Ribeiro M, Pimentel-Nunes P, Libanio D. Neuroendocrine tumors of the gastrointestinal tract: a focused review and practical approach for gastroenterologists. GE Port J Gastroenterol. 2021;28(5):336–48.
5 Basuroy R, Srirajaskanthan R, Prachalias A, Quaglia A, Ramage JK. Review article: the investigation and management of gastric neuroendocrine tumours. Aliment Pharmacol Ther. 2014;39(10):1071–84.
6 Delle Fave G, O'Toole D, Sundin A, Taal B, Ferolla P, Ramage JK, et al. Vienna consensus conference p: ENETS consensus guidelines update for gastroduodenal neuroendocrine neoplasms. Neuroendocrinology. 2016; 103(2):119–24.
7 Vanoli A, La Rosa S, Miceli E, Klersy C, Maragliano R, Capuano F, et al. Prognostic evaluations tailored to specific gastric neuroendocrine neoplasms: analysis of 200 cases with extended follow-up. Neuroendocrinology. 2018;107(2):114–26.
8 Li YL, Qiu XD, Chen J, Zhang Y, Li J, Xu JM, et al. Clinicopathological characteristics and prognosis of 77 cases with type 3 gastric neuroendocrine tumours. World J Gastrointest Oncol. 2020;12:1416–27.
9 Chung CS, Tsai CL, Chu YY, Chen KC, Lin JC, Chen BC, et al. Clinical features and outcomes of gastric neuroendocrine tumors after endoscopic diagnosis and treatment: a Digestive Endoscopy Society of Tawian (DEST). Medicine. 2018;97(38):e12101.
10 Yang Z, Wang W, Lu J, Pan G, Pan Z, Chen Q, et al. Gastric neuroendocrine tumors (G-Nets): incidence, prognosis and recent trend toward improved survival. Cell Physiol Biochem. 2018;45(1):389–96.
11 Mun JY, Chin HM, Jun KH. A 13-year experience with gastric neuroendocrine tumors: a single institute study. Korean J Clin Oncol. 2018;14(1):8–14.
12 Nadler A, Cukier M, Rowsell C, Kamali S, Feinberg Y, Singh S, et al. Ki-67 is a reliable pathological grading marker for neuroendocrine tumors. Virchows Arch. 2013;462(5): 501–5.
13 Pape UF, Jann H, Muller-Nordhorn J, Bockelbrink A, Berndt U, Willich SN, et al. Prognostic relevance of a novel TNM classification system for upper gastroenteropancreatic neuroendocrine tumors. Cancer. 2008;113(2): 256–65.
14 Tian FX, Cai YQ, Zhuang LP, Chen MF, Xiu ZB, Zhang Y, et al. Clinicopathological features and prognosis of patients with gastric neuroendocrine tumors: a population-based study. Cancer Med. 2018;7(11):5359–69.
15 Esposito G, Cazzato M, Rinzivillo M, Pilozzi E, Lahner E, Annibale B, et al. Management of type-I gastric neuroendocrine neoplasms: a 10-years prospective single centre study. Dig Liver Dis. 2022;54(7): 890–5.
16 Sato Y, Takeuchi M, Hashimoto S, Mizuno K, Kobayashi M, Iwafuchi M, et al. Usefulness of endoscopic submucosal dissection for type I gastric carcinoid tumors compared with endoscopic mucosal resection. Hepatogastroenterology. 2013; 60(126):1524–9.
17 Kwon YH, Jeon SW, Kim GH, Kim JI, Chung IK, Jee SR, et al. Long-term follow up of endoscopic resection for type 3 gastric NET. World J Gastroenterol. 2013;19(46): 8703–8.
18 Chin JL, O'Connell J, Muldoon C, Swan N, Reynolds JV, Ravi N, et al. Selective resection of type 1 gastric neuroendocrine neoplasms and the risk of progression in an endoscopic surveillance programme. Dig Surg. 2021;38: 38–45.
19 Deprez PH, Moons LMG, O'Toole D, Gincul R, Seicean A, Pimentel-Nunes P, et al. Endoscopic management of subepithelial lesions including neuroendocrine neoplasms: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2022;54(4): 412–29.
20 Kim HH, Kim GH, Kim JH, Choi MG, Song GA, Kim SE. The efficacy of endoscopic submucosal dissection of type I gastric carcinoid tumors compared with conventional endoscopic mucosal resection. Gastroenterol Res Pract. 2014;2014: 253860.
21 Mahata SK, Corti A. Chromogranin A and its fragments in cardiovascular, immunometabolic, and cancer regulation. Ann N Y Acad Sci. 2019;1455(1):34–58.
22 Marotta V, Zatelli MC, Sciammarella C, Ambrosio MR, Bondanelli M, Colao A, et al. Chromogranin A as circulating marker for diagnosis and management of neuroendocrine neoplasms: more flaws than fame. Endocr Relat Cancer. 2018; 25(1):R11–29.
23 Tsai HJ, Hsiao CF, Chang JS, Chen LT, Chao YJ, Yen CJ, et al. The prognostic and predictive role of chromogranin A in gastroenteropancreatic neuroendocrine tumors: a single-center experience. Front Oncol. 2021; 11:741096.

GE – Portuguese Journal of Gastroenterology

Research Article

GE Port J Gastroenterol 2024;31:246–255
DOI: 10.1159/000530628

Received: October 22, 2022
Accepted: January 14, 2023
Published online: July 19, 2023

Knowledge in Inflammatory Bowel Disease: Translation to Portuguese, Validation, and Clinical Application of the IBD-KNOW Questionnaire

Cristiana Sequeira Mariana Coelho Inês Costa Santos Sara Ramos Lopes
Cristina Teixeira João Mangualde Isabelle Cremers Ana Paula Oliveira

Gastroenterology Department, Centro Hospitalar de Setúbal, Setúbal, Portugal

Keywords
Inflammatory bowel disease · Disease knowledge · Questionnaire · Medication adherence · Healthcare-related quality of life

Abstract

Background/Aims: Inflammatory bowel disease (IBD)-related knowledge empowers patients, providing the development of adaptative coping strategies. Recently, a more comprehensive questionnaire for evaluating IBD-related knowledge was developed, the IBD-KNOW. The main aim of our study was to translate to Portuguese and validate the IBD-KNOW questionnaire. We also explored the predictors of high scores of disease-related knowledge and the effect of knowledge on health-related quality of life (HRQoL) and therapeutic adherence. ***Methods:*** This is an observational, unicentric, and cross-sectional study. We translated and adapted the original English version of the IBD-KNOW questionnaire into Portuguese. Afterwards, IBD patients in the outpatient clinics were invited to fill out a multimodal form including the Portuguese version of IBD-KNOW, a visual analogue scale (VAS) of self-perceived knowledge, the Portuguese version of Short IBD Questionnaire (SIBDQ) and the Portuguese version of Morisky Adherence Scale 8-item (MMAS-8). Demographic and disease characteristics were collected. We assessed validity (through discriminate validity among non-IBD volunteers and correlation between IBD-KNOW and VAS) and reliability (through internal consistency, test-retest, and intraclass correlation). Statistical analysis was performed using SPSS version 25.0. ***Results:*** The mean IBD-KNOW score was significantly different among non-IBD validation group (doctors: 23, nurses: 18, and non-medical volunteers: 12, $p < 0.001$). IBD-KNOW showed a high internal consistency (Cronbach's α 0.78) and intraclass correlation (0.90). As expected, the IBD-KNOW score was positively correlated with VAS for self-perceived knowledge ($r = 0.45$, $p < 0.001$). One hundred and one patients with IBD (54 with ulcerative colitis and 47 with Crohn's disease) completed the questionnaire at baseline. Multivariate analyses showed that a high IBD-KNOW score was associated with longer disease duration (OR: 2.59 [CI 1.11–5.74]; $p = 0.04$), previous hospitalization (OR: 3.63 [CI 1.301–9.96]; $p = 0.01$), current biologic treatment (OR: 3.37 [CI 1.31–8.65]; $p = 0.02$), and higher educational level (OR: 4.66 [CI 1.74–10.21]; $p = 0.02$). Moreover, there was no significant correlation between overall IBD-KNOW and SIBDQ, nor between IBD treatment adherence (MMAS-8 = 8) and a higher mean IBD-KNOW score ($p = 0.552$). ***Conclusion:*** The Portuguese version of IBD-KNOW is a simple, valid, and reliable tool for assessing IBD-related knowledge. Longer disease duration, hospitalization, use of biologics, and higher educational level are

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

Correspondence to:
Cristiana Sequeira, c.afonso.sequeira@gmail.com

associated with higher levels of knowledge. Higher patient knowledge was not associated with higher HRQoL and adherence to therapy.

Conhecimento na doença inflamatória intestinal: tradução para português, validação e aplicação clínica do questionário IBD-KNOW

Palavras Chave
Doença Inflamatória Intestinal · Conhecimento da doença · Questionário · Adesão à terapêutica · Qualidade de vida relacionada com os cuidados de saúde

Resumo
Introdução/objetivos: O conhecimento relacionado com a Doença Inflamatória Intestinal (DII) visa capacitar os doentes, proporcionando o desenvolvimento de estratégias adaptativas de *coping*. Recentemente, foi desenvolvido um questionário mais abrangente para avaliar os conhecimentos relacionados com a DII, o IBD-KNOW. O principal objetivo do nosso estudo foi traduzir para português e validar o questionário IBD-KNOW. Também explorámos os preditores de um elevado nível de conhecimento relacionado com a DII e avaliámos o impacto do conhecimento na qualidade de vida associada a cuidados de saúde (QVACS) e na adesão terapêutica. ***Métodos:*** Este é um estudo observacional, unicêntrico e transversal. Traduzimos e adaptámos para português a versão original inglesa do questionário IBD-KNOW. Posteriormente, os doentes com DII de ambulatório foram convidados a preencher um questionário multimodal que incluía, a versão portuguesa do IBD-KNOW, uma escala visual analógica (EVA) de autoperceção do conhecimento, a versão portuguesa do Short IBD Questionnaire (SIBDQ) e a versão portuguesa do Morisky Adherence Scale 8-item (MMAS-8). Foram colhidos dados referentes a aspetos demográficos e da doença. Avaliámos a validade (através da validade discriminatória entre voluntários sem DII e da correlação entre IBD-KNOW e a EVA) e a fiabilidade (através da consistência interna, do teste-reteste e da correlação intraclasse). A análise estatística foi realizada utilizando a versão 25.0 do SPSS. ***Resultados:*** A pontuação média do IBD-KNOW foi significativamente diferente entre os voluntários não-DII (médicos: 23, enfermeiros: 18 e voluntários não-médicos: 12, p < 0,001). O IBD-KNOW mostrou uma elevada consistência interna (Cronbach's α 0,78) e uma correlação intraclasse (0,90). Como esperado, a pontuação IBD-KNOW correlacionou-se positivamente com a EVA de autoperceção do conhecimento (r=0,45, p < 0,001). Cento e um doentes com DII (54 com colite ulcerosa e 47 com doença de Crohn) preencheram o questionário. A análise multivariada mostrou valores médios de IBD-KNOW superiores em indivíduos com doença de longa duração (OR: 2,59; [IC 1,11-5,74] p=0,04), hospitalização prévia (OR 3,63 [IC 1,301-9,96]; p=0,01), sob tratamento biológico atual (OR 3,37 [1,31-8,65]; p=0,02) e com nível educacional superior (OR 4,66 [IC 1,74-10,21]; p=0,02). Além disso, não houve correlação significativa entre IBD-KNOW e SIBDQ, nem entre a adesão ao tratamento IBD (MMAS-8=8) e um IBD-KNOW acima da média (p=0,552). ***Conclusão:*** A versão portuguesa do IBD-KNOW é uma ferramenta simples, válida e fiável para avaliar os conhecimentos relacionados com a DII. Uma maior duração da doença, hospitalização, utilização de biológicos e um nível de educação mais elevado estão associados a níveis de conhecimento mais elevados. Na nossa coorte, níveis superiores de conhecimento não se associaram a melhor qualidade de vida nem a maior adesão à terapêutica.

Introduction

Inflammatory bowel disease (IBD), that includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic, idiopathic inflammatory disease of the gastrointestinal tract. IBD is characterized by an early onset with a relapsing-remitting disease course that requires lifelong treatment. Unpredictable course and challenging complications or symptoms affect the quality of life (QoL) of IBD patients [1], so providing tools to manage the disease and encouraging patients to play an active role in disease management are of utmost importance. A higher level of disease-related knowledge is associated with the development of more adaptive coping among IBD patients [2]. Moreover, knowledge has relevant implications for health outcomes. A higher level of knowledge is associated with reduced healthcare costs [3] and reduced need for step-up strategy in IBD patients [4]. Finally, knowledge measurement tools evaluate educational programs' effectiveness and identify "gaps" in knowledge [5].

For this purpose, three questionnaires are available. First, in 1993, the Patient Knowledge Questionnaire was developed; however, it is rarely used [6]. Then, Eaden et al. [7], in 1999, published the Crohn's and Colitis

Knowledge (CCKNOW) score; although widely applied, given the emergence of numerous innovative therapies, it currently does not adequately reflect treatment-related knowledge. Recently, Yoon et al. [8] developed a questionnaire, the Inflammatory Bowel Disease Knowledge (IBD-KNOW).

IBD-KNOW is a 24-item questionnaire assessing up-to-date knowledge about IBD, which includes aspects of anatomy, function, diet and lifestyle, epidemiology, general knowledge, medication, complications, surgery, reproduction, and vaccination [8]. The IBD-KNOW was developed and validated in English among patients from various populations.

The main objective of this study was the translation of the IBD-KNOW into Portuguese language and its validation. We also aimed to assess the predictors of a high level of disease-related knowledge and evaluate the association between knowledge and QoL and therapeutic adherence in patients with IBD.

Materials and Methods

Study Design

We conducted an observational, cross-sectional study that included the translation into Portuguese, validation, and application of the IBD-KNOW questionnaire. All participants received a letter explaining the study and gave their written informed consent.

Translation

The English version of IBD-KNOW was translated into Portuguese by two independent bilingual individuals (Portuguese and English). The translations were evaluated, reconciled, and back-translated by two gastroenterologists with English proficiency and experience in following patients with IBD. The back-translators had no prior knowledge of the content of IBD-KNOW. Moreover, a group of five IBD patients filled out the preliminary version to assess comprehensiveness. Finally, the previous gastroenterologists made minor changes to obtain the final translation (online suppl. File 1; for all online suppl. material, see https://doi.org/10.1159/000530628).

Preparation of the Questionnaire

A multimodal self-administered form was developed, including questions regarding (1) sociodemographic data (age, gender, educational level, employment status), (2) clinical information (IBD subtype, date of IBD diagnosis, family history of IBD, smoking status, previous IBD-related hospitalization and surgery, current medications), and (3) sources of IBD knowledge information. The form also included three questionnaires: the translated IBD-KNOW, the Portuguese version of the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) [9], the Portuguese version of the Morisky Adherence Scale 8-item (MMAS-8) [10], and yet the visual analogue scale (VAS) for perceived knowledge.

For the 24 items of the IBD-KNOW, three choices ("true," "false," and "don't know") were applicable, with a maximum score of 24 points. We calculated the mean IBD-KNOW score and assessed the factors affecting the level of knowledge. Total higher values of the IBD-KNOW questionnaire represented higher knowledge of the disease.

The SIBDQ was applied to assess health-related quality of life (HRQoL), consisting of 10 questions scored by a 7-point Likert scale. An absolute SIBDQ score of less than 50 was considered a poor QoL. Medication adherence was assessed with the MMAS-8, which includes seven dichotomous (Y/N) and 1 item of the 5-point Likert Scale. A MMAS-8 score equal to 8 meant good adherence. Finally, we applied a VAS for self-awareness about IBD knowledge. It consists of a 10 cm long line, with a mark at the beginning corresponding to very poor knowledge (0) and another at the end corresponding to very high knowledge (10).

Selection of Patients and Measurement of Patient's Knowledge

Patients were chosen to participate by convenience, with the invitation addressed to patients who attended the IBD outpatient clinic or the Gastroenterology Day Care Unit at Setúbal Hospital between July and November 2021. Patients who met the following criteria were included: older than 18 years; diagnosis of CD or UC at least 3 months before; at least one previous IBD outpatient visit; and signed informed consent. We excluded patients who completed less than 80% of the IBD-KNOW questions. We asked 15 patients to fill out the IBD-KNOW questionnaire twice with a minimum interval of 1 month.

Validation of Questionnaire

Since there are no external criteria for IBD-related knowledge, validity and discriminatory ability were assessed by (1) applying the IBD-KNOW questionnaire in different groups expected to have different levels of IBD-related knowledge, (2) demonstrating the association between IBD-KNOW scores and surrogate markers of IBD-related knowledge, and (3) assessing the correlation between IBD-KNOW and perceived self-awareness of the disease.

Therefore, the IBD-KNOW questionnaire was submitted to 3 groups of non-IBD volunteers with different levels of IBD knowledge (eleven gastroenterologists, ten nurses, and ten non-medical professional volunteers). For the second hypothesis, the IBD-KNOW score should positively correlate with disease duration. The score should also be higher in patients with higher education; however, it should not differ according to gender and disease type (CD or UC). Furthermore, we analysed convergent validity by assessing the correlation between the IBD-KNOW and the VAS for disease self-perceived knowledge.

Reliability was determined as test-retest reliability (reproducibility) and internal consistency. We assessed reproducibility, asking 15 patients to answer the questionnaire twice, with a minimum interval of 1 month, to decrease the possibility of recalling previous answers (recall bias) [8, 9, 11–13].

Statistical Analysis

Statistical analysis was performed using SPSS – Statistical Package for the Social Sciences – version 25.0, with a significance level set at $p < 0.05$. The normality of variables was verified. Descriptive analysis determined the absolute and relative frequency for categorical variables, the mean ± standard deviation for normal continuous variables, and the median and interquartile range

Table 1. Sociodemographic and clinical characteristics

IBD patients' characteristics	Overall cohort (*n* = 101)
Age, years, mean (±SD)	42 (±12)
Sex (females), *n* (%)	51 (50.5)
Type of IBD, *n* (%)	
CD	47 (46.6)
UC	54 (53.4)
Disease duration, years, median (interquartile range)	5 (1–16)
Smoking status, *n* (%)	
Never or past smoker	78 (77.2)
Current smoker	23 (22.8)
History of IBD-related hospitalization, *n* (%)	53 (52.5)
History of IBD-related surgery, *n* (%)	20 (19.8)
Family history of IBD, *n* (%)	22 (21.8)
Current medical therapy, *n* (%)	
5-Aminosalicylates monotherapy	31 (30.6)
Immunomodulators (mono- or combo therapy)	26 (25.7)
Biologic therapy	53 (52.5)
Education level, *n* (%)	
University	21 (20.8)
Secondary	28 (27.8)
None, primary, or basic	52 (51.4)
IBD-KNOW score, mean (±SD)	13 (±4)
SIBDQ score, mean (±SD)	51 (±16)
MMAS-8 score, median (interquartile range)	7 (5–8)
Good adherence (=8)	79 (78.2%)

MMAS-8, Morisky Adherence Scale 8-item; SD, standard deviation.

for non-normal ones. Fisher exact tests were used to compare categorical variables. To analyse the association between the score of IBD-KNOW-IBD and sociodemographic and clinical variables, the Mann-Whitney U test, the Kruskal-Wallis *H* test, Spearman's correlation, and Student's *t* test. Variables significantly associated with high IBD-KNOW score in univariate analysis were included in multiple logistic regression analyses. The internal consistency of the IBD-KNOW was evaluated using Cronbach's alpha coefficient, which was considered high for alpha values ≥0.70. Reproducibility was assessed using the intraclass correlation coefficient, considered appropriate if ≥0.70. We calculated the sample size calculation for intraclass correlation [11, 13, 14].

Results

Patients

From July to November 2021, 108 patients with IBD completed the multimodal questionnaire; we excluded 7 patients from the final analysis due to less than 80% completion of the IBD-KNOW questionnaire. Thus, we included 101 patients (54 with UC and 47 with CD); the mean age was 42 (±12) years, with a similar number of female (*n* = 51) and male (*n* = 50) patients. The mean duration of IBD was 5 years, and most patients were treated with biologics (*n* = 53). Almost one-fifth of patients (19.8%) had undergone surgery at least once when they completed the questionnaire. Of the patients enrolled, 21 (20.8%) had a university degree. The sociodemographic and clinical characteristics of the participants at the time of completing the questionnaire are shown in Table 1.

Validity

The IBD-KNOW questionnaire was first tested on the three groups of non-IBD volunteers with different expected levels of IBD-related knowledge, including ten non-medical volunteers, ten nurses, and eleven gastroenterologists (seven seniors and four fellows). The mean questionnaire score was significantly different between the three validation groups (12 non-medical, 18 nurses, and 23 gastroenterologists; $p < 0.001$) (shown in Fig. 1).

In addition, the IBD-KNOW score was positively correlated with disease duration ($r = 0.606$; $p < 0.001$). The score was also higher in patients with higher level education (secondary or higher vs. primary education or lower: 15.1 ± 4.5 vs. 12.2 ± 4.3; $p = 0.01$) and did not differ according to gender (female vs. male: 12.3 ± 4.4 vs. 13.9 ± 4.3; $p = 0.06$) and IBD subtype (CD vs. UC 13.1 ± 4.7 vs.

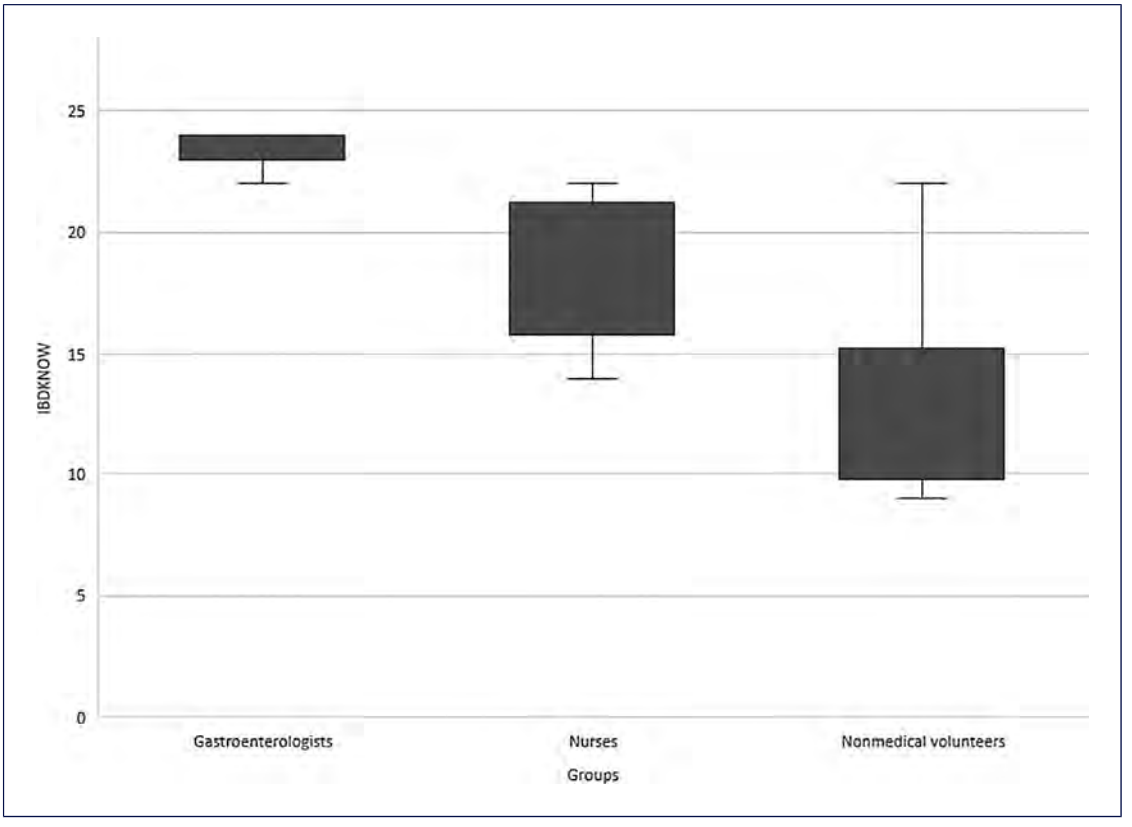


Fig. 1. Level of IBD-KNOW score among the three groups for validation.

12.9 ± 4.7; $p = 0.518$) (shown in Table 2). IBD-KNOW score showed a moderate but significant correlation with VAS for perceived knowledge ($r = 0.45$, $p < 0.001$).

Evaluation of IBD-Related Knowledge

Patients acquired IBD-related knowledge mainly from doctors and the Internet. The sources of information related to IBD are summarized in Table 3.

The mean IBD-KNOW questionnaire score was 13/24, with no significant difference regarding age, gender, and IBD subtype. The correct response rate was 54%; the "vaccination" domain performed the highest (78%). The vast majority of patients (74%) recognized the importance of colorectal cancer (CRC) screening in long-term disease. Among the ten domains of the IBD-KNOW, the correct response rate of the domains "reproduction" (24%), "function" (17%), and "surgery" (16%) was the lowest. The correct answer rate for each domain is shown in Figure 2.

Univariate and multivariate analyses of the predictive factors for high IBD-KNOW are summarized in Tables 2 and 4, respectively. Multivariate analysis showed that a high IBD-KNOW score (higher than the mean score) was associated with longer disease duration, previous IBD-related hospitalization, current biological treatment, and a higher level of education.

HRQoL in IBD patients (SIBDQ) showed no correlation with IBD-KNOW ($r = -0.188$, $p = 0.383$). There was no statistically significant association between adherence to IBD treatment (MMAS-8 = 8) and a mean IBD-KNOW score above the mean ($p = 0.552$).

IBD-KNOW – Internal Consistency and Reproducibility

We assessed the internal consistency between the 24 questions of IBD-KNOW. We obtained high internal consistency (Cronbach's α 0.78). Fifteen patients filled out two sets of questionnaires within 1 month. The intraclass correlation was 0.90 (95% confidence interval 0.70–0.96).

Discussion

Patient education is a critical determinant for managing chronic diseases such as IBD. Patient empowerment has been shown to contribute to improved QoL and therapeutic adherence, with consequent improvement in

Table 2. Univariate analysis

	Mean of IBD KNOW score	*p* value
Sex		
Female	12.3±4.4	0.06
Male	13.9±4.3	
Type of IBD		
CD	13.1±4.7	0.518
UC	12.9±4.7	
Disease duration		
<5 years	14.1±4.3	0.004
≥5 years	11.5±4.3	
Smoking status		
Never or past smoker	14±3.2	0.278
Current smoker	12.9±4.8	
IBD-related hospitalization		
No	11.3±4.4	<0.001
Yes	14.7±3.9	
IBD-related surgery		
No	12.5±4.2	0.003
Yes	15.7±4.5	
Family history of IBD		
No	13.1±4.6	0.974
Yes	13.1±4.4	
Current medical therapy		
5-Aminosalicylates monotherapy		
No	11.9±4.6	0.08
Yes	13.6±4.3	
Immunomodulators (monotherapy or combo)		
No	13.4±4.9	0.339
Yes	12.3±2.8	
Biologics		
No	11.4±3.2	0.01
Yes	14±4.5	
Highest level of education		
Secondary or higher	15.1±4.5	0.01
None, primary, or basic	12.2±4.3	
MMAS-8 score		
Good adherence (=8)	13.0±4.6	0.723
No adherence <8	13.4±3.9	

MMAS-8, Morisky Adherence Scale 8-item.

Table 3. Source of acquired IBD-related information

Source of acquired IBD-related information (multiple selection is possible)	*N* (%)
Doctor	94 (93)
Nurse	35 (34.6)
Internet	51 (50.5)
Books	17 (16.8)
Patient's organization	9 (8.9)

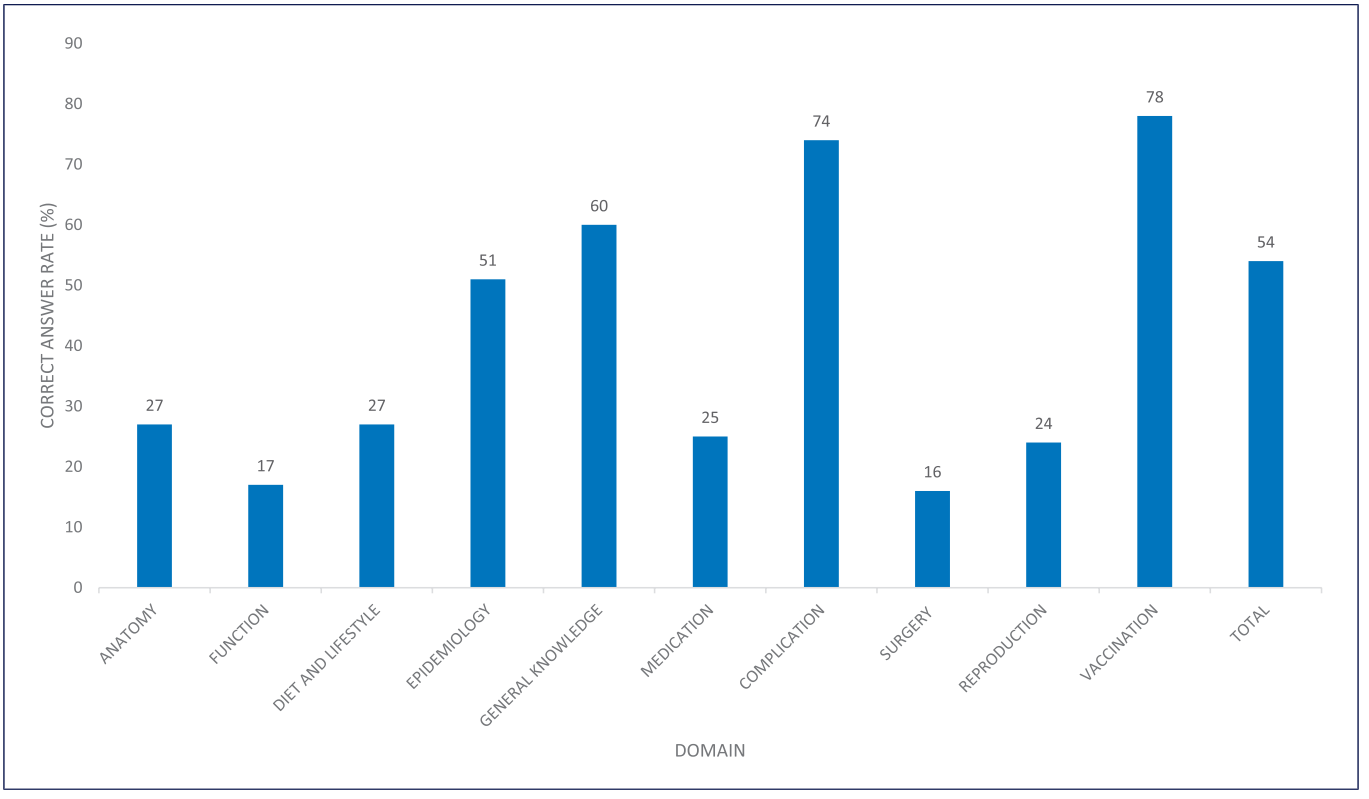


Fig. 2. Correct answer rate of each domain.

Table 4. Multivariate analyses of predictive factors for high IBD-KNOW score (IBD-KNOW above the mean)

	Patients with high IBD KNOW score – multivariate analysis	
	odds ratio (95% confidence interval)	*p* value
Disease duration ≥5 years	2.599 (1.112–5.740)	0.04
Previous IBD-related hospitalization	3.629 (1.309–9.962)	0.01
Previous IBD-related surgery	0.398 (0.105–1.503)	0.174
Biologic treatment	3.366 (1.310–8.651)	0.02
Education level: secondary or higher	4.666 (1.744–10.213)	0.02

the course of the disease [15, 16]. Therefore, an instrument that objectively measures IBD-related knowledge allows for identifying "gaps" in patients' disease-related knowledge in order to improve information strategies. This is the first IBD-specific knowledge questionnaire translated into Portuguese language, which has proven to be a valid and reliable tool to measure IBD-related knowledge in a Portuguese cohort.

There is no gold standard to assess IBD-related knowledge, and there are no previously validated questionnaires in Portuguese. The validity of the IBD-KNOW questionnaire was evaluated, showing that the mean score was significantly different between the groups of non-IBD volunteers, as previously reported in other studies that validated questionnaires assessing IBD-related knowledge [7, 8, 12, 17]. Furthermore, the IBD-KNOW was predicted to correlate with variables which are well-known markers of IBD-related knowledge [6, 7]; these findings were also corroborated by other questionnaire studies [12]. Finally, IBD-KNOW score was significantly correlated with self-perceived knowledge about the disease, similar to previous questionnaire validation studies [18, 19].

The questionnaire also demonstrated excellent test-retest reliability and the Cronbach α of the IBD-KNOW was high (0.78) facilitating comparison between groups of patients. The IBD-KNOW allowed quantification of patients' level of IBD knowledge and highlighted specific areas where knowledge was lacking. The mean score for IBD-KNOW was 13, similar to the score reported in the original IBD-KNOW publication [8]. The mean score obtained in this study is better than that of Eastern IBD patients but lower than that of North American IBD patients [20]. The mean correct answer rate was similar to the original study [8].

The domains "reproduction," "medication," "function," and "surgery" had the lowest correct response rates, similar to those reported by the original study [8]. Reproduction is a well-known area of knowledge deficit [8, 17, 21]; a more focused questionnaire is available to address this issue [22]. The proportion of patients who recognized the importance of screening colonoscopy for CRC in long-term disease is higher than previously reported in the literature [23]. The question on vaccination showed a very high rate of correct answers, reflecting the knowledge gained from the recent vaccination campaign for COVID-19. Physicians and the Internet were the most important reported sources of information; these results are consistent with previous studies [2, 8, 20, 24].

In addition, we also studied variables with potential impact on the level of knowledge related to IBD. According to previously published studies, a higher educational level was positively correlated with higher scores [8, 12, 17, 20, 21], partly explained by the ease of understanding the more technical terms. Despite the attempt to simplify the response method ("true," "false," or "don't know") as opposed to traditional multiple-choice tests, in which the influence of education would tend to be greater [17], the level of education remained a determining factor for knowledge levels.

We found that disease duration (≥5 years), previous IBD-related hospitalization, and use of biologics are associated with higher score in multivariate analysis. These findings may be explained by direct exposure to IBD-related environments over an extended period, providing the patient with more opportunities to obtain disease-related information. Danion et al. [17] showed that an IBD diagnosis ≤3 years and the absence of anti-TNFα treatment for IBD are independent risk factors for low levels of knowledge. In addition, other studies corroborated that disease duration [8, 20], previous hospitalization for IBD [8], and use of biologics [20] affected IBD-KNOW scores. The need for step-up treatment strategy or the development of complicated disease (need for hospitalization or surgery) makes patients more concerned about their condition, which drives the search for information related to their illness. Contrary to the available literature [20], our study revealed no difference in IBD-KNOW score in patients with a family history of IBD, which may be due to the significant impact of direct exposure to IBD-related environments (e.g., hospitalization, surgery) among our patients compared to indirect exposure (e.g., family history).

Lack of knowledge about the chronic nature of IBD and fear of adverse drug effects are the most frequently reported causes of non-adherence among IBD patients, particularly those in clinical remission [25]. Few studies have addressed the impact of knowledge on adherence; however, knowledge appears to have a positive effect on compliance [26]. The MMAS-8 is a self-reported survey, and it was the first adherence scale validated in IBD [27], although there are conflicting data on its performance. This scale is more accurate for assessing adherence to oral therapy; previous data showed that only patients on immunomodulators had the MMAS-8 score positively correlated with knowledge [28]. Taking into account that half of our patients were on biologic therapy and these patients generally present with good adherence, it may have contributed to the lack of association between the level of knowledge and adherence in our cohort. Moreover, our patients had a higher adherence rate than that described in the literature [28].

The authors found no association between knowledge and HRQoL in this population. According to previously published studies [2, 29, 30], although education is desirable, knowledge does not necessarily translate into improved HRQoL and well-being. One reason for this finding is that higher knowledge about IBD empowers patients and also creates more anxiety [16].

Our study has several limitations. First, this study was conducted at a single centre, limiting our findings' generalizability. Second, the relatively small sample size may influence our results. Third, patient association status (e.g., Portuguese Association of Inflammatory Bowel Disease in Portugal) was not recorded, which is a well-known factor of better level of knowledge in the field of IBD. Finally, the present study was designed cross-sectionally, so it did not assess patients' knowledge longitudinally. Therefore, further longitudinal studies and multicentre studies would be needed.

In conclusion, the Portuguese version of the IBD-KNOW is a valid and reliable instrument for measuring patients' IBD-related knowledge. Further evidence of the validity and reliability of IBD-KNOW will be mostly based on its continued use in the clinical setting.

Considering the growing interest in patient-tailored care model, IBD-KNOW allows the identification of significant knowledge deficits and factors affecting the level of IBD-related knowledge. This is of great interest as it allows rethinking methods of informing patients to increase their health and well-being. IBD teams can develop educational programs that address potential knowledge gaps among IBD patients. Furthermore, IBD-KNOWs allow the objective assessment of the impact of these educational programs. Finally, future studies may explore the role the impact of IBD-KNOW score on patient behaviour (adherence), medical outcomes (medical acceleration), and QoL.

Statement of Ethics

This observational study was reviewed and approved by the Ethics Committee at Centro Hospitalar de Setúbal (Ethics Committee for Health of CHS; n. 013/2022), and it was performed in accordance with the Declaration of Helsinki. Participation in this study was voluntary, and all patients provided consent before enrolment.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There is no funding source to report.

Author Contributions

Cristiana Sequeira, Cristina Teixeira, and Isabelle Cremers: study design; Cristiana Sequeira, Mariana Coelho, and Inês Costa Santos: data collection; Cristiana Sequeira: statistical analysis, interpretation of data, and manuscript drafting; and all authors: final approval of the article.

Data Availability Statement

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

References

1 Moradkhani A, Beckman LJ, Tabibian JH. Health-related quality of life in inflammatory bowel disease: psychosocial, clinical, socioeconomic, and demographic predictors. J Crohns Colitis. 2013 Jul;7(6):467–73.
2 Moradkhani A, Kerwin L, Dudley-Brown S, Tabibian JH. Disease-specific knowledge, coping, and adherence in patients with inflammatory bowel disease. Dig Dis Sci. 2011 Oct;56(10):2972–7.
3 Colombara F, Martinato M, Girardin G, Gregori D. Higher levels of knowledge reduce health care costs in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2015 Mar;21(3):615–22.
4 Park J, Yoon H, Shin CM, Park YS, Kim N, Lee DH. Higher levels of disease-related knowledge reduce medical acceleration in patients with inflammatory bowel disease. PLoS One. 2020 Jun 5;15(6):e0233654.
5 Malter L, Jain A, Cohen BL, Gaidos JKJ, Axisa L, Butterfield L, et al. Identifying IBD providers' knowledge gaps using a prospective web-based survey. Inflamm Bowel Dis. 2020 Aug 20;26(9):1445–50.
6 Jones SC, Gallacher B, Lobo AJ, Axon ATR. A patient knowledge questionnaire in inflammatory bowel disease. J Clin Gastroenterol. 1993 Jul;17(1):21–4.
7 Eaden JA, Abrams K, Mayberry JF. The Crohn's and colitis knowledge score: a test for measuring patient knowledge in inflammatory bowel disease. Am J Gastroenterol. 1999 Dec;94(12):3560–6.
8 Yoon H, Yang SK, So H, Lee KE, Park SH, Jung SA, et al. Development, validation, and application of a novel tool to measure disease-related knowledge in patients with inflammatory bowel disease. Korean J Intern Med. 2019 Jan 1;34(1):81–9.
9 Roseira J, Sousa HT, Marreiros A, Contente LF, Magro F. Short inflammatory bowel disease questionnaire: translation and validation to the Portuguese language. Health Qual Life Outcomes. 2021 Dec;19(1):59.
10 Cabral AC, Moura-Ramos M, Castel-Branco M, Fernandez-Llimos F, Figueiredo IV. Cross-cultural adaptation and validation of a European Portuguese version of the 8-item Morisky medication adherence scale. Rev Port Cardiol. 2018 Apr;37(4):297–303.
11 Hernaez R. Reliability and agreement studies: a guide for clinical investigators. Gut. 2015 Jul;64(7):1018–27.
12 Haaland D, Day AS, Otley A. Development and validation of a pediatric IBD knowledge inventory device: the IBD-KID. J Pediatr Gastroenterol Nutr. 2014 Mar;58(3):313–9.
13 Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. Qual Life Res. 2010 May;19(4):539–49.
14 Bonett DG. Sample size requirements for estimating intraclass correlations with desired precision. Stat Med. 2002 May 15;21(9):1331–5.
15 Tae CH, Jung SA, Moon HS, Seo JA, Song HK, Moon CM, et al. Importance of patients' knowledge of their prescribed medication in improving treatment adherence in inflammatory bowel disease. J Clin Gastroenterol. 2016 Feb;50(2):157–62.
16 Waters BM, Jensen L, Fedorak RN. Effects of formal education for patients with inflammatory bowel disease: a randomized controlled trial. Can J Gastroenterol. 2005;19(4):235–44.
17 Danion P, Buisson A, Roblin X, Mathieu N, Charlois AL, Borgerding JN, et al. IBD-INFO questionnaire: a multicenter French up-to-date survey of patient knowledge in inflammatory bowel disease. Inflamm Bowel Dis. 2018 Apr 23;24(5):943–52.
18 Soares JB, Nogueira MC, Fernandes D, Gonçalves BM, Gonçalves R. Validation of the Portuguese version of a questionnaire to measure quality of care through the eyes of patients with inflammatory bowel disease (QUOTE-IBD). Eur J Gastroenterol Hepatol. 2015 Dec;27(12):1409–17.
19 Casellas F, Navarro E, Amil P, Barber C, Marín L, Guardiola J, et al. Development and validation of the QUECOMIICAT questionnaire: a tool to assess disease-related knowledge in patients with inflammatory

bowel disease. Rev Esp Enferm Dig. 2019; 111(8):586–92.
20 Kim JY, Yoon H, Hwang JS, Yang SK, Park SH, Loftus EV. Comparison of disease-related knowledge of patients with inflammatory bowel disease between the west and the east using an updated questionnaire (IBD-KNOW). J Clin Gastroenterol. 2020 Sep;54(8):720–4.
21 Wardle RA, Mayberry JF. Patient knowledge in inflammatory bowel disease: the Crohn's and Colitis Knowledge Score. Eur J Gastroenterol Hepatol. 2014 Jan;26(1):1–5.
22 Selinger CP, Eaden J, Selby W, Jones DB, Katelaris P, Chapman G, et al. Patients' knowledge of pregnancy-related issues in inflammatory bowel disease and validation of a novel assessment tool ('CCPKnow'). Aliment Pharmacol Ther. 2012 Jul;36(1):57–63.
23 Lopez A, Collet-Fenetrier B, Belle A, Peyrin-Biroulet L. Patients' knowledge and fear of colorectal cancer risk in inflammatory bowel disease: colorectal cancer risk in IBD. J Dig Dis. 2016 Jun;17(6):383–91.
24 Burisch J, Vegh Z, Pedersen N, Cuković-Čavka S, Turk N, Kaimakliotis I, et al. Health care and patients' education in a European inflammatory bowel disease inception cohort: an ECCO-EpiCom study. J Crohns Colitis. 2014 Aug;8(8):811–8.
25 Aluzaite K, Braund R, Seeley L, Amiesimaka OI, Schultz M. Adherence to inflammatory bowel disease medications in Southern New Zealand. Crohns Colitis 360. 2021 Jul 1;3(3):otab056.
26 Červený P, Bortlík M, Kuběna A, Vlček J, Lakatos PL, Lukáš M. Nonadherence in inflammatory bowel disease: results of factor analysis. Inflamm Bowel Dis. 2007 Oct;13(10):1244–9.
27 Trindade AJ, Ehrlich A, Kornbluth A, Ullman TA. Are your patients taking their medicine? Validation of a new adherence scale in patients with inflammatory bowel disease and comparison with physician perception of adherence. Inflamm Bowel Dis. 2011 Feb;17(2): 599–604.
28 Chan W, Chen A, Tiao D, Selinger C, Leong R. Medication adherence in inflammatory bowel disease. Intest Res. 2017;15(4):434–45.
29 Hou JK, Turkeltaub JA, McCarty Iii TR, El-Serag HB. Assessment of disease specific knowledge and health-related quality of life among United States military veterans with inflammatory bowel disease. WJG. 2015 May 21;21(19):6001–7.
30 Bregenzer N, Lange A, Fürst A, Gross V, Schölmerich J, Andus T. Patient education in inflammatory bowel disease does not influence patients knowledge and long-term psychosocial well-being. Z Gastroenterol. 2005 Apr;43(4):367–71.

GE – Portuguese Journal of Gastroenterology

Research Article

GE Port J Gastroenterol 2024;31:256–261
DOI: 10.1159/000531234

Received: February 11, 2023
Accepted: May 16, 2023
Published online: July 19, 2023

Portuguese Results of the ETICC Study: Impact of the Pandemic COVID-19 in the Diagnosis and Management of Colorectal Cancer in 2020 in Portuguese Hospitals

Maria Ana Rafael[a, b] Cristiana Sequeira[b, c] Sónia Isabel da Silva Barros[b, d] Bárbara Silva Abreu[b, e] Cristina Teixeira[b, f] Pierre Lahmek[f, g] Marine Besnard[f, h] Bruno Lesgourgues[f, h]

[a]Gastroenterology Department, Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal; [b]Núcleo de Gastrenterologia dos Hospitais Distritais, Lisboa, Portugal; [c]Gastroenterology Department, Centro Hospitalar de Setúbal, Setúbal, Portugal; [d]Gastroenterology Department, Centro Hospitalar Universitário do Algarve, Faro, Portugal; [e]Gastroenterology Department, Hospital Beatriz Ângelo, Loures, Portugal; [f]Association Nationale des Gastroentérologues des Hôpitaux Généraux, Montfermeil, France; [g]Gastroenterology Department, Hôpital Emile Roux, Limeil-Brevannes, France; [h]Gastroenterology Department, Centre Hospitalier de Montfermeil, Montfermeil, France

Keywords
COVID-19 · Colorectal cancer · Pandemic

Abstract

Introduction: The outbreak of coronavirus disease 2019 (COVID-19) had affected clinical practice in several ways, including the restriction of nonessential endoscopic procedures. Therefore, our aim was to evaluate how colorectal cancer (CRC) diagnosis and management was affected during the first year of pandemics in Portugal. ***Methods:*** This is a Portuguese substudy of the French retrospective multicentric study ETICC (*Etude de l'Impact de la pandémie COVID-19 sur le diagnostic et la prise en charge du Cancer Colorectal*). We compared patients' characteristics, clinical manifestations, CRC staging at diagnosis, delay to first medical appointment, histological diagnosis, surgical and medical treatments between the year previous to the pandemics (control) and the first year of pandemics. ***Results:*** We included 766 patients: 496 in the control group and 270 in the COVID group. There was no significant difference in CRC staging at diagnosis between both groups, with 21% being diagnosed as metastatic in the control group and 22% in the first year of pandemics ($p = 0.770$). Contrary to what happened in France, there was a significant decrease in CRC diagnosis in asymptomatic patients (25–8.4%; $p < 0.001$) and after a positive fecal immunochemical test (20.8–11.3%; $p = 0.002$) during the pandemics. Although the increase in the overall complication rate at diagnosis was nonsignificant, in Portugal, there was a significant increase in diagnosis of abdominal occlusion (12.1–18.1%; $p = 0.033$). In Portugal, time between the beginning of symptoms and the first medical appointment significantly increased from a median of 50 days to 64 days during COVID ($p < 0.001$). On the contrary, time between histological diagnosis and tumor resection had significantly decreased from a median of 65 to 39 days ($p < 0.001$). Time between histological diagnosis and neoadjuvant treatment was not statistically different (median of

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

Correspondence to:
Maria Ana Rafael, maria.monteiro.rafael@gmail.com

64–67 days; $p = 0.590$), as was time between histological diagnosis and palliative chemotherapy (median of 50–51 days; $p = 1.000$). Time from CRC resection and adjuvant treatment has significantly decreased from a median of 54 to 43 days ($p = 0.001$). ***Discussion:*** We found a significant impact in CRC diagnosis in the first year of pandemics, more pronounced than what was found in France. These are likely related not only with the closing of endoscopy units but also with the difficulties patients had in finding an appointment with their general practitioners. On the other hand, both in France and Portugal, the first year of pandemics did not worsen CRC staging at diagnosis and did not significantly affect medical and surgical treatments once the diagnosis was made.

Resultados Portugueses do Estudo ETICC: Impacto da pandemia COVID-19 no diagnóstico e tratamento do cancro colorretal em 2020

Palavras Chave
COVID-19 · Cancro colorretal · Pandemia

Resumo
Introdução: A pandemia provocada pelo coronovírus (COVID-19) condicionou a prática clínica de múltiplas formas, incluindo a restrição a exames endoscópicos não urgentes. Por este motivo, decidimos avaliar o impacto do primeiro ano de pandemia no diagnóstico e tratamento do cancro colorretal (CCR) em Portugal. ***Métodos:*** Este é um subestudo do estudo Francês retrospetivo multicêntrico ETICC (*Etude de l'Impact de la pandémie COVID-19 sur le diagnostic et la prise en charge du Cancer Colorectal*). Foram comparadas as características dos doentes, manifestações clínicas, estadiamento do CCR ao diagnóstico, intervalos entre primeiro contacto médico neste contexto, diagnóstico histológico e tratamentos, entre o primeiro ano de pandemia e o ano precedente. ***Resultados:*** Foram incluídos 766 doentes, 496 no grupo controlo e 270 no grupo COVID. Em França e em Portugal não se verificou um agravamento no estadiamento do CCR à data do diagnóstico no primeiro ano de pandemia, com 21% dos casos metastáticos à data de diagnóstico no grupo controlo e 22% no primeiro ano da pandemia ($p = 0.770$). Contudo, apenas em Portugal se constatou uma redução significativa do número de CCR em doentes assintomáticos (25% para 8.4%; $p < 0.001$) ou após uma pesquisa de sangue oculto positiva (20.8% para 11.3%; $p = 0.002$) durante a pandemia. Apesar do aumento na taxa de complicações ao diagnóstico não ser significativa, em Portugal a taxa de diagnósticos em contexto de oclusão intestinal aumentou significativamente (12.1% para 18.1%; $p = 0.033$). Em Portugal, o tempo entre início dos sintomas e a primeira consulta médica aumentou significativamente, de uma mediana de 50 para 64 dias durante o COVID ($p < 0.001$). Por outro lado, o tempo entre diagnóstico histológico e resseção tumoral reduziu significativamente de 65 para 39 dias ($p < 0.001$). O tempo entre diagnóstico histológico e tratamento neoadjuvante (mediana de 64 para 67 dias; $p = 0.590$) ou quimioterapia paliativa (mediana de 50 para 51 dias; $p = 1.000$) não foi estatisticamente significativo, tendo decrescido significativamente o tempo entre ressecção e adjuvância (mediana de 54 para 43 dias, $p = 0.001$). ***Discussão:*** Este estudo evidenciou um impacto significativo no diagnóstico de CCR durante o primeiro ano de pandemia, mais pronunciado que em França. Este achado dever-se-á não só à limitação do acesso aos exames endoscópicos, mas também à dificuldade da população portuguesa em aceder aos Cuidados de Saúde Primários. Por outro lado, tanto em França como em Portugal, no primeiro ano de pandemia não se verificou um agravamento no estadiamento ou atraso no tratamento médico e cirúrgico do CCR.

Introduction

The outbreak of coronavirus disease 2019 (COVID-19), caused by coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly around the world, constituting an unprecedented pandemic that has influenced various aspects of daily activity in hospitals. The Portuguese government officially declared the lockdown on March 18, 2020, which lasted until May 2020 [1].

COVID-19 has affected clinical practice in several ways and disrupted health care delivery systems worldwide. Measures were taken to prevent the transmission of SARS-CoV-2, including the restriction of nonessential endoscopic procedures [2]. However, despite the benefits in terms of pandemic control, the prolonged suspension of everyday gastrointestinal practice has already resulted in a compromised colorectal cancer (CRC) screening and management [3–8]. Additionally, the fear of getting infected with SARS-CoV-2 has led to a delay in hospital admission in some patients, with harmful consequences

concerning cancer management [9]. During the lockdown period, CRC detection rates decreased 72% in the UK [3] and 37% in Hong Kong [4]. Despite the recovery by the second semester of 2020, the rates of CRC diagnosis have not exceeded those previous to the pandemic [7]. Therefore, the pandemic has led to an overall delay in CRC diagnosis. In Portugal, CRC is the most prevalent cancer, accounting for 17.4% of new cancer cases in 2020, and is the second cause of cancer-related death [10]. Since mortality rate is highly dependent on the TNM staging [11] at diagnosis, an increase in the morbidity and mortality rate from CRC is expected with the pandemics. In England, it has been calculated that over 3,500 fewer people were diagnosed and treated for CRC between April and October 2020 [7].

In Portugal, during the lockdown period, about half of the hospitals only performed emergency endoscopies. Of the 15 public hospitals involved in CRC screening, which is recommended for asymptomatic patients between 50 and 74 years old [12], only 1 did not suspend this screening. Although by May 2020, most Portuguese gastroenterology departments and endoscopy clinics had started resuming their usual activity, by September 2020, most departments had not recovered to levels similar to those pre-pandemic [1].

The authors considered it important to evaluate how the pandemic has affected the CRC diagnosis and management during the first year of COVID-19 pandemic. Therefore, this study aimed to compare the context in which the CCR diagnosis was made, the CCR staging at diagnosis, and all the timings between the beginning of symptoms and CCR medical/surgical management.

Materials and Methods

This is a Portuguese substudy of the French retrospective matched case-control multicentric study ETICC (*Etude de l'Impact de la pandémie COVID-19 sur le diagnostic et la prise en charge du Cancer Colorectal*) coordinated by the *Association Nationale des Gastroentérologues des Hôpitaux Généraux*. The French study included 11 centers, with a total of 961 patients – 470 in the COVID group (CRC diagnosed between the 1st of March 2020 and the 28th of February 2021) and 491 in the control group (CRC diagnosed in 2019), with preliminary results already presented in France [13]. In Portugal, 4 centers were included. Patients included in the control group had a diagnosis of CRC made between 1 January 2019 and 29 February 2020 and patients included in the COVID group had a diagnosis performed between 1 March 2020 and 28 February 2021.

Data were collected regarding patients' characteristics (sex, age at diagnosis, comorbidities) and tumors' characteristics (clinical manifestations, staging according to the 8th TNM classification from the Union for International Cancer Control [10], complications at diagnosis). Dates of the first medical consultation concerning CRC, histological diagnosis, surgical resection, neoadjuvant treatment, adjuvant, or palliative chemotherapy were also collected. It was registered if there was a perception of a delay in the diagnosis or treatment of the CRC.

To compare the "control" and "COVID" groups, nonparametric tests were used to compare quantitative variables, and χ^2 and the conditional independence Mantel-Haenszel test were used to compare qualitative variables. A p value <0.05 was considered statistically significant.

Results

We included 766 patients: 496 in the control group and 270 in the COVID group, with similar median ages (70 years old, IQR 58–82) and sex distribution (60% men) between groups. Although there were more patients with comorbidities in the COVID group (10.4%) than in the control group (7.7%), this was not statistically different ($p = 0.202$).

Concerning the staging of the CRC at the time of diagnosis, no statistical difference was found between groups ($p = 0.770$). About one-fourth of patients had a metastatic cancer (TNM 4) at diagnosis (21% in the control group and 22% in the COVID group). Early stages (TNM 0 and 1) represented 19% of those in the control group and 15% in the COVID group (Fig. 1). Similar results were found in France, with 28% of metastatic CRC at diagnosis in both control and COVID groups and without significant differences in TNM staging before and during the pandemics.

In the control group, 25% of patients were asymptomatic at the time of diagnosis, whereas in the COVID group, this proportion significantly decreased to 8.4% ($p < 0.001$). There was also a significant decrease in diagnosis after a positive fecal immunochemical test (FIT): 20.8% in the control group and 11.3% in the COVID group ($p = 0.002$). In France, no significant decrease in CRC diagnosis in asymptomatic patients was found and the proportion of patients with a CRC diagnosis after a positive FIT has significantly increased (Table 1). 31.7% and 41.1% of patients initiated their follow-up at the hospital after going to the emergency room in the control and COVID groups, respectively, and 53.6% and 48.5% after consulting their general practitioner ($p = 0.020$).

The rate of complications at the time of diagnosis has increased, but without statistical significance, from 17.8% in the control group to 23.7% in the COVID group ($p = 0.050$). Abdominal occlusion was the principal complication and has significantly increased during COVID,

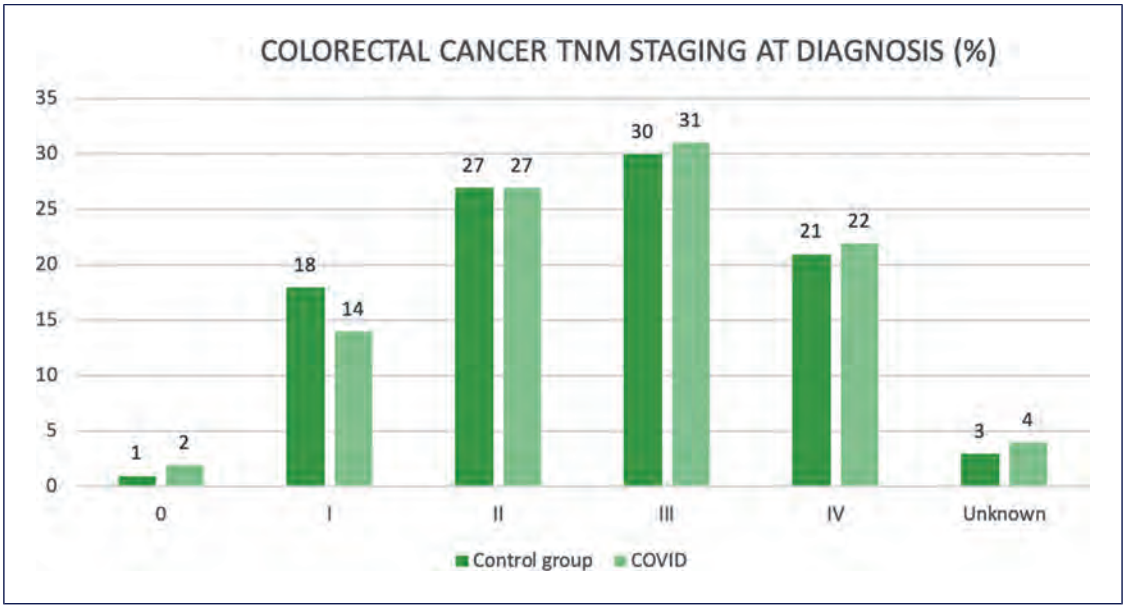


Fig. 1. CRC TNM staging at diagnosis in the control and COVID groups.

Table 1. Comparison of clinical presentation at CRC diagnosis between control and COVID groups

	Control group	COVID group	*p* value
Asymptomatic patients, %			
Portugal	25.0	8.4	<**0.001**
France	20.8	25.5	0.081
Diagnosis after a positive FIT, %			
Portugal	20.8	11.3	**0.002**
France	19.0	10.0	<**0.001**
Presence of a complication at diagnosis, %			
Portugal	17.8	23.7	0.05
France	20.6	18.5	0.377
Type of complication, %			
Occlusion	72.6	82.3	0.145
Perforation	6.0	9.7	
Abscess	11.9	3.2	
Hemorrhage	9.5	4.8	

CRC, colorectal cancer; FIT, fecal immunochemical test.

from 12.1 to 18.1% ($p = 0.033$). In France, there was no significant difference in the rate of all complications or abdominal occlusion at the time of diagnosis.

A delay in the diagnosis and management was inferred in 16.6% of patients in the control group and in 33.6% in the COVID group ($p < 0.001$). Time between the beginning of symptoms and the first medical appointment significantly increased from a median of 50 days in the control group to 64 days in the COVID group ($p < 0.001$). On the contrary, time between histological diagnosis and tumor resection has decreased from a median of 65 days in the control group to 39 days in the COVID group ($p < 0.001$). Time between histological diagnosis and neoadjuvant treatment was not statistically different (median of 64–67 days; $p = 0.590$), as was time between histological diagnosis and palliative chemotherapy (median of 50–51 days; $p = 1.000$). Time from CRC resection and adjuvant treatment has significantly decreased from 54 days in the control group to 43 days in the COVID group ($p = 0.001$). In France, the only statistically significant interval difference was between CRC histological diagnosis and resection, which, similarly to what happened in Portugal, decreased from 29.5 in the control group to 23 days in the COVID group ($p = 0.013$).

Discussion

This study only included 4 district hospitals: 3 from the Lisbon region and 1 from southern Portugal. Therefore, and since our study has a relatively small sample size, these results might not represent the real impact of the first year of COVID-19 pandemic on CRC diagnosis and treatment in Portugal. Moreover, the data were collected retrospectively, leading to some missing and misleading data regarding timings, reducing the reliability of the analysis concerning the delays between symptoms, diagnosis, and treatment. Although it was not the end point of our study and since we cannot directly compare the number of CRC diagnosis

between the control group (which included not only the year 2019 but also the first 2 months of 2020) and the COVID group (which included 12 months), we can still admit that fewer CRCs were diagnosed and treated during the first year of pandemics (average of 35.4 CRC diagnosis per month in the control group against 22.5 in the COVID group).

Nonetheless, our study revealed that in Portugal, unlike what happened in France, it took more time for patients to find medical care after the appearance of symptoms, with less CRC diagnosis in asymptomatic patients or after a positive FIT. We also identified a significant increase in the proportion of patients presenting with bowel obstruction. These findings might be biased by the smaller sample size in the Portuguese cohort, but we also believe that they are likely related not only with the closing of endoscopy outpatient clinics during the lockdown but also to the difficulties that Portuguese patients encountered in making an appointment with their general practitioner since general practitioners were overwhelmed with the follow-up of patients infected with COVID.

On the other hand, both in France and Portugal, the first year of pandemics did not worsen the TNM stage at diagnosis and did not significantly affect most medical and surgical treatments once the diagnosis was made. In fact, time between histological diagnosis and surgical resection has decreased in both countries, probably because most elective non-oncological surgeries were postponed during the pandemics. However, the significant increase in abdominal occlusion can mislead these results since histological diagnosis and surgical resection are usually simultaneous in these situations. What is still unknown is whether we were able to resume consultations and colonoscopies in time and number to recover without further damage or whether a significant increase in advanced CRC at diagnosis will occur after the first year of pandemics.

Our results are in line with the previously published data concerning the impact of COVID-19 in digestive cancers in Portugal, with more patients presenting at the emergency department and referred after urgent surgery and fewer patients referred from the outpatient clinic. Similarly, tumor staging in CCR was not significantly different before and during the first months of pandemics [13]. The significant decrease we found in CCR diagnosis in asymptomatic patients or after a positive FIT is probably related to the already published data concerning the decrease in the number of colonoscopies performed during the first months of pandemics in Portugal [1].

In conclusion, although we might already assume the pandemics negatively affected CRC diagnosis and management, this study has a short follow-up to deduce the real impact of COVID-19 in overall CRC burden. Further research including the subsequent years of pandemics must be pursued to infer its real consequences regarding CRC morbimortality.

Statement of Ethics

The study protocol was reviewed and approved by the ethics committees of the hospitals involved. Written informed consent was not obtained. Exemption was granted due to the retrospective and anonymous design of the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received for this study.

Author Contributions

Maria Ana Rafael: data collection and manuscript writing. Cristiana Sequeira, Sónia Isabel da Silva Barros, and Bárbara Silva Abreu: data collection. Cristina Teixeira: Portuguese coordinator of the ETICC study and manuscript revision. Pierre Lahmek: statistical analysis. Marine Besnard and Bruno Lesgourgues: coordinators of the ETICC study.

Data Availability Statement

Data collected are available to editors, reviewers, and readers in a total anonymity excel file.

References

1 Leal T, Gonçalves M, Mocanu I, Carvalho R, Glória L. COVID-19 in gastroenterology departments: the impact of the first wave. GE Port J Gastroenterol. 2021;4(6):1–7.

2 Gralnek IM, Hassan C, Beilenhoff U, Antonelli G, Ebigbo A, Pellisè M, et al. ESGE and ESGENA Position Statement on gastrointestinal endoscopy and the COVID-19 pandemic. Endoscopy. 2020;52(6):483–90.

3 Rutter MD, Brookes M, Lee TJ, Rogers P, Sharp L. Impact of the COVID-19 pandemic on UK endoscopic activity and cancer detection: a National Endoscopy Database Analysis. Gut. 2021;70(3):537–43.

4 Lui TKL, Leung K, Guo CG, Tsui VWM, Wu JT, Leung WK. Impacts of the coronavirus 2019 pandemic on gastrointestinal endoscopy volume and diagnosis of gastric and colorectal cancers: a population-based study. Gastroenterology. 2020 Sep;159(3):1164–6.e3.
5 Mazidimoradi A, Tiznobaik A, Salehiniya H. Impact of the COVID-19 pandemic on colorectal cancer screening: a systematic review. J Gastrointest Cancer. 2022;53(3): 730–44.
6 Aguiar S Jr, Riechelmann RP, de Mello CAL, da Silva JCF, Diogenes IDC, Andrade MS, et al. Impact of COVID-19 on colorectal cancer presentation. Br J Surg. 2021 Mar 12;108(2):e81–2.
7 Morris EJA, Goldacre R, Spata E, Mafham M, Finan PJ, Shelton J, et al. Impact of the COVID-19 pandemic on the detection and management of colorectal cancer in England: a population-based study. Lancet Gastroenterol Hepatol. 2021 Mar;6(3):199–208.
8 Brito M, Laranjo A, Sabino J, Oliveira C, Mocanu I, Fonseca J. Digestive oncology in the COVID-19 pandemic era. GE Port J Gastroenterol. 2021 Mar 22;579(5):1–8.
9 Sutcuoglu O, Yazici O, Ozet A, Ozdemir N. Harmful consequences of COVID-19 fear in patients with cancer. BMJ Support Palliat Care. 21 Dec 2020:bmjspcare-2020-002628.
10 GLOBOCAN. The global cancer observatory; 2020.
11 Brierly JD, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours: eighth edition; 2016.
12 Dinis-Ribeiro M, Areia M, Dias-Pereira A. Rastreio de cancro colorretal (CCR) - parecer SPED (Sociedade Portuguesa de Endoscopia Digestiva); 2019.
13 Besnard M, Locher C, Macaigne G, Cuillerier E, Bouazza L, et al. Journées Francophone D'Hépato-Gastroentérologie et d'Oncologie Digestive 2022.033 - etude de l'impact de la crise sanitaire Covid-19 sur le diagnostic et la prise en charge du cancer colorectal dans les hôpitaux généraux français en 2020: ETICC.

GE – Portuguese Journal of Gastroenterology

Research Article

GE Port J Gastroenterol 2024;31:262–272
DOI: 10.1159/000533178

Received: March 27, 2023
Accepted: July 18, 2023
Published online: September 5, 2023

The Initial Journey of Patients with Metastatic Pancreatic Cancer (PaCTO Project): A Nationwide Survey among Portuguese Specialist Physicians

Anabela G. Barros[a] Hélder Mansinho[b] Nuno Couto[c] Manuel R. Teixeira[d, e] Fernanda S. Tonin[f, g] Rudolfo Francisco[h] Filipa Duarte-Ramos[i, j, k]

[a]Department of Medical Oncology, University Hospital of Coimbra, Coimbra, Portugal; [b]Hemato Oncology Department, Garcia de Orta Hospital, Almada, Portugal; [c]Digestive Unit, Champalimaud Clinical Centre, Champalimaud Research Centre, Lisbon, Portugal; [d]Department of Laboratory Genetics, Portuguese Oncology Institute of Porto (IPO Porto), Porto Comprehensive Cancer Center, Porto, Portugal; [e]Cancer Genetics Group, IPO Porto Research Center (CI-IPOP)/RISE@CI-IPOP (Health Research Network), School of Medicine and Biomedical Sciences (ICBAS), University of Porto, Porto, Portugal; [f]Pharmaceutical Sciences Postgraduate Program, Federal University of Parana, Curitiba, Brazil; [g]H&TRC–Health & Technology Research Center, ESTeSL- Escola Superior de Tecnologia da Saúde, Instituto Politécnico de Lisboa, Lisbon, Portugal; [h]Oncology-Medical Department, AstraZeneca, Barcarena, Portugal; [i]Department of Pharmacy, Pharmacology and Health Technologies, Faculty of Pharmacy, University of Lisbon, Lisbon, Portugal; [j]Research Institute for Medicine (iMed.ULisboa), Faculty of Pharmacy, University of Lisbon, Lisbon, Portugal; [k]EPIUnit, Instituto de Saúde Pública da Universidade do Porto (ISPUP), Laboratório para a Investigação Integrativa e Translacional em Saúde Populacional (ITR), Porto, Portugal

Keywords

Pancreatic neoplasms · Immunotherapy · Cross-sectional studies · Surveys and Questionnaires

Abstract

Introduction: We aimed to characterize the initial healthcare journey of metastatic pancreatic ductal adenocarcinoma (mPDAC) patients in Portugal, including healthcare provision and factors affecting therapeutic decisions, namely BRCA mutations testing. ***Methods:*** This is a descriptive cross-sectional, web-based survey using a convenience sampling approach. Portuguese oncologists and pathologists that routinely work with mPDAC patients from the different geographical regions and settings were invited to participate in the study via email (December 2020). Descriptive statistical analyses were performed, with categorical variables reported as absolute and relative frequencies, and continuous variables with non-normal distribution as median and interquartile range (IQR) (Stata v.15.0). ***Results:*** Seventy physicians participated in the study (43 oncologists, 27 pathologists). According to the responses, a median of 28 patients per center (IQR 12–70) was diagnosed with PDAC in the previous year; 22 of them referring (IQR 8–70) to mPDAC. The pointed median time from patients' first hospital admission until disease diagnosis/staging is between 2 and 4 weeks. Endoscopic ultrasound with fine-needle biopsy is available in most hospitals (86%). Around 50% of physicians request BRCA testing; the assessment of additional biomarkers besides BRCA is requested by 40% of professionals. Half of them stated that BRCA testing should be requested earlier–upon histological diagnosis, especially because the

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

Correspondence to:
Anabela G. Barros, anabelabsa@gmail.com

median time for results is of 4.0 weeks (IQR 4–8). PARP inhibitors such as olaparib, when available, would be the therapy of choice for most oncologists (71%) if no disease' progression occurs after 4 months. Treatments' selection is usually grounded on clinical criteria (e.g., performance status, liver function). Around 45% of patients use FOLFIRINOX/mFOLFIRINOX as the first-line therapy. Gemcitabine + nab-paclitaxel is used by 35% of patients as the second-line therapy. ***Conclusions:*** Physicians in Portugal support the increasing role of patient-tailored treatments in mPDAC, whose selection should be grounded on tumoral subtyping and molecular profiling. Further efforts to develop multidisciplinary teams, standardized clinical practice, and optimize the implementation of new target therapies are needed.

A jornada inicial dos doentes com cancro de pâncreas metastático (projeto PaCTO): um inquérito nacional a médicos especialistas portugueses

Palavras Chave
Cancro pancreatico · Imunoterapia · Estudo transversal · Questionários

Resumo
Introdução: Este estudo teve como objetivo caracterizar o percurso inicial dos doentes com adenocarcinoma ductal pancreático metastático (ACDPm) em Portugal, incluindo a prestação de cuidados de saúde e determinação de fatores que afetam as decisões terapêuticas, nomeadamente o teste de mutações BRCA. ***Métodos:*** Trata-se de um estudo descritivo transversal (web-based) usando uma abordagem de amostragem por conveniência. Médicos oncologistas e anatomopatologistas portugueses dedicados ao ACDPm e de diferentes regiões geográficas e instituições foram convidados a participar do estudo por email (Dez-2020). Foram realizadas análises estatísticas descritivas, com variáveis categóricas relatadas como frequências absolutas e relativas, e variáveis contínuas com distribuição não-normal como mediana e intervalo interquartil (IIQ) (Stata v.15.0). ***Resultados:*** Setenta médicos participaram do estudo (43 oncologistas, 27 patologistas). De acordo com as respostas, uma mediana de 28 doentes por centro (IIQ 12–70) foi diagnosticada com ACDP no ano anterior; 22 deles (IIQ 8–70) referentes a ACDPm. O tempo médio desde a primeira admissão hospitalar dos doentes até o diagnóstico/estadiamento da doença foi entre 2–4 semanas. A ultrassonografia endoscópica com biópsia por agulha fina é realizada pela maioria dos hospitais (86%). Aproximadamente 50% dos médicos referem solicitar o teste BRCA; a avaliação de biomarcadores adicionais além do BRCA é solicitada por 40% dos profissionais. Metade dos médicos assume que o teste BRCA deveria ser solicitado mais precocemente – durante o diagnóstico histológico, principalmente porque o tempo médio para obtenção do resultado é de 4,0 semanas (IIQ 4–8). Os inibidores PARP, como o olaparibe, quando disponíveis, seriam a terapia de escolha para a maioria dos oncologistas (71%) caso não haja progressão da doença após quatro meses. A seleção dos tratamentos é usualmente baseada em critérios clínicos (por exemplo, *performance status*, função hepática). Em cerca de 45% dos doentes é utilizado FOLFIRINOX/mFOLFIRINOX como terapia de primeira linha. Um esquema com Gemcitabina + nab-paclitaxel é usado em 35% dos doentes como terapia de segunda linha. ***Conclusões:*** Os médicos em Portugal apoiam o papel crescente do tratamento individualizado no ACDPm, cuja seleção deve ser baseada na subtipagem tumoral e no perfil molecular. São necessários mais esforços para capacitar as equipas multidisciplinares, desenvolver práticas clínicas padronizadas e otimizar a implementação de novas terapias-alvo.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is currently the seventh leading cause of cancer death worldwide with 495,773 new cases and 466,003 deaths reported in 2020 [1]. In the next few years, PDAC is estimated to become the second cause of cancer mortality in developed countries – including in Portugal where annual deaths should surpass 2,000 (n = 2,137; 95% CI, 1,862–2,413) by 2035 reflecting an increase of 51% [2–4]. Without treatment, median survival of metastatic PDAC (mPDAC) lies between 3 and 6 months. Although few patients (15–20%) are amenable to surgery combined with adjuvant chemotherapy, overall survival is of 11–25 months [5, 6].

The mainstay of current therapeutic approach for mPDAC is the combination of cytotoxic drugs such as FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, oxaliplatin), gemcitabine with nab-paclitaxel, and gemcitabine

plus capecitabine [7–10]. Additional attempts to further improve survival include modifying the sequence of combination regimens, adding other cytotoxic agents, or performing maintenance strategies [11–13].

The recent implementation of target therapies was especially important for the management of pancreatic tumors, given that an unstable genotype with numerous structural variations (e.g., BRCA1, BRCA2, or PALB2 genes or mutational signatures of DNA-damage repair deficiency) is present in about 10–15% of patients. Germline mutations in *BRCA* genes are identifiable in around 4–7% of patients with mPDAC [14–16]. As these cells with a deficient DNA repair are usually sensitive to adenosine diphosphate-ribose polymerase (PARP) inhibition [17, 18], there is growing role for PARP inhibitors as potential therapies [19–21]. The efficacy of the PARP inhibitor olaparib as a single agent in germline BRCA mutation and PDAC was initially suggested in a phase II trial that demonstrated median progression-free survival and overall survival rates of 4.6 and 9.8 months, respectively [19]. The effect of olaparib as a maintenance therapy in patients who had a germline BRCA1 or BRCA2 mutation with mPDAC not progressing during the first-line platinum-based chemotherapy was assessed in the phase III POLO trial [22] showing progression-free survivals of 7.4 months versus 3.8 months in placebo ($p = 0.004$) [23]. Based on these findings, olaparib was approved by the US Food and Drug Administration (FDA) on December 2019 and by the European Medicines Agency (EMA) in July 2020 and is currently recommended by the ASCO guidelines (2020) for the maintenance treatment of adult patients with germline BRCA mutations mPDAC whose disease has not progressed during at least 16 weeks of the first-line platinum-based chemotherapy [24]. Other drugs that are being currently tested in this scenario include nimotuzumab (anti-EGFR), durvalumab (anti-PDL-1), nivolumab (anti-PD-1) [13].

Nonetheless, the late integration of target therapies in clinical practice accentuates the need for multidisciplinary and consensual decision-making processes, which arouses new challenges, as well as changes in work routines, that are daily faced by pancreatic cancer specialists. Several questions regarding patients' journey still need to be clarified, including the use of new techniques for disease early diagnosis and staging (e.g., endoscopic ultrasound-guided fine-needle biopsy – EUS-FNB), identification of biomarkers and criteria that influence therapies' selection [25–28]. Thus, the aim of this study was to characterize the initial healthcare journey of mPDAC patients in Portugal (after reaching a referral center), including healthcare provision, and major factors currently affecting therapeutic decisions, namely BRCA mutations testing.

Materials and Methods

Study Design and Variables

A descriptive cross-sectional web-based survey (Google form) using a convenience sampling approach was performed. Portuguese oncologists and pathologists that routinely work with mPDAC patients from the different geographical regions and settings (public, private hospitals) were invited to participate in the study via email (December 2020) (the list of potentially eligible physicians with clinical practice experience in this field was provided by the Grupo de Estudos em Cancro Digestivo–GECD – Portugal). Physicians were fully informed regarding the nature of the study, the procedures for data recording, and the voluntary nature of their participation. Responders provided their informed consent before survey's completion, and anonymity was guaranteed. Participants' withdrawal was allowed at any time. This study was waived of bioethical approval (National Legislation-Law 21/2014) because it does not contain any intervention on human subjects nor individual health data collection.

The questionnaire was divided into two sections that aim to assess physicians' perception on mPDAC patients journey in Portugal in the previous year, 2019 (i.e., to avoid bias from COVID-19 potential disruptions in health services). The first section (18-items) was answered by both oncologists and pathologists and included information on: sociodemographic data (e.g., medical specialty, working place), current histopathological diagnosis, disease staging procedures, and biomarkers evaluation. The second part of the questionnaire (12-items) was intended only for oncologists and covered topics on therapeutic approaches and complementary procedures for mPDAC management.

The questionnaire was specifically developed for this study by the Coordinator Committee (Anabela G. Barros [oncologist], Hélder Mansinho [oncologist], Nuno Couto [oncologist], Manuel R. Teixeira [pathologist], Filipa Duarte-Ramos [pharmacist, epidemiologist]). Responders took an average time of 10 min to complete the survey. Standards for scientific research were performed according to the Declaration of Helsinki. The complete questionnaire (original language, Portuguese) is available in online supplementary Appendix (for all online suppl. material, see https://doi.org/10.1159/000533178).

Data Analysis

The normality of the variables was assessed using Kolmogorov-Smirnov and Shapiro-Wilk tests with additional visual inspection of Q-Q plots. Descriptive statistics were used to summarize the data, with absolute and relative frequencies to describe categorical variables and median and interquartile range (IQR) for continuous non-normal variables. The association between categorical variables was assessed through Pearson's χ^2 test (alternatively, when few observations, e.g., less than 5, exist, the Fisher's exact test was

Table 1. Physicians' perception on mPDAC characterization

Variables (categories)	Oncologists (n = 43), n (%)	Pathologists (n = 27), n (%)	p value[1]
Working institution			
Public	33 (76.7)	16 (59.3)	0.031*
Private	5 (11.6)	1 (3.7)	
Both	5 (11.6)	10 (37.0)	
Geographical region (Portugal)			
Center	5 (11.6)	4 (14.8)	0.844
Lisbon region	19 (44.2)	10 (37.0)	
North	16 (37.2)	12 (44.4)	
Others (Algarve, Azores, Madeira)	3 (7.0)	1 (3.7)	
Request molecular profiling for pancreatic adenocarcinoma[a]			
No	5 (21.7)	6 (37.5)	0.298
Only for BRCA mutation	10 (43.5)	3 (18.8)	
BRCA and other biomarkers	8 (34.8)	7 (43.8)	
When is BCRA mutation profiling done[b]			
During histological diagnosis	3 (14.3)	4 (57.1)	0.050
During metastatic disease diagnosis	4 (19.1)	0 (0.0)	0.545
During multidisciplinary consultation	0 (0.0)	1 (14.3)	0.250
During the oncologic consultation	13 (61.9)	2 (28.6)	0.198
When lacking therapeutic alternatives	1 (4.8)	0 (0.0)	1.000
When should BCRA mutation profiling be done[c]			
During histological diagnosis	7 (58.3)	7 (53.8)	1.000
During metastatic disease diagnosis	6 (50.0)	0 (0.0)	**0.005**
During multidisciplinary consultation	3 (25.0)	0 (0.0)	0.095
During the oncologic consultation	1 (8.3)	1 (7.7)	1.000
When lacking therapeutic alternatives	0 (0.0)	0 (0.0)	–
If germline mutation profiling is not requested, when should BRCA be done[d]			
During histological diagnosis	5 (26.3)	10 (58.8)	0.089
During metastatic disease diagnosis	8 (42.1)	2 (11.8)	0.065
During multidisciplinary consultation	1 (5.3)	4 (23.5)	0.167
During the oncologic consultation	2 (10.5)	1 (5.9)	1.000
When lacking therapeutic alternatives	3 (15.8)	0 (0.0)	0.230
Cases of BRCA1 and BRCA2 profiling request[c]			
According to family history	3 (25.0)	2 (15.4)	0.299
According to patients' age at diagnosis	2 (16.7)	0 (0.0)	
All cases	7 (58.3)	11 (84.6)	
Samples of BRCA1 and BRCA2 profiling[e]			
Only in peripheral blood (germline mutations)	14 (73.7)	4 (50.0)	0.310
Only in the tumor (somatic or germline mutations)	1 (5.3)	1 (12.5)	
On the tumor and peripheral blood	4 (21.1)	3 (37.5)	
Mutation's profiling request[e]			
Only BRCA1 and BRCA2	10 (52.6)	4 (50.0)	1.000
Genetic panel	9 (47.4)	4 (50.0)	
Median time for obtaining BRCA results[f]			
<6 weeks	9 (47.4)	7 (100.0)	**0.023**
≥6 weeks	10 (52.6)	0 (0.0)	

Given the small sample size and few observations for some variables, no test was performed aiming at avoiding misleading interpretation (i.e., only percentages are presented). *Adjusted post hoc analysis for the pairs (Fisher's exact test): public × private (p = 0.654), public × both (p = 0.101), private × both (p = 0.127). [a]Total sample n = 39 (23 + 16); [b]Total sample n = 28 (21 + 7); [c]Total sample n = 25 (12 + 13); [d]Total sample n = 36 (19 + 17); [e]Total sample n = 27 (19 + 8); [f]Total sample n = 26 (19 + 7). [1]Pearson χ^2 test or Fisher's exact test.

used). Analyses were conducted in Stata Statistical Software version 15.0 SE (College Station, TX: StataCorp LL, USA) and *p* values below 0.05 were considered statistically significant.

Results

Diagnosis of mPDAC: Oncologists and Pathologists' Overview

Overall, 70 physicians (from *n* = 34 invited Centers in Portugal) participated in the study, of which 43 were oncologists and 27 were pathologists, mostly from Lisbon and Vale do Tejo (41.4%) and North (40.0%) regions. Table 1 shows the sociodemographic characteristics of the participants and their perception on the initial journey of patients with mPDAC in Portugal. Most physicians (*n* = 49; 70.0%) work only in public health institutions. Although oncologists may have a greater representation in this setting (76.8% vs. 59.3% of pathologists), pathologists also labor in both public and private centers (37.0% vs. 11.6% of oncologists).

The most frequent types of pancreatic cancer diagnosed in the physicians' institutions are adenocarcinoma–found in 90% of patients, followed by undifferentiated tumors (5%). Adenosquamous carcinoma and cystadenocarcinoma are poorly reported (around 2% of cases). According to the clinicians, in the past year (12 months – perception over the period from Jan to Dec 2019), a median of 28 patients (IQR 12–70) was diagnosed with PDAC in their center; 22 (IQR 8–70) of them referred to mPDAC. Endoscopic procedures, like ERCP (endoscopic retrograde cholangiopancreatography) or endoscopic ultrasound, complemented with cytology or forceps biopsy sampling, are performed in a median of 50% of admitted patients (IQR 30–70) as part of the histological diagnosis. Metastasis biopsy (percutaneous) is performed in around 50% of cases (IQR 30–70). Almost half of the oncologists (43.5%) request only BRCA mutation as molecular/genetic profiling for mPDAC, while pathologists (43.8%) additionally request the assessment of other biomarkers (e.g., PALB2, ATM, MLH1, MSH2, MSH6 e CDKN2A). Yet around one-third of pathologists stated they do never request this procedure (37.5%) (see Table 1). According to most physicians (*n* = 18/27; 66.7%), BRCA1 and BRCA2 profiling are done in all cases regardless of patient's age or family history, using only peripheral blood samples for germline mutations.

According to most oncologists (61.9%), BRCA mutation profiling request is usually performed during the oncologic consultation in their centers, which is slightly different from the perceived clinical routine reported by the pathologists (see Table 1). Most physicians (*n* = 14 out of 25 responding to this question; 56.0%) recommended BRCA testing to be requested earlier – upon histological diagnosis, especially because the overall median time for results is of 4.0 weeks (IQR 4–8). Yet half of the oncologists (52.6%) believe that this median time is usually over 6 weeks, while for all the responding pathologists this procedure is significantly faster, occurring within 6 weeks ($p = 0.023$). It was estimated that around 5% of all patients diagnosed in the physicians' centers present germline mutations. Most pathologists agree that BRCA test should be done during histological diagnosis (58.8%) or requested upon multidisciplinary consultation (23.5%) if germline mutation profiling is not requested at that time; conversely, around 40% of oncologists believe this procedure should be performed at diagnosis of metastatic disease (see Table 1).

Management of mPDAC: Oncologists' Perception

Oncologists (*n* = 43) additionally described the current practices for mPDAC management in Portugal, which are depicted in Tables 2, 3. Most physicians state that Oncology (53.5%), Imagiology (51.2%), Gastroenterology (46.5%), and Hepato bilio pancreatic surgery (46.5%) are part of multidisciplinary teams, being other specialties less frequently reported.

Over 65% of oncologists are satisfied or very satisfied with the support provided by different hospital services for the management of the oncologic patients, especially with nursing staff and pain units. Yet around one-third of experts believe that there is room for improvement in the nutrition and palliative care units (see Fig. 1).

EUS-FNB is available in most institutions/hospitals (according to 86.4% of clinicians) as primary diagnosis approach, being the results generally released in less than 2 weeks–even if performed outside the physicians' hospital (Table 2). Yet, this procedure (EUS-FNB) for primitive tumor and others such as PET-CT and CT pancreas protocol are often required as complementary exams (according to around 40–50% of physicians) for disease diagnosis and staging. ERCP was also frequently mentioned by the physicians as a complementary procedure, although this is not mandatory for pancreatic cancer. Conversely, abdominal MR and CA 19.9 are rarely performed as complementary procedures (see Fig. 2).

According to the experts, median time from first hospital admission until mPDAC diagnosis and staging is usually between 2 and 4 weeks. PARP inhibitors, when approved, would be the therapy of choice for most oncologists (71.4%) for patients with BRCA mutations

Table 2. Oncologists' perception on mPDAC patients' journey

Variables (categories)	Oncologists (n = 43), n (%)
Clinical specialties in the multidisciplinary consultation*	
Oncology	23 (53.5)
General surgery	14 (32.6)
Hepato bilio pancreatic surgery	20 (46.5)
Pathological anatomy/genetics	16 (32.2)
Gastroenterology	20 (46.5)
Imaging	22 (51.2)
Radiotherapy	17 (39.5)
Does your hospital perform endoscopic ultrasound with fine-needle biopsy exam?[a]	
Yes	19 (86.4)
No	3 (13.6)
Median time from first hospital admission to mPDAC diagnosis and staging[b]	
<2 weeks	2 (8.7)
Between 2 and 4 weeks	13 (56.5)
>4 weeks	8 (34.8)
Treatment of choice in case of no progression after 4 months of platinum-based therapy[c]	
Maintain therapy as long as there is clinical response and tolerance	4 (19.0)
Therapy discontinuation and patient monitoring	1 (4.8)
Maintain therapy + PARP inhibitor	1 (4.8)
PARP inhibitor	15 (71.4)
Criteria that influence 1st line therapy decision-making*	
Performance status	22 (51.3)
Symptoms	6 (13.9)
Liver function	14 (32.6)
Age	7 (16.3)
Comorbidities	14 (32.6)
Patients' preferences	3 (6.9)
Criteria that influence 2nd line therapy decision-making*	
1st line protocol	21 (48.8)
Performance status	22 (51.2)
Symptoms	2 (4.7)
Liver function	6 (13.9)
Age	1 (2.3)
Comorbidities	9 (20.9)
Patients' preferences	6 (13.9)

*Physicians could select more than one answer (sum of variables' category may be over 100%). [a]Sample n = 22; [b]Sample n = 23; [c]Sample n = 21.

without progression after 4 months of chemotherapy treatment. The first-line treatments are usually selected after an oncology evaluation, grounded mostly on clinical criteria (e.g., performance status, liver function) and patients' comorbidities. The second-line therapy selection usually considers the previous first-line protocols and patients' performance status. During these therapeutic decisions, less than 15% of physicians consider patients preferences (see Table 2). According to the oncologists, FOLFIRINOX/mFOLFIRINOX is used as the first-line therapy in 45.0% of patients [IQR 30–50], followed by gemcitabine plus nab-paclitaxel (32.5% [IQR 20–40]). This last regimen is also commonly used as the second-line therapy (35.0% [IQR 10–50]) followed by gemcitabine alone (25.0% [IQR 10–40]) (Table 3).

Discussion

This study was triggered by the ongoing debate on the need for improving pancreatic cancer diagnosis and reducing the burden of this disease caused by the high rates of morbidity and mortality in Portugal. Through a nationwide survey with physicians that routinely manage mPDAC patients (i.e., pathologists and oncologists) from

Table 3. Patients in use of the first and second-line therapies according to oncologists' practice

Therapies	Percentage of patients, median [interquartile range]
1st line therapies	
FOLFIRINOX/ mFOLFIRINOX	45.0 [IQR 30–50]
Gemcitabine + nab-paclitaxel	32.5 [IQR 20–40]
Gemcitabine	10.0 [IQR 10–25]
FOLFOX/CAPOX	5.0 [IQR 0–10]
5-FU/LV/Capecitabine	2.0 [IQR 0–5]
2nd line therapies	
FOLFIRINOX/ mFOLFIRINOX	5.0 [IQR 0–10]
Gemcitabine + nab-paclitaxel	35.0 [IQR 10–50]
Gemcitabine	25.0 [IQR 10–40]
FOLFOX/OFF	15.0 [IQR 5–30]
5-FU/LV/Capecitabine	5.0 [IQR 5–20]
Irinotecan	0.0 [IQR 0–10]

all Portuguese regions, we were able to identify their perception on some barriers for rapid diagnosis and beginning of treatment – including heterogeneous practices related to criteria for requesting molecular tests and delays for obtaining BRCA results that may impact on clinical and economic outcomes.

According to the Global Cancer Observatory, in 2020 the estimated crude incidence and prevalence (5-years) rates for PDAC in Portugal were of 17.6 and 11.7 per 100,000 habitants, respectively, with a mortality rate (2020) of 5.9 per 100,000 habitants [1]. In our study, we found pancreatic adenocarcinoma as the most reported type of tumor among patients, with around 30 cases per institution per year in Portugal, of which around 75% diagnosed in a metastatic stage or in progression, with a large dispersion (varying from 8 to 70 patients/institution/year). According to the Portuguese National Health System (SNS), the country currently has around 55,000 registered physicians, of which 30,000 work on public health institutions, especially in Lisbon and North regions that concentrate approximately 60% of all healthcare professionals [29]. These figures highlight some geographical asymmetries that are also reflected in our study.

The goal of rapid investigation and treatment of cancer is to maximize cure rate for patients with early-stage disease, to increase the number of patients with resectable disease, and to avoid tumor growth and upstaging [24]. We found that physicians perform upper endoscopic ultrasound with cytology, biopsy procedures, and metastasis investigation in around half of patients admitted in their institution as part of the histological diagnosis. Complementary procedures such as PET-CT and CA 19.9 are fairly used. Although ERCP is not mandatory for pancreatic cancer (i.e., therapeutic procedure indicated in case of obstructive jaundice), it was frequently mentioned by the physicians as a complementary requested procedure for diagnosis. These differences may occur due to the limited access to these techniques or availability of resources in each center, together with the current local protocols for clinical practice. Nonetheless, precise staging of PDAC, including TNM staging and determination of tumor resectability is highly recommended by international guidelines and should be always performed [24, 30]. In the last few decades, the importance of EUS-FNB significantly increased worldwide, as it represents a step forward to a more accurate diagnosis and, consequently, to a more frequent use of neoadjuvant chemotherapy and personalized medicine. This approach has surpassed percutaneous sampling techniques, as it provides tissue core biopsies, allowing histological assessment. New generation FNB needles demonstrated a diagnostic accuracy of over 95% for solid pancreatic lesions and provide samples appropriate for ancillary testing, such as immunohistochemistry and tumor molecular profiling [25, 31].

We also verify the need to enlarge molecular characterization in patients with mPDAC, as only around 40% of physicians request the assessment of additional biomarkers besides BRCA1 and BRCA2. These data are in consonance with previous literature stating that although clinically relevant subtypes of mPDAC exist, molecular profiling is not yet standard in clinical care. Nonetheless, several groups and international cancer networks now advocate for universal multigene germline testing for all patients, irrespective of family history or age at diagnosis [24, 30]. The current challenges for expanding molecular analyses and precision medicine for mPDAC include, among others, the heterogeneous cellular composition of biopsy specimens, the low neoplastic cellularity of tumors and rapid progression of the disease and decisions related to clinical practice and available resources (e.g., human and technical resources, access to drug therapies toward different mutations' treatment) [32, 33]. Interestingly, a study implementing a biopsy protocol to perform time-sensitive whole-exome sequencing and RNA sequencing for mPDAC showed that therapeutically relevant genomic alterations were identified in 48% of patients and pathogenic/likely pathogenic germline alterations in 18%.

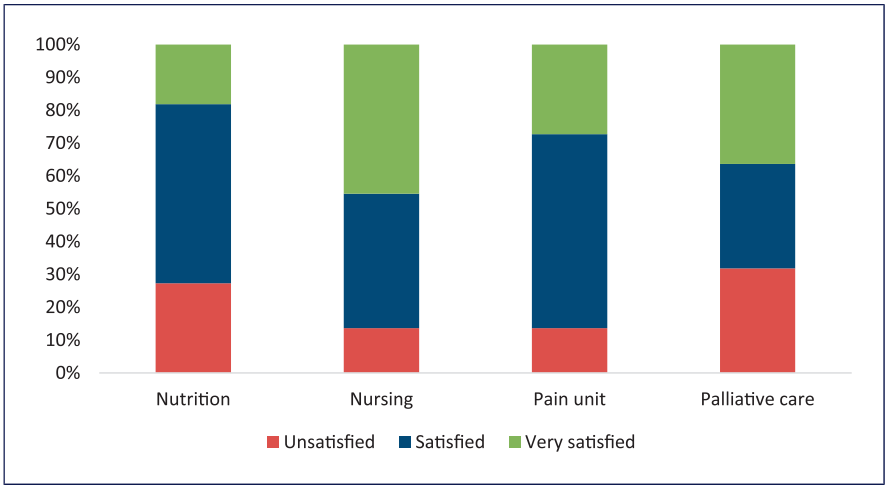


Fig. 1. Oncologists' perception on the support provided by the different services on mPDAC patients' management.

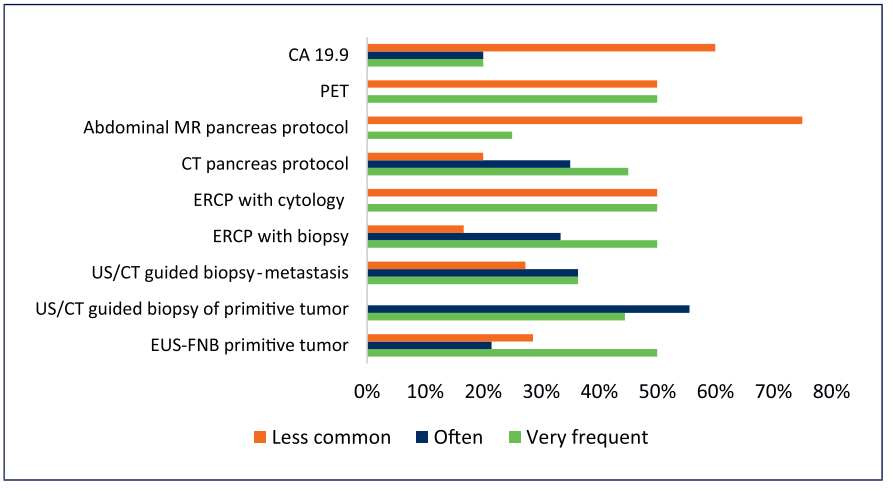


Fig. 2. Oncologists' perception on the use of complementary procedures for the diagnosis of mPDAC.

This results, promoted in around one-third of patients a change in clinical management as a result of genomic data. The most important alterations found were germline or somatic alterations on DNA-damage repair genes (in 40%) and almost 3% had oncogenic in-frame BRAF deletions, which could confer sensitivity to MAPK pathway inhibition. Besides, the aforementioned technical issues, the clinical application of a molecular profiling in mPDAC patients should also consider the difficulty to propose non-approved drugs in this setting, especially considering the high costs and the doubts in response associated with those drugs. These results additionally highlight the difficulties in implementing these protocols in real-world settings [34].

Another dilemma in mPDAC management in Portugal refers to the discrepancies between pathologists and oncologists perceived clinical routines, especially regarding time to mutations' profiling requests and results. This may occur as most pathologists usually require BRCA mutation characterization earlier–during the histological diagnosis, and receive the results within 6 weeks. On the other hand, most oncologists refer to this procedure only during the oncologic consultation in their centers, with half of them obtaining the results after 6 weeks. In this scenario, the pointed median time from patients' admission until mPDAC diagnosis may be longer than 2 months. Comparatively, in England, the median time from patients' first presentation to the healthcare system to diagnosis is of 76 days (IQR 28–161) for metastatic pancreatic cancer, which represents around 2–3 months [35]. In Italy, the overall median diagnostic delay for PDAC is of 2 months, varying from 1 to 5 months [36]. Regarding only the mutation profiling process for advanced cancers, in the USA, the median

time to transmission of results to patients after testing is of around 1 month, but with a very large dispersion (ranging from 0 to 16 months) [37].

These findings highlight the need to standardize and accelerate disease diagnosis and staging aiming at reducing the times for decision-making regarding patients' treatment. In an international level, both germline and tumor BRCA mutational analyses are being increasingly used for selecting patients who could benefit from PARP inhibitors. These tests should be requested during the initial diagnosis of the patient, thus providing appropriate information on all aspects associated with the disease and allowing prompt actions for managing mPDAC [38].

One approach to enhance clinical practice homogeneity and reduce time for cancer diagnosis and treatment is by implementing functional multidisciplinary (MDT) teams' meetings and referral centers [39]. However, several factors influencing presentation of all pancreatic cancer patients to MDT meetings still exist. We found that clinical specialties such as general surgery, pathology, gastroenterology, and radiotherapy – that are paramount for PDAC management, participate in only around one-third of the so-called MDT consultations. The rationale for MDT is to be multidimensional, aiming at ensuring that complex patients receive all care services, including timely diagnosis and treatment, to meet their individual needs. These teams should bring together the expertise and skills of different professionals to assess, plan, and manage care jointly [40]. A recent study performed in Australia showed that barriers influencing MDT practices include: absence of palliative care representation, the number of MDT meetings, the cumulative cost of staff time, the lack of capacity to discuss all patients within the allotted time and reduced confidence to participate in discussions [41]. These factors can lead to a reduced quality of care management and failure to reach decisions in around 27–52% of cases [42]. Additionally, a systematic review showed that MDT decisions frequently lack on considering nursing personnel opinions and patients preferences [42]. In our study, although most oncologists feel satisfied with the support provided by different hospital services, including nursing staff and pain units, there is room for improvement in coordination with the nutrition and palliative care units. This is important as a study recently demonstrated that around 93% of patients with PDAC need palliative care referral, 45% receive palliative chemotherapy and around 80% have a dietitian referral [43]. In this scenario, key enablers influencing MDT practices include a strong organizational focus (e.g., leadership, training) that should be strengthened with the development of agreed evidence-based protocols and referral pathways, use of technology (e.g., videoconferences), resource allocation and capabilities, and a culture that fosters widespread collaboration for all stages of PDAC (e.g., motivation to provide good quality care) [41, 42].

According to surveyed oncologists, the first-line treatments for mPDAC in Portugal are currently selected grounded on clinical criteria (e.g., performance status, liver function) and patients' comorbidities, being chemotherapy combinations such as FOLFIRINOX or mFOLFIRINOX or gemcitabine plus nab-paclitaxel the most prescribed. Selection of the second-line therapies follows similar patterns, being grounded on the use of previous chemotherapy protocols and patients' performance status. Factors such as the access to therapies (e.g., regulatory issues, costs, reimbursement criteria) and real-world practices in the country (e.g., delayed or lack of molecular profiling, inflexible treatment protocols, physicians' preferences) can be associated with this heterogenous scenario. This also highlights the difficulties for approving and implementing new target drugs, such as olaparib, into daily practice, which could support answering the needs of both patients and healthcare professionals in the country. Yet, around 70% of oncologists in our study stated that PARP inhibitors, when approved, would be the therapeutic choice for patients with BRCA mutations without progression after 4 months of chemotherapy treatment.

Our study has some limitations. Non-probabilistic convenience sampling in cross-sectional studies may carry out a bias in data collection and due to under-representation of subgroups considering that more committed responders usually get involved in mPDAC care. However, our inferences were grounded on the results obtained with this sample, without further extrapolation. We also acknowledged the relatively small sample size with limited number of participants reported by physicians from some regions of the country. Yet, this geographical asymmetry is similar to that observed in the country in previous studies [2]. We were able to portray the perception of both pathologists and oncologists that routinely manage mPDAC patients in Portugal. Although the questionnaire was applied in the end of 2020, which could raise concerns about the impact of the COVID-19 on the clinical activities evaluated in this study, all questions were retrospective regarding the routinely scenario previous to the pandemic.

Portuguese physicians support the increasing role of target therapies and patient-tailored treatments for mPDAC, whose selection should be grounded on tumoral subtyping and molecular profiling by means of accurate diagnostic and staging techniques. However, further efforts from both healthcare institutions and the health system to develop functional multidisciplinary teams and provide technical and qualified human resources are required. This may reduce the time between patients' diagnosis and beginning of treatment and standardize daily clinical practice in the country. Additionally, there is a need to optimize the approval and implementation process of new target therapies for conditions such as mPDAC that would benefit from the availability of further therapeutic strategies.

Acknowledgments

The authors would like to acknowledge Dr. Filipa Duarte-Ramos (FDR LDA Company, Portugal) for medical writing support that was funded by AstraZeneca in accordance with Good Publications Practice (GPP3) guidelines (http://www.ismpp.org/gpp3). We also acknowledge every physician participating in the survey.

Statement of Ethics

This study was waived of bioethical approval (National Legislation-Law 21/2014) because it does not contain any intervention on human subjects nor individual health data collection.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This work was supported by AstraZeneca. The funders had no role in study design, data collection, and analysis nor in the preparation of the manuscript.

Author Contributions

Anabela G. Barros, Rudolfo Francisco, and Filipa Duarte-Ramos designed the study and wrote the protocol with contributions from Hélder Mansinho, Nuno Couto, Manuel R. Teixeira, and Fernanda S. Tonin. Data acquisition was performed by Anabela G. Barros, Hélder Mansinho, Nuno Couto, and Manuel R. Teixeira. Filipa Duarte-Ramos and Fernanda S. Tonin wrote the draft of the manuscript with contributions from Anabela G. Barros, Hélder Mansinho, Nuno Couto, Manuel R. Teixeira, and Rudolfo Francisco and analyzed the data, which was interpreted by all authors; the final version of the manuscript was approved by all authors.

Data Availability Statement

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

References

1 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.
2 Marques da Costa P, Tato Marinho R, Cortez-Pinto H, Costa L, Velosa J. Twenty-five years of increasing mortality from pancreatic cancer in Portugal. Pancreas. 2020;49(1):e2–3.
3 Are C, Chowdhury S, Ahmad H, Ravipati A, Song T, Shrikandhe S, et al. Predictive global trends in the incidence and mortality of pancreatic cancer based on geographic location, socio-economic status, and demographic shift. J Surg Oncol. 2016;114(6):736–42.
4 Wong MCS, Jiang JY, Liang M, Fang Y, Yeung MS, Sung JJY. Global temporal patterns of pancreatic cancer and association with socioeconomic development. Sci Rep. 2017;7(1):3165.
5 Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014;74(11):2913–21.
6 Carrato A, Falcone A, Ducreux M, Valle JW, Parnaby A, Djazouli K, et al. A systematic review of the burden of pancreatic cancer in europe: real-world impact on survival, quality of life and costs. J Gastrointest Cancer. 2015;46(3):201–11.
7 Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25.
8 Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691–703.
9 Rapposelli IG, Casadei-Gardini A, Vivaldi C, Bartolini G, Bernardini L, Passardi A, et al. Equivalent efficacy but different safety profiles of gemcitabine plus nab-paclitaxel and FOLFIRINOX in metastatic pancreatic cancer. Biomolecules. 2021;11(6):780.
10 Giommoni E, Maiello E, Vaccaro V, Rondini E, Vivaldi C, Tortora G, et al. Activity and safety of NAB-FOLFIRI and NAB-FOLFOX as first-line treatment for metastatic pancreatic cancer (NabucCO study). Curr Oncol. 2021;28(3):1761–72.
11 Christenson ES, Jaffee E, Azad NS. Current and emerging therapies for patients with advanced pancreatic ductal adenocarcinoma: a bright future. Lancet Oncol. 2020;21(3):e135–45.
12 Hue JJ, Bingmer K, Sugumar K, Markt SC, Rothermel LD, Hardacre JM, et al. Immunotherapy is associated with a survival benefit in patients receiving chemotherapy for metastatic pancreatic cancer. J Pancreat Cancer. 2021;7(1):31–8.
13 Hammel P, Vitellius C, Boisteau E, Wisniewski M, Colle E, Hilmi M, et al. Maintenance therapies in metastatic pancreatic cancer: present and future with a focus on PARP inhibitors. Ther Adv Med Oncol. 2020;12:1758835920937949.

14 Holter S, Borgida A, Dodd A, Grant R, Semotiuk K, Hedley D, et al. Germline BRCA mutations in a large clinic-based cohort of patients with pancreatic adenocarcinoma. J Clin Oncol. 2015;33(28):3124–9.
15 Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015;518(7540):495–501.
16 Heeke AL, Pishvaian MJ, Lynce F, Xiu J, Brody JR, Chen WJ, et al. Prevalence of homologous recombination-related gene mutations across multiple cancer types. JCO Precis Oncol. 2018;2018(2):1–13.
17 O'Connor MJ. Targeting the DNA damage response in cancer. Mol Cell. 2015;60(4): 547–60.
18 Murai J, Huang SY, Das BB, Renaud A, Zhang Y, Doroshow JH, et al. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. Cancer Res. 2012;72(21):5588–99.
19 Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmana J, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015;33(3):244–50.
20 Golan T, Kanji ZS, Epelbaum R, Devaud N, Dagan E, Holter S, et al. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. Br J Cancer. 2014; 111(6):1132–8.
21 Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med. 2017;377(6): 523–33.
22 Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med. 2019; 381(4):317–27.
23 Hammel P, Kindler HL, Reni M, Van Cutsem E, Macarulla T, Hall MJ, et al. Health-related quality of life in patients with a germline BRCA mutation and metastatic pancreatic cancer receiving maintenance olaparib. Ann Oncol. 2019;30(12):1959–68.
24 Sohal DPS, Kennedy EB, Cinar P, Conroy T, Copur MS, Crane CH, et al. Metastatic pancreatic cancer: ASCO guideline update. J Clin Oncol. 2020;38(27):3217–30.
25 Marques S, Bispo M, Rio-Tinto R, Fidalgo P, Deviere J. The impact of recent advances in endoscopic ultrasound-guided tissue acquisition on the management of pancreatic cancer. GE Port J Gastroenterol. 2021;28(3): 185–92.
26 Sivapalan L, Kocher HM, Ross-Adams H, Chelala C. Molecular profiling of ctDNA in pancreatic cancer: opportunities and challenges for clinical application. Pancreatology. 2021;21(2):363–78.
27 Arias-Pinilla GA, Modjtahedi H. Therapeutic application of monoclonal antibodies in pancreatic cancer: advances, challenges and future opportunities. Cancers. 2021;13(8): 1781.
28 Diab M, Azmi A, Mohammad R, Philip PA. Pharmacotherapeutic strategies for treating pancreatic cancer: advances and challenges. Expert Opin Pharmacother. 2019;20(5): 535–46.
29 Sistema Nacional de Saúde (SNS). Trabalhadores por grupo profissional; 2021. Available from: https://wwwsnsgovpt/transparencia/.
30 National Comprehensive Cancer Network (NCCN). Pancreatic Cancer Guidelines; 2021. Available from: https://wwwnccnorg/patients/guidelines/content/PDF/pancreatic-patientpdf.
31 Bispo M, Marques S, Rio-Tinto R, Fidalgo P, Deviere J. The role of endoscopic ultrasound in pancreatic cancer staging in the era of neoadjuvant therapy and personalised medicine. GE Port J Gastroenterol. 2021;28(2): 111–20.
32 Yurgelun MB. Germline testing for individuals with pancreatic cancer: the benefits and challenges to casting a wider net. J Clin Oncol. 2017;35(30):3375–7.
33 Aung KL, Fischer SE, Denroche RE, Jang GH, Dodd A, Creighton S, et al. Genomics-driven precision medicine for advanced pancreatic cancer: early results from the COMPASS trial. Clin Cancer Res. 2018;24(6):1344–54.
34 Aguirre AJ, Nowak JA, Camarda ND, Moffitt RA, Ghazani AA, Hazar-Rethinam M, et al. Real-time genomic characterization of advanced pancreatic cancer to enable precision medicine. Cancer Discov. 2018; 8(9):1096–111.
35 Walter FM, Mills K, Mendonca SC, Abel GA, Basu B, Carroll N, et al. Symptoms and patient factors associated with diagnostic intervals for pancreatic cancer (SYMPTOM pancreatic study): a prospective cohort study. Lancet Gastroenterol Hepatol. 2016;1(4): 298–306.
36 Stornello C, Archibugi L, Stigliano S, Vanella G, Graglia B, Capalbo C, et al. Diagnostic delay does not influence survival of pancreatic cancer patients. United Eur Gastroenterol J. 2020;8(1):81–90.
37 Mandelker D, Zhang L, Kemel Y, Stadler ZK, Joseph V, Zehir A, et al. Mutation detection in patients with advanced cancer by universal sequencing of cancer-related genes in tumor and normal DNA vs guideline-based germline testing. JAMA. 2017;318(9):825–35.
38 Pujol P, Barberis M, Beer P, Friedman E, Piulats JM, Capoluongo ED, et al. Clinical practice guidelines for BRCA1 and BRCA2 genetic testing. Eur J Cancer. 2021;146:30–47.
39 Kirkegard J, Aahlin EK, Al-Saiddi M, Bratlie SO, Coolsen M, de Haas RJ, et al. Multicentre study of multidisciplinary team assessment of pancreatic cancer resectability and treatment allocation. Br J Surg. 2019;106(6):756–64.
40 Patkar V, Acosta D, Davidson T, Jones A, Fox J, Keshtgar M. Cancer multidisciplinary team meetings: evidence, challenges, and the role of clinical decision support technology. Int J Breast Cancer. 2011;2011:831605.
41 Maharaj AD, Evans SM, Zalcberg JR, Ioannou LJ, Graco M, Croagh D, et al. Barriers and enablers to the implementation of multidisciplinary team meetings: a qualitative study using the theoretical domains framework. BMJ Qual Saf. 2021;30(10):792–803.
42 Lamb BW, Brown KF, Nagpal K, Vincent C, Green JS, Sevdalis N. Quality of care management decisions by multidisciplinary cancer teams: a systematic review. Ann Surg Oncol. 2011;18(8):2116–25.
43 Choi CC, Choi J, Houli N, Smith M, Usatoff V, Lipton L, et al. Evaluation of palliative treatments in unresectable pancreatic cancer. ANZ J Surg. 2021;91(5):915–20.

GE – Portuguese Journal of Gastroenterology

Clinical Case Study

GE Port J Gastroenterol 2024;31:273–277
DOI: 10.1159/000533179

Received: March 18, 2023
Accepted: July 12, 2023
Published online: August 16, 2023

Acute Abdominal Pain as the Initial Presentation of an Acquired C1 Inhibitor Deficiency

Ana Raquel Pinto Fabrícia Carolino

Allergy and Clinical Immunology Department, Centro Hospitalar Universitário do Porto, Porto, Portugal

Keywords
Abdominal pain · Angioedema · C1 esterase inhibitor · Lymphoproliferative disorders · Monoclonal gammopathy

Abstract
Introduction: Acquired angioedema (AAE), a rare cause of adult-onset non-urticarial mucocutaneous angioedema, can present as acute abdomen, a frequent complaint in the emergency room (ER), often leading to unnecessary and potentially harmful procedures. ***Case Presentation:*** We report a 47-year-old hypertense male, controlled with an angiotensin converting enzyme inhibitor (ACEI), who presented in the ER with progressively worsening abdominal pain, nausea, and vomiting, and a radiologic workup revealing small intestine thickening, initially diagnosed with ACEI-induced angioedema. However, further investigation revealed low serum levels of C4, C1q, and C1 inhibitors, with an abnormal function of the latter, favoring the diagnosis of AAE instead. The frequent association of this condition with lymphoproliferative disorders encouraged further studies, which unveiled a monoclonal gammopathy IgM/Kappa, representing an increased risk of Waldenström macroglobulinemia, non-Hodgkin lymphoma, and multiple myeloma. ***Discussion:*** AAE should be regarded as an important differential diagnosis in patients presenting with acute abdomen in the ER, especially when more common causes are excluded. A correct and early diagnosis may represent a chance for a better prognosis of underlying diseases.

Abdómen agudo como apresentação inicial de deficiência adquirida de C1 inibidor

Palavras Chave
Dor abdominal · Angioedema · Inibidor da C1 esterase · Distúrbios linfoproliferativos · Gamopatia monoclonal

Resumo
Introdução: O angioedema adquirido (AA), causa rara de angioedema mucocutâneo não urticariforme de início tardio, pode ter como apresentação inicial abdómen agudo, motivo frequente de admissão no serviço de urgência (SU), promovendo frequentemente procedimentos desnecessários e potencialmente prejudiciais. ***Apresentação do caso:*** Um homem de 47 anos, hipertenso e controlado com um inibidor da enzima conversora de angiotensina (IECA), recorreu ao SU por um quadro de dor abdominal com agravamento progressivo,

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

Correspondence to:
Ana Raquel Pinto, araquel2@hotmail.com

náuseas e vómitos. A investigação radiológica inicial revelou espessamento do intestino delgado, culminando num diagnóstico preliminar de angioedema induzido por IECA. No entanto, uma investigação mais aprofundada em regime ambulatório revelou níveis séricos reduzidos de C4, C1q e de inibidor de C1, com função anormal deste último, favorecendo o diagnóstico de AA. A associação frequente desta condição com distúrbios linfoproliferativos incentivou investigação adicional, que revelou uma gamopatia monoclonal IgM/Kappa, representando um risco aumentado de macroglobulinemia de Waldenström, linfoma não-Hodgkin e mieloma múltiplo. ***Discussão:*** O AA deve ser considerado um diagnóstico diferencial de abdómen agudo, principalmente após exclusão de causas mais frequentes. Um diagnóstico precoce pode contribuir para um melhor prognóstico da patologia subjacente.

Introduction

Acquired angioedema (AAE) due to deficiency of C1 esterase inhibitor is a rare cause of adult-onset non-urticarial mucocutaneous angioedema, characterized by recurrent episodes of cutaneous, gastrointestinal, and life-threatening laryngeal edema, similar to those observed in hereditary forms. Its presentation as acute abdominal pain, a frequent complaint in the emergency room (ER), can lead to unnecessary and potentially harmful procedures [1]. These episodes follow an overactivation of the classical complement pathway with serum C1 inhibitor (C1-INH) consumption, leading to an upregulation of the kallikrein-kinin system with bradykinin accumulation, vasodilation, and angioedema. This process can be secondary to the formation of autoantibodies that neutralize C1-INH function or due to an underlying lymphoproliferative disorder, being monoclonal gammopathy of uncertain significance and non-Hodgkin's lymphoma the most prevalent [2]. While some episodes appear to be triggered by emotional/mechanical stress or viral infections, frequently there is no identifiable trigger [3]. This disorder significantly impairs patients' quality of life, so a prompt diagnosis and establishment of appropriate therapy are essential [1].

The laboratory assessment should involve the evaluation of C1-INH function, typically abnormal, and serum levels of C4, C1q, and C1-INH, generally decreased (although a normal value of the latter is not unusual). Most patients have identifiable autoantibodies against the C1-INH protein, though this analysis is not routinely available. A serum protein electrophoresis is relevant to rule out the presence of an underlying lymphoproliferative disorder [2]. Due to scarce understanding of the disease and limited published data, treatment options are essentially borrowed from hereditary forms [1]. We intend to highlight AAE as a differential diagnosis to consider in a patient presenting with acute and severe abdominal pain in the ER and the importance of excluding underlying lymphoproliferative disorders in this context.

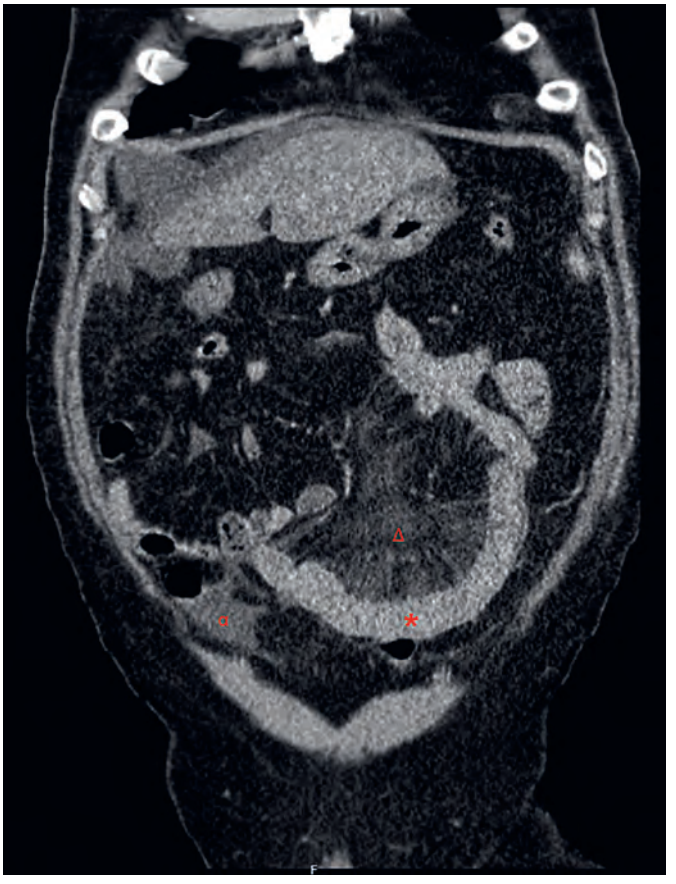


Fig. 1. Contrasted computed tomography of the abdomen and pelvis performed in the emergency department revealing a continuous and concentric thickening of the small intestine with more than 10 cm of extension (*), particularly in the lower abdominal quadrants, engorgement of vasa recta (Δ), and a moderate peritoneal effusion (α) (coronal plane).

Case Presentation

A 47-year-old male, with a personal history of smoking, obesity, and arterial hypertension controlled with an angiotensin converting enzyme inhibitor (ACEI), presented to the ER with diffuse cramping

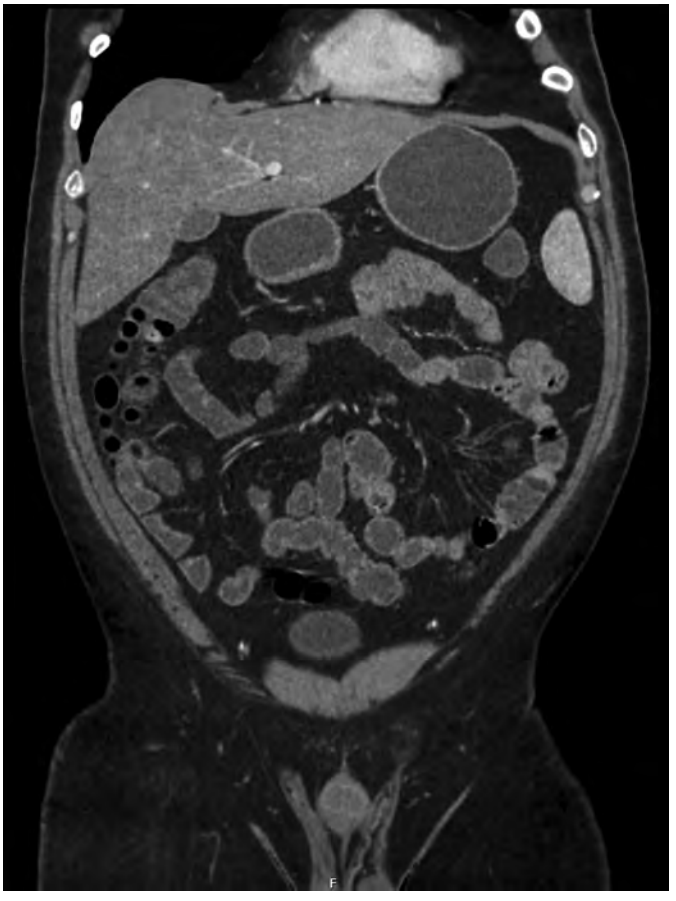


Fig. 2. Computed tomography enterography of the abdomen and pelvis performed before patient's discharge without the previously observed abnormalities (identical coronal plane as Fig. 1).

abdominal pain, predominantly in the lower quadrants, which had started 15 days prior and with increasing intensity, associated with nausea and vomiting. There were no additional manifestations, namely, fever, diarrhea, respiratory, or cutaneous symptoms. Initial analytical study performed in the ER revealed lymphopenia (1,090 lymphocytes/μL) and elevated gamma-glutamyl transferase (178 U/L) and C-reactive protein (37 mg/L); the remaining blood work, including hepatic, pancreatic, renal, and protein panels, was normal. Urinary sediment assessment was normal, and stool parasitological examination was negative. An abdominal ultrasound unveiled, besides hepatomegaly, hepatic steatosis, and splenomegaly, a concentric thickening of the small intestine, hyperechogenicity of adjacent fat tissue, and a peritoneal effusion, suggesting further evaluation with computer tomography. The latter exam reenforced the previous findings, revealing a continuous and concentric thickening of the small intestine with more than 10 cm of extension, particularly in the lower abdominal quadrants, engorgement of vasa recta, and a moderate peritoneal effusion (as shown in Fig. 1). At this point, information obtained from clinical, analytical, and radiologic findings allowed exclusion of more frequent causes of acute abdomen, such as acute gastroenteritis, pancreatitis, cholecystitis/choledocholithiasis, appendicitis, diverticulitis, or gastrointestinal obstruction, and the main suspected diagnosis was inflammatory enteropathy versus ACEI-induced angioedema. The patient was admitted to the ward and, under symptomatic treatment, along with ACEI suspension, complete resolution was achieved in a period of 8 days. Additional assessment during the hospital stay involved a negative measurement of antibodies anti-*Saccharomyces cerevisiae* (ASCA) and antineutrophil cytoplasmic (ANCA), and endoscopic exams with biopsies, without abnormal findings, further excluding acute infectious causes, inflammatory bowel disease, and gastrointestinal malignancy. An eco-guided paracentesis revealed a peritoneal transudate, with discretely increased lymphocyte levels (417 mononuclear cells/μL and 144 polymorphonuclear cells/μL) and no other altered parameters, namely, glucose, albumin, proteins, pancreatic alpha-amylase, lactate dehydrogenase, and adenosine deaminase. Mycobacteriological assessment of the ascitic fluid was negative. Before discharge, a computer tomography enterography was performed, revealing normalization of the initial acute findings (as shown in Fig. 2).

After referral to our Allergy and Clinical Immunology Department, a detailed anamnesis ruled out personal and family history of angioedema or urticaria. Of note, he also reported living a stressful lifestyle and a loss of about 9% of his body weight during the previous 12 months, following a voluntary increase in physical activity and a more controlled diet. Analytical study revealed persistence of the initial findings (with normalization of C-reactive protein) and low serum levels of C4 (<2 mg/dL), C1q (9 mg/dL), and C1-INH (9.2 mg/dL), together with an abnormal C1-INH function, favoring the diagnosis of AAE in detriment to ACEI-induced angioedema.

Once the diagnosis of AAE was established, it became essential to exclude secondary causes. To start with, the patient denied B symptoms, and further assessment revealed a high sedimentation rate (19 mm/h) and high beta-2 microglobulin (3.14 mg/L). Serum protein electrophoresis and immunofixation also revealed a monoclonal gammopathy IgM/Kappa. Due to these findings, having a shared long-term follow-up in mind, the patient was referred to a Hematology/Oncology appointment.

A rare disease card containing a detailed treatment plan in case of ER admission was issued (privileging endovenous C1-INH concentrate or subcutaneous bradykinin receptor antagonist icatibant or, if irresponsive, endovenous tranexamic acid), and an ambulatory emergency and short-term prophylaxis treatment plan with tranexamic acid was provided and explained to the patient. Additionally, a request addressed to the Pharmacy and Therapeutics Committee was formalized for the acquisition and dispensation of icatibant for treatment of acute flares on an outpatient basis. During a 12-month follow-up, he reported 2 episodes of non-severe angioedema that resolved without specific treatment, one with facial involvement and another affecting the extremities, both associated with stressful life events.

Discussion

Acute abdominal pain is a common cause of ER admission. Despite its rarity, AAE should be regarded as a differential diagnosis and actively investigated following proper exclusion of more common diagnosis. Considering

the fact that abdominal flares are less frequent than in hereditary forms, there is an even higher risk of missing AAE diagnosis in this context [4].

In the case reported, the patients' age and absence of personal and familiar history of urticaria and/or angioedema led the ER physician toward more common causes of acute abdomen, such as acute pancreatitis, diverticulitis, and appendicitis [5]. The absence of significant analytical abnormalities, together with the radiologic findings and the personal history of ACEI intake, made the diagnosis of ACEI-induced angioedema the most plausible. Symptoms' resolution after its suspension further corroborated this line of thought, and, on top of that, other differential diagnosis – inflammatory, infectious, and neoplastic – were excluded during the hospital stay. However, the complementary study requested upon ambulatory evaluation revealed low serum levels of C4, C1q, and C1-INH, together with an abnormal C1-INH function, findings not compatible with ACEI-induced angioedema, favoring the diagnosis of AAE instead [5]. Nevertheless, although not directly linked to the etiology of this condition, the ACEI intake could have played a more indirect role by predisposing symptoms' induction in a patient with a preexisting asymptomatic AAE.

This diagnosis, due to its association with lymphoproliferative disorders, raised concern to the existence of secondary causes. Further investigation revealed findings consistent with a monoclonal gammopathy IgM/Kappa, one of the most frequent underlying diagnoses [2], representing an increased risk of developing Waldenström macroglobulinemia, non-Hodgkin lymphoma, and, rarely, multiple myeloma [6]. Regular evaluation of the underlying hematological abnormalities is essential to assess evolution and early detection and management of more serious diagnoses.

The practical approach to this condition might entail, besides close medical surveillance, according to each individual's clinical evolution – specifically regarding episode's frequency, location, and severity – treatment of acute flares, short-term or long-term prophylaxis. Due to the rarity of AAE, treatment options are essentially borrowed from hereditary forms, and their effectiveness and safety are based on limited research. C1-INH concentrate is by far the most commonly used drug to manage acute flares. Icatibant, a bradykinin receptor antagonist, and ecallantide, a recombinant peptide highly specific for inhibiting plasma kallikrein, have also been successfully used in these circumstances. Currently, there is no consensus or approved drugs for short- or long-term prophylaxis, although antifibrinolytic agents, such as tranexamic acid, and attenuated androgens have been reported to be effective treatments [2, 4]. Considering this, tranexamic acid was recommended for ambulatory management of non-severe acute flares and as short-term prophylaxis to prevent flares during planned exposure to known triggers such as minor surgical procedures, in addition to the emergency treatment plan in case of ER admission. Until the last patient's assessment before loss of follow-up, he was not a candidate to long-term prophylaxis. Future investigation about whether novel safe therapies for hereditary angioedema are also effective for the treatment of patients with AAE is essential.

Overall data regarding long-term prognosis are lacking – available literature suggests that, in general, patients with a timely diagnosis and under clinician's close monitoring are able to achieve partial or complete symptomatic control, either of AAE flares and underlying lymphoproliferative disorders. Nevertheless, there are many reports of fatalities due to AAE complications, particularly laryngeal edema and lymphoproliferative disorders' evolution [4].

In conclusion, AAE should be regarded as an important differential diagnosis in patients presenting with acute abdomen in the ER, especially when more common causes are excluded. A correct and early diagnosis may represent a chance for a better prognosis.

Statement of Ethics

Written informed consent for the publication of this medical case's details was obtained. Ethical approval was not required for this study in accordance with local/national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no financial support.

Author Contributions

All authors contributed equally to the writing and revision of this manuscript.

Data Availability Statement

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

References

1 Shi Y, Wang C. Where we are with acquired angioedema due to C1 inhibitor deficiency: a systematic literature review. Clin Immunol. 2021;230:108819.

2 Kesh S, Bernstein JA. Isolated angioedema: a review of classification and update on management. Ann Allergy Asthma Immunol. 2022;129(6):692–702.

3 Otani IM, Banerji A. Acquired C1 inhibitor deficiency. Immunol Allergy Clin North Am. 2017;37(3):497–511.

4 Zanichelli A, Azin GM, Wu MA, Suffritti C, Maggioni L, Caccia S, et al. Diagnosis, course, and management of angioedema in patients with acquired C1-inhibitor deficiency. J Allergy Clin Immunol Pract. 2017;5(5):1307–13.

5 Pines JM, Poarch K, Hughes S. Recognition and differential diagnosis of hereditary angioedema in the emergency department. J Emerg Med. 2021; 60(1):35–43.

6 Khwaja J, D'Sa S, Minnema MC, Kersten MJ, Wechalekar A, Vos JM. IGM monoclonal gammopathies of clinical significance: diagnosis and management. Haematologica. 2022;107(9):2037–50.

GE – Portuguese Journal of Gastroenterology

Clinical Case Study

GE Port J Gastroenterol 2024;31:278–282
DOI: 10.1159/000533499

Received: April 12, 2023
Accepted: July 25, 2023
Published online: September 1, 2023

Obinutuzumab-Induced Inflammatory Bowel Disease-Like Pancolitis: A First Case Report

Raquel R. Mendes[a] Pedro C. Figueiredo[a] Isabel Andrade[b]

[a]Gastroenterology Department, Centro Hospitalar de Lisboa Ocidental, Lisboa, Portugal; [b]Pathology Department, Centro Hospitalar de Lisboa Ocidental, Lisboa, Portugal

Keywords
Obinutuzumab · Colitis · Inflammatory bowel disease

Abstract
Introduction: Obinutuzumab is a type II anti-CD20 monoclonal antibody associated with a higher rate of toxicity when compared to rituximab. Gastrointestinal side-effects have been reported but data is still sparse. ***Case Presentation:*** A 47-year-old female with medical history of stage IV follicular non-Hodgkin lymphoma under chemotherapy presented with chronic bloody diarrhea and iron deficiency anemia. Endoscopic and histologic features resembled inflammatory bowel disease (IBD), imposing a thorough differential diagnosis. The diagnosis of obinutuzumab-induced pancolitis was made and the drug was suspended with subsequent clinical improvement. ***Conclusion:*** This is the first case report of obinutuzumab-induced pancolitis. The challenging differential diagnosis of IBD required a multidisciplinary approach with subsequent outcome and management implications.

Pancolite induzida por Obinutuzumab: a propósito de um caso clínico

Palavras Chave
Obinutuzumab · Colite · Doença inflamatória intestinal

Resumo
Introdução: Obinutuzumab é um anticorpo monoclonal anti-CD20 tipo II, com aparente maior taxa de toxicidade relativamente ao rituximab. Alguns efeitos adversos gastrointestinais têm sido reportados, no entanto, a evidência científica mantém-se escassa. ***Caso Clínico:*** Mulher de 47 anos, com antecedentes de linfoma não-Hodgkin folicular estádio IV sob quimioterapia, apresenta-se com diarreia crónica sanguinolenta e anemia ferropénica. Os achados endoscópicos e histológicos assemelham-se a uma doença inflamatória intestinal (DII), impondo um diagnóstico diferencial exaustivo. Foi diagnosticada com uma pancolite induzida por obinutuzumab, tendo este sido suspenso, com melhoria clínica subsequente. ***Conclusão:*** Este é o primeiro caso documentado de pancolite induzida por obinutuzumab. A apresentação

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

Correspondence to:
Raquel Rodrigues Mendes, raquelrmendes@gmail.com

com aspetos sugestivos de DII obrigou a uma abordagem holística e multidisciplinar com implicações na abordagem e seguimento da doente.

Introduction

Obinutuzumab is a humanized glycoengineered type II anti-CD20 monoclonal antibody used in B-cell mediated malignancies. Compared with the well-known rituximab, obinutuzumab mediates an enhanced induction of antibody dependent cell-mediated cytotoxicity and direct cell death. Consequently, it has been associated with a higher rate of toxicity [1]. Diarrhea is a common side-effect reported in more than 10% of patients [2, 3].

Nevertheless, no clinical, endoscopic, or pathologic features have specifically been reported for obinutuzumab-induced gastrointestinal adverse events. In fact, herein is presented the first case report of an inflammatory bowel disease (IBD)-like pancolitis induced by obinutuzumab.

Currently, several drugs, infections, vascular and immune disorders are known to simulate IBD, not only clinically but also histologically. In fact, a holistic and comprehensive clinical assessment with close communication between clinicians and pathologists is crucial for the differential diagnosis between most entities [4].

Drug-induced enterocolitis is usually unspecific and may have pancolonic involvement in 27% of patients [4]. Its mechanisms may range from direct vasoconstriction or dysbiosis to direct cytotoxicity and immune activation. Immune checkpoint inhibitors, nonsteroidal anti-inflammatory drugs, and mycophenolate mofetil are known examples of drugs able to induce enterocolitis. Moreover, some reports have suggested a possible relation between rituximab and *de novo* or exacerbation of previous IBD and microscopic colitis [4–7].

In a rituximab-associated colitis cohort, gastrointestinal symptoms began on average more than 8 months after drug initiation and included diarrhea (56%), abdominal pain (27%), blood or mucous per rectum (16%), and vomiting (16%). Endoscopic abnormalities were more common in symptomatic patients showing both ulcerative and non-ulcerative features, with pancolonic involvement in 58% of cases. Histological characteristics included mixed inflammatory infiltrate, erosions, ulceration, reactive epithelial changes, and apoptotic bodies [8]. The present case describes a similar obinutuzumab-induced pancolitis with clinical, endoscopic, and histologic features resembling IBD, therefore imposing an exhaustive differential diagnosis.

Case Report

A 47-year-old female with previous medical history of stage IV follicular non-Hodgkin lymphoma was treated with R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) followed by rituximab-only maintenance, with prolonged clinical remission. After 7 years of complete remission, the disease relapsed and the patient was submitted to a new induction cycle with obinutuzumab-bendamustine chemotherapy with clinical response and subsequent transition to obinutuzumab-only maintenance.

After 1 year of treatment, the patient presented to a gastroenterology appointment with a 3-month history of diarrhea, occasionally accompanied by blood and fecal urgency. She denied fever, night sweats, weight loss, abdominal pain, tenesmus, rectal mucus or pus discharge, mucocutaneous or musculoskeletal symptoms. Physical examination including anorectal examination was unremarkable.

Laboratory studies revealed iron-deficiency anemia (hemoglobin level 10.6 g/dL), with microcytosis (VGM 73.8 fL), hypochromia (HGM 23.8 pg), and iron deficiency (iron 25 µg/dL, ferritin 44.9 ng/mL, transferrin saturation 8%). Leukocyte and platelet counts were normal. C-reactive protein was 1.69 mg/dL (reference range <0.5 mg/dL), fecal calprotectin was 928 mg/kg (reference range <50 mg/kg), and protein electrophoresis showed hypogammaglobulinemia. No signs of dehydration or malnutrition were found. Stool cultures isolated *Campylobacter jejuni*. Ova and parasite stool tests were negative. In this context, the patient was prescribed azithromycin 500 mg for 3 days without any symptom improvement.

Ileocolonoscopy was performed revealing normal ileal and rectal mucosa. However, the colon mucosa was diffusely erythematous, friable, and superficially ulcerated, with focally adherent exudate (shown in Fig. 1a, b). Colonic biopsies showed a mixed inflammatory infiltrate with focal architectural distortion, cryptitis, crypt abscesses, apoptosis, and epithelioid granulomas (shown in Fig. 2a, c). Acid-fast bacilli smear was negative. Cytomegalovirus was negative by immunohistochemistry.

Considering all clinical, pathological, endoscopic, and histologic findings, we postulated the hypothesis of an obinutuzumab-induced pancolitis. Therefore, in collaboration with the hemato-oncologist team, the drug was suspended and the patient was kept under close surveillance.

Three months after drug withdrawal, the patient showed complete resolution of symptoms, with 2 formed non-bloody stools per day without fecal urgency. Blood work showed resolution of anemia (Hb 13.1 g/dL) and a sharp decrease of fecal calprotectin (100 mg/kg). Endoscopic and histologic assessment demonstrated mucosal healing (shown in Fig. 3a, b), preserved mucosal architecture, inactive inflammation, and absence of granulomas (shown in Fig. 4a, b).

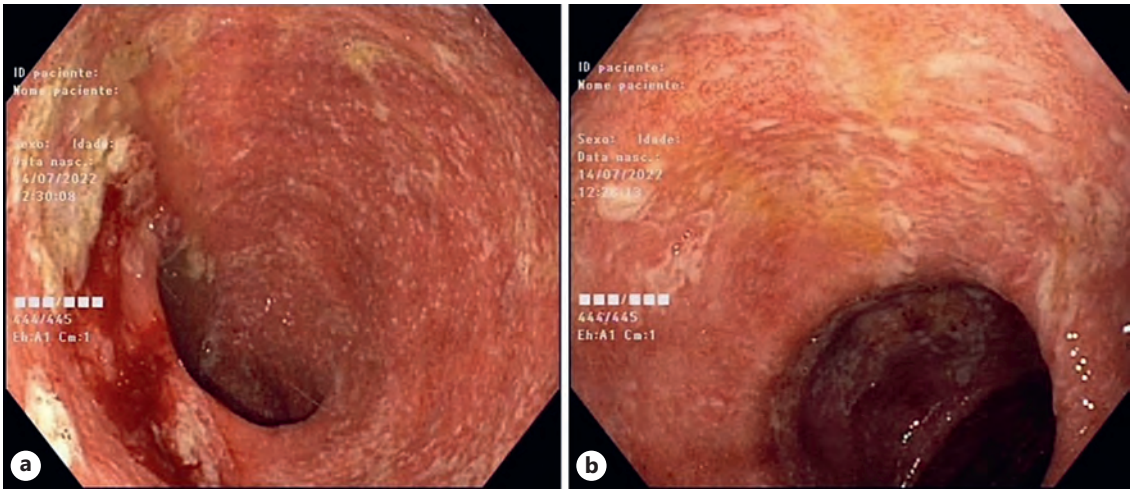


Fig. 1. a, **b** Erythematous, friable, and superficially ulcerated colonic mucosa.

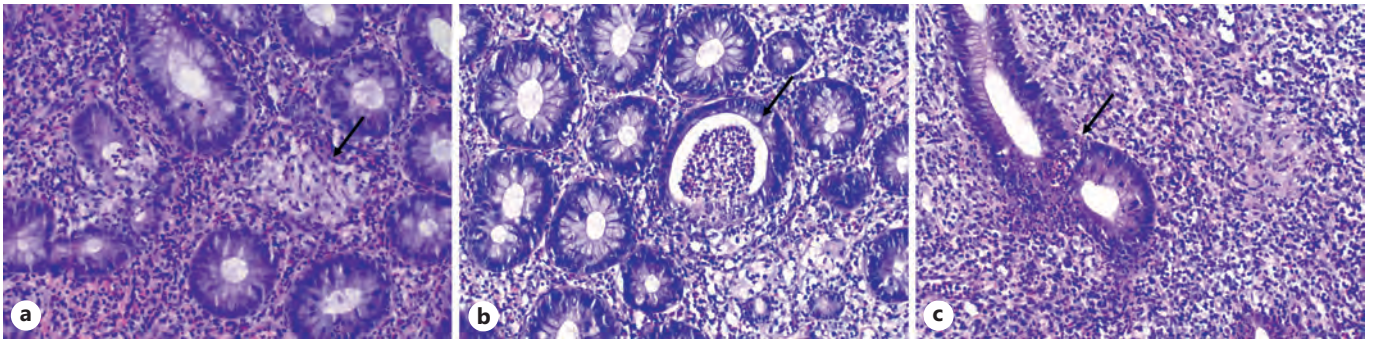


Fig. 2. a Epithelioid non-necrotizing granuloma delineation (arrow) in lamina propria and in relation to crypts (HE, 20 × 10). **b** Crypt abscess (arrow) (HE, 20 × 10). **c** Mixed inflammatory infiltrate, cryptitis, and apoptosis (arrow) (HE, 20 × 10).

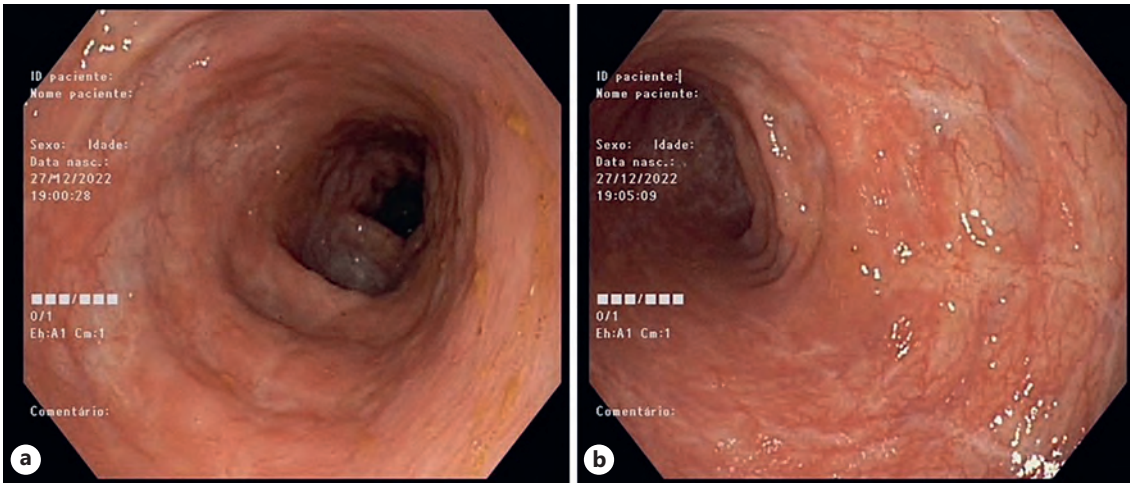


Fig. 3. a, **b** Healed and scarred colonic mucosa, 3 months after drug withdrawal.

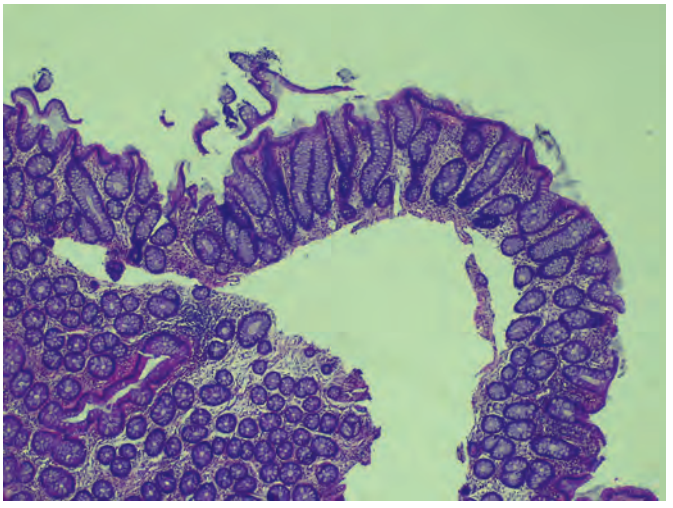


Fig. 4. Preserved mucosal architecture and inactive inflammation (HE, 10 × 10).

Discussion

Throughout the last decades, numerous drugs and chemicals have been recognized as triggers for medication-induced enterocolitis and IBD flares [4]. In this context, a multidisciplinary assessment is crucial to correctly diagnose and manage these patients. In fact, by gathering all clinical, pathological, endoscopic, and histologic findings, the presented clinical case suggested a possible obinutuzumab-induced pancolitis.

The clinical presentation of *de novo* chronic bloody diarrhea with urgency in a 47-year-old patient could suggest IBD or malignancy [9]. However, the absence of weight loss, fever, abdominal pain, or extraintestinal symptoms did not support these hypotheses.

Regarding laboratory data, iron-deficiency anemia and elevation of fecal calprotectin could have suggested an IBD diagnosis [9]. However, these features are unspecific and the latter one has also been suggested to help predict disease activity and prognosis in drug-related colitis [6]. Endoscopically, the continuous colonic disease resembled extensive ulcerative colitis, except for rectal sparing, which is atypical in a patient not on topical therapy and with no evidence of primary sclerosing cholangitis [9].

Endoscopic biopsies demonstrated both IBD-like features, such as architectural distortion, cryptitis, crypt abscesses, and noncaseating granulomas; and drug-induced features, such as mixed inflammatory infiltrate and apoptotic bodies [4, 5]. Noncaseating granulomas could have suggested a broad spectrum of differential diagnosis, including inflammatory (Crohn's disease, sarcoidosis), infectious, or drug-induced diseases [4].

Regarding the possibility of *de novo* IBD, our patient achieved complete clinical, endoscopic, and histological remission with only supportive therapy, which is not typical or suggestive of IBD. However, there might still be a role for drug-induced immune dysregulation and dysbiosis as a trigger for a future IBD diagnosis [10]. An IBD misdiagnosis in this context would have implied futile immunosuppression, with short- and long-term potential complications. Additionally, the temporal relation between drug introduction and symptom onset, nearly 1 year of sustained treatment before the beginning of symptoms, and the improvement after drug withdrawal were solid clues pointing to medication-related injury [4].

Moreover, the isolation of *C. jejuni* from stool culture was considered a confounding factor in this case. The chronic course and the absence of clinical improvement after antibiotics refute the hypothesis that this diagnosis was responsible for the clinical presentation [4]. The authors believe that the bacteria was an innocent bystander in this case.

Despite the lack of literature, the authors propose the obinutuzumab-induced colitis' pathogenesis relies on host immune dysregulation, through potent antibody-dependent cell-mediated cytotoxicity, phagocytosis, direct cell death, and dysfunction of B and T-regulatory cells, with consequent dysbiosis and abnormal mucosal barrier [8, 11]. The previous prolonged exposure to rituximab might have enhanced this pathophysiology through previous cellular immune dysregulation and damage build-up on the colonic mucosa [12].

Additionally, grading severity according to the Common Terminology Criteria for Adverse Events and managing it similarly to the well-known immune checkpoint inhibitor-induced colitis seems plausible. Our patient presented with grade 2 colitis and medication withdrawal was enough to achieve complete clinical resolution. Nevertheless, in the absence of improvement or if a more serious clinical picture was noted, steroids or biologics might have been required. Resuming obinutuzumab can be considered, although permanent drug discontinuation might be advised [10, 13].

This is, to the best of our knowledge, the first case report of obinutuzumab-induced pancolitis presenting with not only clinical and analytical but also endoscopic and histologic IBD-like features. A thorough differential

diagnosis and careful multidisciplinary approach were key to correctly manage this case which had therapeutic and prognostic implications.

Statement of Ethics

The study did not require ethics approval. Informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There are no funding sources to declare.

Author Contributions

Raquel R. Mendes: conception, original draft, and revision. Pedro C. Figueiredo: conception, revision, and editing. Isabel Andrade: histology assessment and revision.

Data Availability Statement

All data generated or analyzed during this study are included in this article.

References

1 Amitai I, Gafter-Gvili A, Shargian-Alon L, Raanani P, Gurion R. Obinutuzumab-related adverse events: a systematic review and meta-analysis. Hematol Oncol. 2021;39(2):215–21.
2 Goede V, Fischer K, Busch R, Engelke A, Eichhorst B, Wendtner CM, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med. 2014;370(12):1101–10.
3 Morschhauser F, Le Gouill S, Feugier P, Bailly S, Nicolas-Virelizier E, Bijou F, et al. Obinutuzumab combined with lenalidomide for relapsed or refractory follicular B-cell lymphoma (GALEN): a multicentre, single-arm, phase 2 study. Lancet Haematol. 2019;6(8):e429–37.
4 Feakins R, Torres J, Borralho-Nunes P, Burisch J, Cúrdia Gonçalves T, De Ridder L, et al. ECCO topical review on clinicopathological spectrum and differential diagnosis of inflammatory bowel disease. J Crohns Colitis. 2022;16(3):343–68.
5 Reggiani Bonetti L, Leoncini G, Daperno M, Principi MB, Baronchelli C, Manenti S, et al. Histopathology of non-IBD colitis practical recommendations from pathologists of IG-IBD Group. Dig Liver Dis. 2021;53(8):950–7.
6 Tang L, Wang J, Lin N, Zhou Y, He W, Liu J, et al. Immune checkpoint inhibitor-associated colitis: from mechanism to management. Front Immunol. 2021;12:800879.
7 Eckmann JD, Chedid V, Quinn KP, Bonthu N, Nehra V, Raffals LE. De novo colitis associated with rituximab in 21 patients at a tertiary center. Clin Gastroenterol Hepatol. 2020;18(1):252–3.
8 Mallepally N, Abu-Sbeih H, Ahmed O, Chen E, Shafi MA, Neelapu SS, et al. Clinical features of rituximab-associated gastrointestinal toxicities. Am J Clin Oncol. 2019;42(6):539–45.
9 Magro F, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. J Crohns Colitis. 2017;11(6):649–70.
10 Bellaguarda E, Hanauer S. Checkpoint inhibitor–induced colitis. Am J Gastroenterol. 2020;115(2):202–10.
11 Davies A, Kater AP, Sharman JP, Stilgenbauer S, Vitolo U, Klein C, et al. Obinutuzumab in the treatment of B-cell malignancies: a comprehensive review. Future Oncol. 2022;18(26):2943–66.
12 Tsuzuki Y, Shiomi R, Ashitani K, Miyaguchi K, Osaki A, Ohgo H, et al. Rituximab-induced ileocolitis in a patient with gastric MALToma: a case report and literature review. Intern Med. 2021;60(5):731–8.
13 Hashash JG, Francis FF, Farraye FA. Diagnosis and management of immune checkpoint inhibitor colitis. Gastroenterol Hepatol. 2021;17(8):358–66.

GE – Portuguese Journal of Gastroenterology

Clinical Case Study

GE Port J Gastroenterol 2024;31:283–287
DOI: 10.1159/000533959

Received: May 10, 2023
Accepted: August 19, 2023
Published online: September 27, 2023

Desmoid Tumor after Sleeve Gastrectomy: Case Report and Literature Review

Renato Medas[a, b] Rosa Coelho[a, b] Renato Bessa-Melo[c] Pedro Pereira[a, b] Guilherme Macedo[a, b]

[a]Gastroenterology Department, Centro Hospitalar Universitário São João, Porto, Portugal; [b]Faculty of Medicine of the University of Porto, Porto, Portugal; [c]General Surgery Department, Centro Hospitalar Universitário São João, Porto, Portugal

Keywords
Desmoid tumor · Mesenteric tumor · Sleeve gastrectomy · Bariatric surgery

Abstract
Desmoid tumor is a rare mesenchymal neoplasm of unknown etiology. Despite rare, the diagnosis of desmoid tumors after bariatric surgery is increased over the last few years. We report a case of a 26-year-old male with complains of abdominal pain and postprandial fullness, diagnosed with a locally advanced large intra-abdominal mass (40 × 21 × 11.7 cm) centered in the mesentery, developed 3 years after sleeve gastrectomy. Percutaneous biopsy was suggestive of a mesenquimatous tumor and the patient underwent surgery. R0 surgical resection was achieved, despite intimal contact and common vascularization with a jejunal loop. Histopathology examination of the surgical specimen revealed fusiform to stellate cells with mild atypia, thin-walled vessels, and diffuse beta-catenin expression (negative for DOG-1, CD117, CD34, S100, desmin, and alpha-actin). The diagnosis of a desmoid tumor was made. The patient remained asymptomatic, and no recurrence occurred over a 4-year follow-up. With the increasing number of bariatric surgeries, owing to the alarming growing incidence of obesity and related conditions, it is expected that desmoid tumors reports will gradually increase over the next few years. Thus, both gastroenterologists and surgeons should be aware of the potential for desmoid tumor development shortly after surgery, to offer a prompt diagnosis and treatment.

Tumor desmóide após gastrectomia vertical: caso clínico e revisão da literatura

Palavras Chave
Tumor desmóide · Tumor mesentérico · Gastrectomia vertical · Cirurgia bariátrica

Resumo
O tumor desmóide é uma neoplasia mesenquimatosa rara de etiologia desconhecida. Apesar de raros, temos assistido a um aumento do número de diagnósticos, ao longo dos últimos anos, de tumores desmóides que se desenvolvem após cirurgia bariátrica. Descrevemos o caso de um homem de 26 anos

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

Correspondence to:
Renato Medas, renatogmedas@gmail.com

com queixas de dor abdominal e enfartamento pós-prandial, diagnosticado com uma massa intra-abdominal centrada no mesentério (40 × 21 × 11.7 cm), localmente avançada, 3 anos após ter realizado gastrectomia vertical. Foi efetuada biópsia percutânea, cujo resultado foi sugestivo de tumor mesenquimatoso e o paciente foi referenciado para cirurgia. O doente foi submetido a cirurgia e o tumor foi passível de ressecção cirúrgica R0, apesar de contacto íntimo e vascularização comum com uma ansa jejunal. O exame anatomopatológico revelou células fusiformes a estreladas com atipia ligeira e vasos de parede fina, bem como expressão difusa de beta-catenina (na ausência de expressão de DOG-1, CD117, CD34, S100, desmina e alfa-actina), sendo compatível com o diagnóstico de um tumor desmóide. O doente permanece assintomático e sem evidência de recidiva ao longo de 4 anos de vigilância. Com o aumento do número de cirurgias bariátricas devido ao aumento alarmante da incidência de obesidade e condições relacionadas, espera-se que os diagnósticos de tumores desmóides aumentem nos próximos anos. Assim, tanto gastroenterologistas quanto cirurgiões devem estar alerta para o desenvolvimento desta entidade, de forma a oferecer um diagnóstico e tratamento adequado e atempado.

Introduction

Desmoid tumor (DT) is a rare mesenchymal neoplasm of unknown etiology. Most cases are sporadic (85–90%) and related to somatic mutations in *CTNNB1* gene, while 5–10% arises from a germline mutation in *APC* gene, in the context of familial adenomatous polyposis (FAP) [1]. Previous trauma, abdominal surgery, pregnancy, and hormonal therapy are known risk factors for DT development in sporadic cases [2]. Typically, DT is characterized by slow growth and no potential of metastasis but is known to be locally aggressive, leading to significant morbidity and mortality. Despite margin-free surgical resection, DTs have a high recurrence rate, ranging between 5 and 67% [3]. A recent meta-analysis reported a recurrence rate of 17.7% [4].

Over the last years, an increased number of DT development after bariatric surgery have been reported [5–9]. The increasing number of bariatric surgery procedures performed worldwide, owing to the alarming growing incidence of obesity and related conditions [10], may explain the raise in DT diagnosis related to bariatric procedures. Herein, we report a case of an intra-abdominal DT developed 3 years after sleeve gastrectomy.

Case Report

A 26-year-old male with a past medical history of vertical sleeve gastrectomy 3 years before, presented to the Gastroenterology consultation with abdominal pain and postprandial fullness of progressive worsening during the last 2 months. He denied associated symptoms such as nausea, vomits, fever, or weight loss. He also denied other medical conditions or a family history of FAP.

Abdominal ultrasound revealed a bulky intra-abdominal mass that prompted further investigation. Abdominal computed tomography confirmed the presence of an intra-abdominal homogeneous mass (40 × 21 × 11.7 cm), centered in the mesentery, causing compression of the adjacent organs but without radiological signs of local invasion. No signs of bowel distension/obstruction or suspicious adenopathy were observed (Fig. 1).

Percutaneous biopsy with an 18-gauge *tru-cut* needle was performed. Histopathological examination revealed fusiform cells arranged in bundles with beta-catenin expression (negative for desmin, DOG-1, CD117, and CD34), suggestive of a mesenquimatous tumor.

Considering the tumor dimension and the symptomatic course of the disease, after discussion of the treatment options with the patient, elective surgery was decided. Laparotomy revealed a large mass arising from the mesentery root in intimal contact with a jejunal loop. After ligation of the vessels responsible for the tumor supply, segmental ischemia of the adjacent jejunal loop occurred. Thus, a 10 cm segmental enterectomy was also performed. The postoperative course was uneventful, and the patient was discharged 5 days later.

The resected specimen measured 40 × 22.5 × 14.5 cm and weighed 5,550 g. Macroscopic evaluation revealed a smooth and brownish-white capsule with a homogeneous and whitish gelatinous core, with focal hemorrhagic areas. Histopathological examination showed fusiform to stellate cells with mild atypia and thin-walled vessels (Fig. 2). Immunohistochemical staining demonstrated diffuse beta-catenin expression, in the absence of expression for DOG-1, CD117, CD34, S100, desmin, and alpha-actin, consistent with desmoid-type fibromatosis (Fig. 3). Invasion of adipose tissue and small intestine wall (*muscularis propria* and submucosa) was present. Resection margins were negative. After 4-year follow-up, the patient remains asymptomatic without evidence of local recurrence.

Discussion

DTs are a rare neoplasm derived from mesenchymal origin, with an estimated incidence of 2–4 per million, accounting for 0.03% of all neoplasms [11]. The peak of incidence occurs between 30 and 40 years and is more

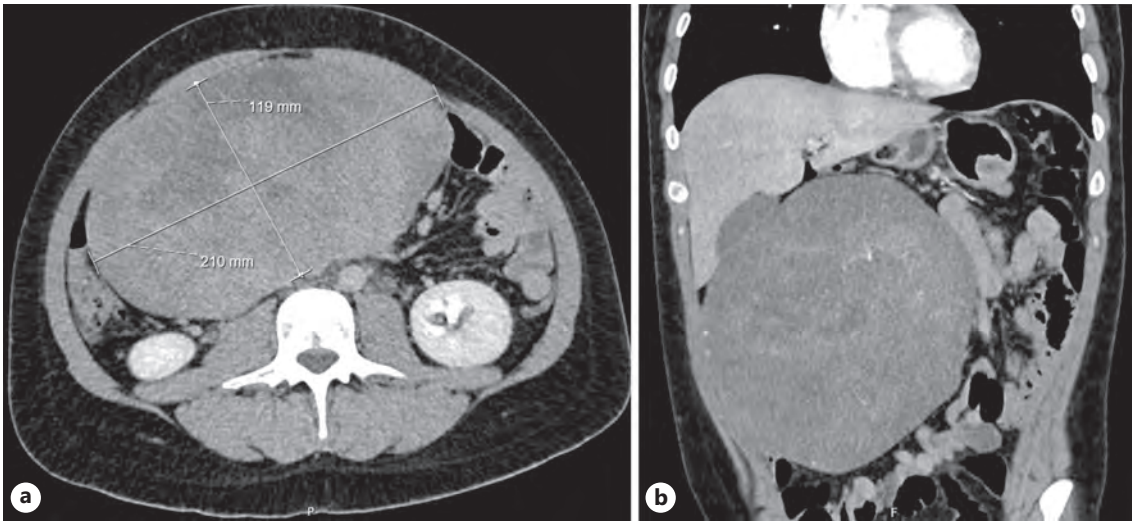


Fig. 1. a Bulky intra-abdominal mass, measuring 21.0 × 11.9 cm in axial axis, centered in mesentery. **b** Causing compression in the small bowel without imaging features suggestive of intestinal occlusion.

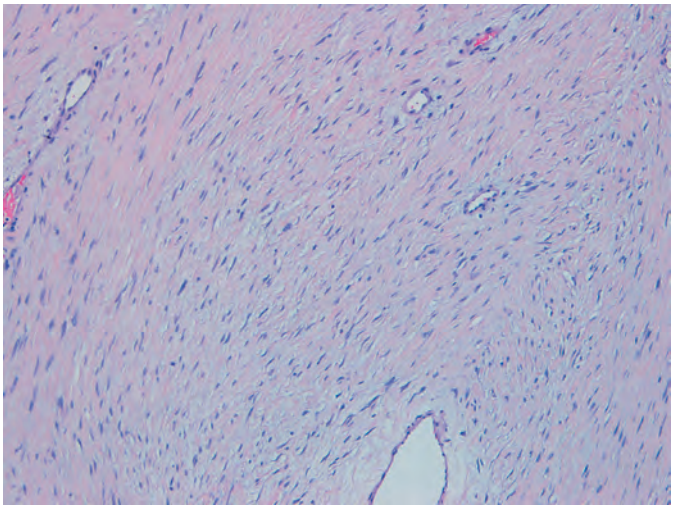


Fig. 2. Fusiform to stellate cells with mild atypia and thin-walled vessels. Presence of myxoid stroma, without mitosis or necrosis (×200).

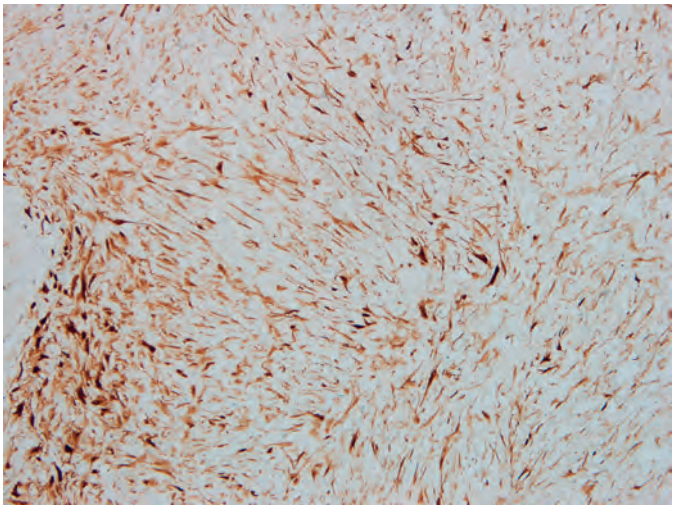


Fig. 3. Diffuse beta-catenin expression on immunohistochemical staining (×100).

common among women [12]. DTs etiology is not fully understood, but *Wnt* pathway plays a key role in DT pathogenesis [13]. Both sporadic DT and FAP-associated DT are linked to constitutive activation of the *Wnt* signaling pathway, resulting in cytoplasmic accumulation of β-catenin, followed by its translocation into the nucleus. Ultimately this results in the overexpression of genes involved in proliferation, fibrosis, and angiogenesis [14]. Since *Wnt* pathway has an active role in wounding repair [15], emerging data suggest that there is a dysregulated healing process after trauma (surgical or not) that favors DT development [14].

DTs can occur anywhere in the body but are more frequent in the abdominal wall, intra-abdominal cavity, and limbs [12]. Clinical presentation is variable, depending on its location, size, and growth rate. Intra-abdominal tumors are initially asymptomatic until they reach large dimensions, causing abdominal pain, palpable abdominal mass, bowel obstruction, ischemia, and rarely perforation or bleeding [12]. Focusing on DTs after bariatric surgery, Table 1

Table 1. Summary of described cases of desmoid tumors after bariatric surgery in the literature

Reference	Sex/age, years	Bariatric surgery	Surgery to diagnosis, years	Symptoms	Tumor location	Tumor size	Resection margins	Follow-up	Recurrence
Perez et al. [7] (2015)	Female/47	Roux-en-Y gastric bypass	1.5	Abdominal pain	Small bowel mesentery	19.0 × 15.3 × 12.4 cm	R0	NA	NA
Sedeyn et al. [8] (2015)	Female/44	Vertical sleeve gastrectomy	2	Shortness of breath Nausea Abdominal pain	NA[a]	20.2 × 12.0 × 18.0 cm	R0	NA	NA
Navarini et al. [6] (2020)	Female/37	Roux-en-Y gastric bypass	1	Abdominal pain Palpable mass	Small bowel mesentery	9.3 × 9.4 × 10.4 cm	NA	NA	NA
Sierra-Davidson et al. [9] (2020)	Female/27	Roux-en-Y gastric bypass	2	Abdominal pain Palpable mass	Small bowel mesentery	15.0 × 14.2 × 2.5 cm	NA	NA	NA
Mahnashi et al. [5] (2020)	Male/48	Mini-gastric bypass	3	Abdominal pain Early satiety	Gastrojejunal anastomosis[b]	15.8 × 14.6 × 12.8 cm	R0	NA	No

NA, not available. [a]Only described as an intra-abdominal mass. [b]Supplied by a small bowel mesentery artery.

summarizes the described cases available in the literature. Abdominal pain is the most frequent symptom (100%), followed by palpable abdominal mass (40%) [5–9]. All previously reported cases revealed an abdominal mass of at least 10 cm, confirming the potential of local aggressiveness. These tumors mostly occurred in women (80%) and the median age at diagnosis was 44 years (interquartile range 10). Median time from surgery to diagnosis was 2 years (interquartile range 0.5) [5–9].

Imaging studies are usually the initial diagnostic method, followed by histopathological characterization of tissue sample to confirm the diagnosis [16]. When feasible, surgical resection used to be the first-line approach. More recently, *The Desmoid Tumor Working Group* suggest active surveillance for asymptomatic patients regardless of tumor size [1]. Surgery may be considered *ad initium* in symptomatic patients or critical locations such as mesentery or head and neck [1]. During active surveillance, an active treatment, either surgery or medical therapy, should only be considered in case of persistent progression (especially if become symptomatic or is located in critical sites) [1]. However, the choice of treatment should be individualized according to patient and lesion characteristics. In some cases, radiotherapy or chemotherapy alone or combined with surgery may also be an option [1].

All previously reported cases were approached surgically, without significant morbidity or mortality [5–9]. Negative margins on surgical specimens (R0 resection) were reported in 3 cases [5, 7, 8]. Absence of recurrence was reported in only 1 case, but follow-up time was not reported [8]. In our case, R0 resection was achieved, and the patient did not develop complications related to surgery despite a locally advanced tumor. No recurrence was seen 4 years after DT removal.

To our knowledge, this is the first literature review approaching the development of DTs after bariatric surgery. With the increasing number of bariatric procedures performed worldwide, it is expected that DTs reports will gradually increase over the next few years. Thus, both gastroenterologists and surgeons should be aware of the potential for DT development shortly after surgery, to offer a prompt diagnosis and treatment.

Acknowledgments

The authors have nothing to declare.

Funding Sources

The authors have no funding sources to declare.

Statement of Ethics

Informed consent was obtained from the patient for publication of the medical case and any accompanying images. Ethical approval by Ethical Committee was not required due to local laws.

Author Contributions

Renato Medas collected the patient data, did the literature review, and created the first draft. Rosa Coelho planned and reviewed the manuscript. Renato Bessa-Melo and Pedro Pereira did a critical expert review of the manuscript. Guilherme Macedo did a critical expert review and approved the final version.

Conflict of Interest Statement

None of the authors acted as Reviewer or Editor of this article. None of the authors disclosed personal conflicts of interest or financial relationships relevant to this publication.

Data Availability Statement

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

References

1 Desmoid Tumor Working Group. The management of desmoid tumours: a joint global consensus-based guideline approach for adult and paediatric patients. Eur J Cancer. 2020;127:96–107.
2 Shinagare AB, Ramaiya NH, Jagannathan JP, Krajewski KM, Giardino AA, Butrynski JE, et al. A to Z of desmoid tumors. AJR Am J Roentgenol. 2011;197(6):1008–14.
3 van Broekhoven DL, Grunhagen DJ, Verhoef C. Abdominal desmoid tumors: hands off? Ann Surg Oncol. 2016;23(7):2128–30.
4 Moore D, Burns L, Creavin B, Ryan E, Conlon K, Kelly ME, et al. Surgical management of abdominal desmoids: a systematic review and meta-analysis. Ir J Med Sci. 2023;192(2):549–60.
5 Mahnashi Y, Alotaibi AS, Aldakhail M, Alshahrani A. Desmoid tumor at the gastrointestinal anastomosis after a one-anastomosis gastric bypass (mini-gastric bypass): a case report. J Surg Case Rep. 2020;2020(1):rjz411.
6 Navarini D, Albuquerque A, Rovani A, Silva V, Ranzolin B, Reffatti D, et al. Mesenteric desmoid tumor after Roux-en-Y gastric bypass: a case report. Clin Biomed Res. 2020;40:54–7.
7 Perez YL, Webber JD, Edelman DA. Mesenteric fibromatosis of the small bowel mesentery after gastric bypass surgery. CRSLS. 19(2), 2015. e2013.00264.
8 Sedeyn J, Nauts M, Faynberg T, Neff M. A hidden danger: case report of massive desmoid tumor in a post-bariatric surgery patient. Surg Obes Relat Dis. 2015;11(6):S148–9.
9 Sierra-Davidson K, Anderson G, Tanabe K, Meireles OR. Desmoid tumor presenting 2 years after elective Roux-en-Y gastric bypass: a case report and review of the literature. J Surg Case Rep. 2020;2020:rjz379.
10 Welbourn R, Hollyman M, Kinsman R, Dixon J, Liem R, Ottosson J, et al. Bariatric surgery worldwide: baseline demographic description and one-year outcomes from the fourth IFSO global registry report 2018. Obes Surg. 2019;29(3):782–95.
11 Nieuwenhuis MH, Casparie M, Mathus-Vliegen LM, Dekkers OM, Hogendoorn PC, Vasen HF. A nation-wide study comparing sporadic and familial adenomatous polyposis-related desmoid-type fibromatoses. Int J Cancer. 2011;129(1):256–61.
12 Fiore M, MacNeill A, Gronchi A, Colombo C. Desmoid-type fibromatosis: evolving treatment standards. Surg Oncol Clin N Am. 2016;25(4):803–26.
13 Ganeshan D, Amini B, Nikolaidis P, Assing M, Vikram R. Current update on desmoid fibromatosis. J Comput Assist Tomogr. 2019;43(1):29–38.
14 Federman N. Molecular pathogenesis of desmoid tumor and the role of γ-secretase inhibition. NPJ Precis Oncol. 2022;6(1):62.
15 Whyte JL, Smith AA, Helms JA. Wnt signaling and injury repair. Cold Spring Harb Perspect Biol. 2012;4(8):a008078.
16 Rosa F, Martinetti C, Piscopo F, Buccicardi D, Schettini D, Neumaier CE, et al. Multimodality imaging features of desmoid tumors: a head-to-toe spectrum. Insights Imaging. 2020;11(1):103.

GE – Portuguese Journal of Gastroenterology

Clinical Case Study

GE Port J Gastroenterol 2024;31:288–295
DOI: 10.1159/000534300

Received: March 29, 2023
Accepted: August 3, 2023
Published online: October 25, 2023

Schwannoma of Common Bile Duct: A Clinico-Radiologic Diagnostic Quagmire – A Case Report

Shilpi Thakur[a] Nihar Ranjan Dash[b] Adarsh Barwad[a] Prasenjit Das[a] Kumble S. Madhusudhan[c] Rajni Yadav[a]

[a]Department of Pathology, All India Institute of Medical Sciences, New Delhi, India; [b]Gastrointestinal Surgery, All India Institute of Medical Sciences, New Delhi, India; [c]Radiodiagnosis, All India Institute of Medical Sciences, New Delhi, India

Keywords
Schwannoma · Benign nerve sheath tumor · Common bile duct · Porta hepatis

Abstract
Background: Schwannomas are benign nerve sheath tumors that are extremely rare in the biliary tract. A comprehensive review of literature enumerated approximately 30 case reports of schwannoma in the biliary tract tree and porta hepatis region. ***Case Presentation:*** We report a case of a 40-year-old female who presented with abdominal pain. Imaging revealed a mass at the porta hepatis extending from the portal bifurcation till the hilum encasing the main portal vein and abutting the right portal vein. Differentials of carcinoma, lymphoma, and mesenchymal tumor were kept. Ultrasound-guided biopsy of the mass showed a benign nerve sheath tumor, immunopositive for S100. The histopathological evaluation of the excised mass confirmed the origin of mass in the common bile duct. ***Conclusions:*** Our case highlights that schwannomas, though benign, can mimic a carcinoma or lymphoma if present at a rare site such as bile ducts. An exhaustive clinical and radiological workup with diligent histopathological evaluation is mandatory in dealing with such rare cases as radical surgery and chemotherapy can be avoided in such patients.

Schwanoma da via biliar biliar comum: Um diagnóstico clinico-patologico volúvel

Palavras Chave
Schwannoma · Tumor benigno da bainha nervosa · CBD · Porta hepatis

Resumo
Introdução: Os schwannomas são tumores benignos da bainhas nervosas, que são extremamente raros ao nível das vias biliares. Uma revisão abrangente da literatura enumerou cerca de 30 casos de schwannomas com envolvimento da árvore biliar e da região da Porta Hepatis. ***Apresentação do caso:*** Relatamos um caso de uma doente de 40 anos que apresentava dor abdominal. A imagem revelou uma massa que se prolonga desde a bifurcação da veia porta até ao hilo hepático, com

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

Correspondence to:
Rajni Yadav, drrajniyadav@gmail.com

"encasement" da veia porta principal e "abutement" da veia porta direita. Foram considerados os diagnósticos diferenciais de carcinoma, linfoma e tumor mesenquimatoso. A biópsia guiada por ecografia da massa mostrou um tumor benigno da bainha nervosa, imunopositivo para o S100. A avaliação histopatológica da massa excisada confirmou a sua origem na via biliar comum. ***Conclusões:*** O nosso caso realça que os schwannomas, embora benignos, podem imitar um carcinoma ou linfoma se estiverem presentes num local raro, como os canais biliares. Um trabalho clínico e radiológico exaustivo com uma avaliação histopatológica diligente é obrigatória para orientar com casos tão raros, em que a cirurgia radical e a quimioterapia podem ser evitadas.

Background

Schwannomas are benign encapsulated nerve sheath tumors, usually attached to peripheral nerves and arise from differentiated Schwann cells. Mostly, they are sporadic, while some are associated with syndromes such as neurofibromatosis type 2, schwannomatosis, or Carney's complex [1]. These are spindle cell tumors that generally occur in the upper limbs, head, and neck, followed by the trunk and flexor surfaces of the lower extremities. Approximately 0.2% of all gastrointestinal (GI) tumors are constituted by schwannomas [2]. The commonest site is the stomach followed by the colon, cecum, and rectum and rarely the jejunum [3]. GI schwannomas are uncommon and usually occur in sixth to seventh decade [4]. Herein, we report a rare case of schwannoma of the common bile duct (CBD) presenting as a porta hepatis mass. Few case reports of porta hepatis schwannomas arising from CBD, hepatoduodenal ligament, hepatic vein, or artery have been published in the literature.

Case Presentation

A 40-year-old female, presented with the chief complaint of pain in the abdomen for the past 10 months. Pain was located in the right upper quadrant, dull in nature with no aggravating factors. There was no history of fever, jaundice, vomiting, and upper or lower GI bleeding. The patient did not report any altered bowel habits, loss of appetite, or weight. Patient had no medical comorbidities. The general physical and abdominal examination was unremarkable. Complete hemogram and renal function tests were within normal limits. SGOT and SGPT were 26 and 25 IU/L, respectively. Serum bilirubin was 1.2 mg% while alkaline phosphatase was 186 IU/L.

Ultrasonography (USG) of the abdomen showed a hypoechoic mass at the porta abutting the right portal vein and the main portal vein (shown in Fig. 1). The liver was normal with no intrahepatic biliary radicle dilation and showed a normal echotexture. No ascites was reported. Contrast-enhanced computed tomography abdomen revealed a mass at the porta extending from the portal bifurcation till the hilum encasing the main portal vein and abutting the right portal vein (shown in Fig. 1). Common hepatic artery was free. Contrast-enhanced magnetic resonance imaging (MRI) abdomen showed a mass at the porta abutting the right portal vein, main portal vein, right hepatic artery, and the common hepatic artery (shown in Fig. 1). The mass was extending between the head of the pancreas and the inferior vena cava. Vertically, the mass was extending between the hilum and retropancreatic region. Endoscopic ultrasound was also done which revealed a mass from the superior mesenteric vein/portal vein confluence till the hilum (shown in Fig. 2). Fat planes with the main portal vein were maintained. Based on overall clinical and imaging findings, possibilities of carcinoma, lymphoma, and mesenchymal tumor were considered.

USG-guided biopsy was performed on the mass which showed a benign nerve sheath tumor, immunopositive for S100 (shown in Fig. 3). Following the above investigations, the patient was undertaken for surgery. En bloc excision of the mass and CBD with Roux-en-Y hepatico-jejunostomy was performed. The resection specimen was submitted to the department of pathology. Gross examination showed an encapsulated, circumscribed, yellow-white firm tumor measuring 7.5 cm in maximum dimension (shown in Fig. 3). On microscopy, it was a biphasic tumor composed of hypercellular areas with fascicular arrangement of spindle cells and palisades (Verocay bodies) along with myxoid hypocellular areas and focal hyalinization. The spindle-shaped tumor cells contained moderately ill-defined cytoplasm, wavy tapering nuclei with fine granular nuclear chromatin, and inconspicuous nucleoli. In addition, there were many interspersed blood vessels with hyalinized walls along with lymphoid infiltrate at the tumor periphery (shown in Fig. 3). No significant nuclear pleomorphism, mitosis, or necrosis was noted. On immunohistochemistry, the tumor cells were immunopositive for vimentin, S100, and SOX10 while they were negative for CK, CD34, smooth muscle actin, CD117, DOG1, myogenin, ALK, STAT6, CD21, and HMB45. Ki67 proliferation index was less than 1% (shown in Fig. 4). Based on the immunohistomorphological profile, the tumor was diagnosed as schwannoma. Patient recovered well postoperatively and was discharged on postoperative day 10. The patient is disease-free on follow-up after 36 months.

Discussion

Schwannomas in porta hepatis and biliary tree are very rare and approximately 30 cases have been reported in literature till date. There are 22 reported cases of schwannoma in the biliary tract alone details of which have been summarized in Table 1 [3–24].

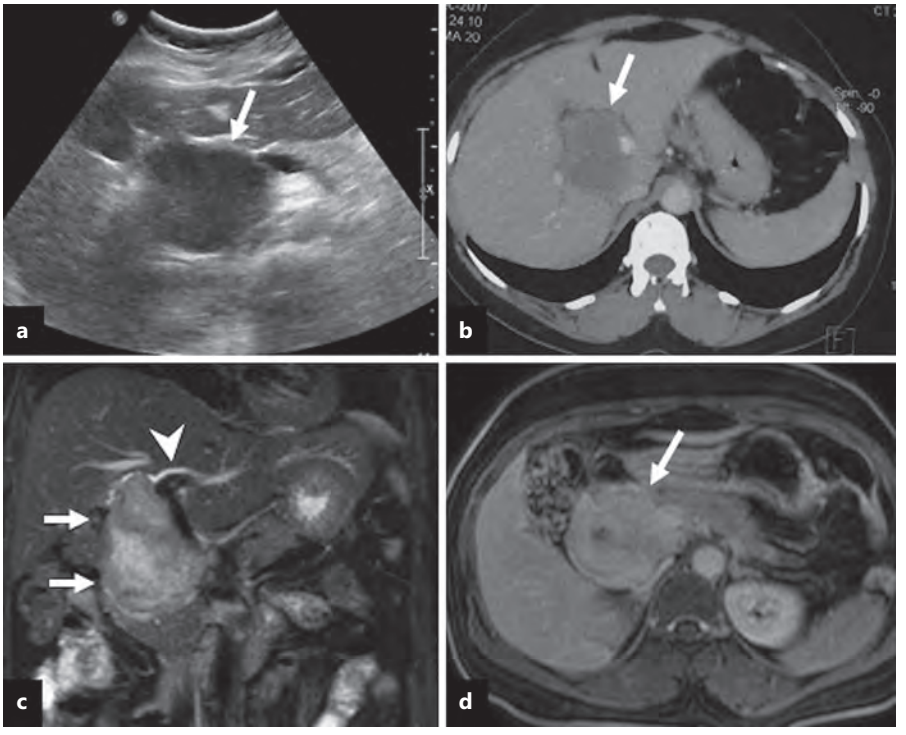


Fig. 1. a Ultrasound image shows a hypoechoic mass (arrow) at the porta hepatis. **b** Axial contrast-enhanced CT image shows a hypodense mass (arrow) at the porta hepatic splaying the portal veins. **c** Coronal T2-weighted MR image shows an oblong hyperintense mass (arrows) along the course of the CBD with mild intrahepatic bile duct dilatation (arrowhead). **d** Axial contrast-enhanced T1-weighted MR image (5 min delayed) shows late enhancement of the mass (arrow).

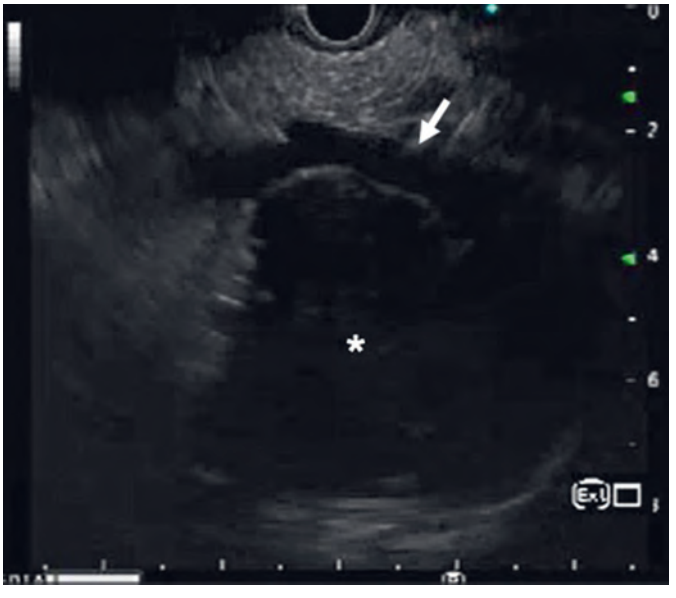


Fig. 2. Endoscopic ultrasound shows a hypoechoic mass (asterisk) at the porta hepatis abutting the portal vein (arrow). Image courtesy of: Dr Deepak Gunjan.

A significant female predominance with male-to-female ratio of 1:5.5 was seen in these patients. The mean age at presentation was 48.3 years (range 15–78 years). Abdominal pain and jaundice were the most common presenting symptoms in these patients (jaundice in 38%, abdominal pain in 19%, both pain and jaundice in 23% of patients, respectively). The most common location was CBD (57%). The preoperative clinico-radiological diagnoses were quite variable and comprised metastatic melanoma, gastrointestinal stromal tumor (GIST), lymphoma, adenocarcinoma, leiomyosarcoma.

In all the cases, it was extremely difficult to correctly diagnose this tumor preoperatively, mainly due to the fact that tumors at this site can easily mimic bile duct adenocarcinoma and other malignancies such as lymphoma and IgG4-related diseases. Moreover, the location is difficult to approach for a minimally invasive technique such as fine needle aspirate. Surgical resection was carried out in most cases with unremarkable postoperative period [3–24]. In our case, a correct preoperative diagnosis on USG-guided biopsy helped in the adequate surgical management.

Radiologically, contrast-enhanced MRI is better suited to visualize the extent and size of such soft tissue tumors and dilatation of bile duct radicles due to mass effect [25]. On MRI, schwannomas are hypointense on T1-weighted images and homogeneously hyperintense on T2-weighted images [26]. Usually, degenerative

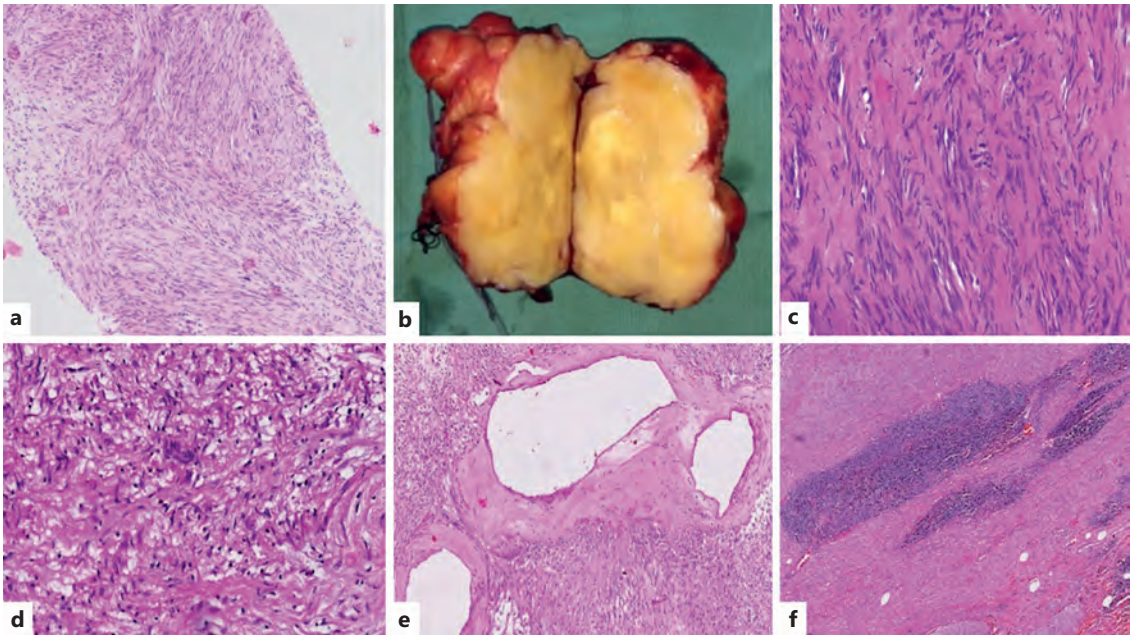


Fig. 3. a Biopsy section shows a benign spindle cell tumor (×100, H&E). **b** Gross examination shows nodular circumscribed yellow-white firm tumor. The tumor shows hypercellular areas with Verocay bodies (**c**) (×400, H&E) and hypocellular areas (**d**) (×400, H&E). Also, many dilated vessels with perivascular hyalinization (**e**) (×200, H&E) and lymphoid cuff at tumor periphery (**f**) (×200, H&E) are seen.

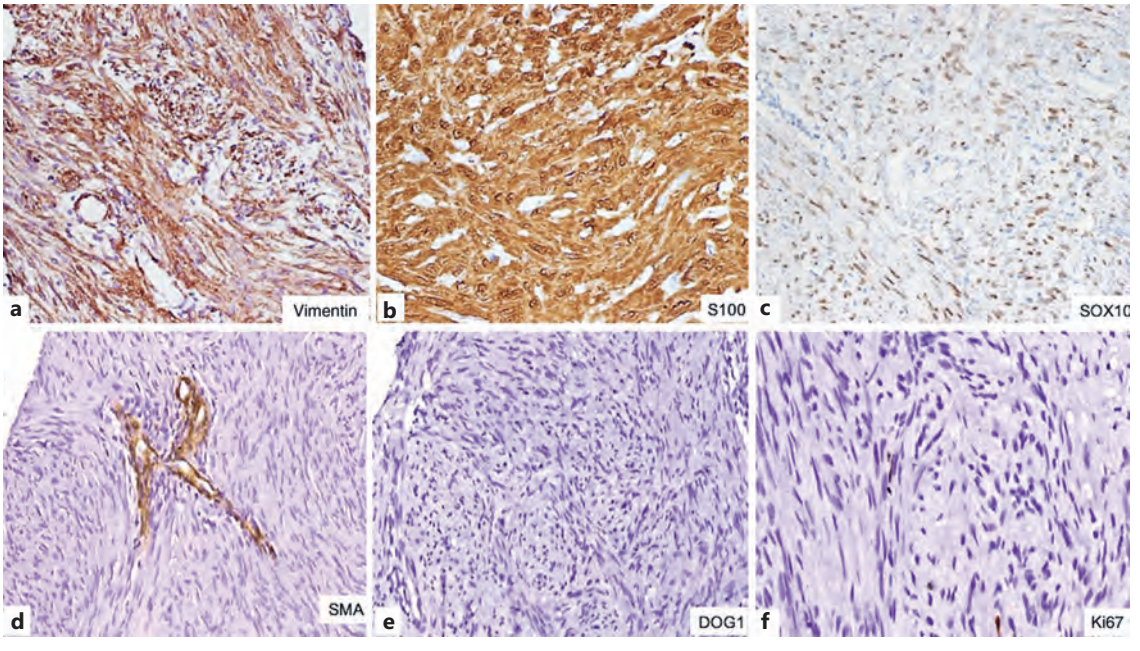


Fig. 4. The tumor cells are immunopositive for vimentin (**a**), S100 (**b**), and SOX10 (**c**) while they are immunonegative for SMA (**d**), DOG1 (**e**), and show low Ki67 proliferation index (**f**) (×200). SMA, smooth muscle actin.

Table 1. Details of previously reported cases of schwannoma in the biliary tract [3–24]

No.	Authors	Age, years/sex	Site	Presentation	Treatment	Outcome
1	Oden et al. 1955 [3]	40/F	CBD	Jaundice	SR	DF
2	Whisnant et al. 1974 [4]	15/F	Distal CBD	Abdominal pain, jaundice	SR	DF (12 months)
3	Balart et al. 1983 [5]	56/F	EHBD	Pain, jaundice	SR	DF
4	Honjo et al. 2003 [6]	48/F	CBD	Jaundice	EL + SR	DF (36 months)
5	Jakobs et al. 2003 [7]	37/M	CBD	Jaundice	SR	DF (12 months)
6	Otani et al. 2005 [8]	59/F	Remnant choledochal cyst	Abdominal pain	SR	DF (15 years)
7	Vyas et al. 2006 [9]	29/F	CBD	Jaundice	SR	DF (12 months)
8	Park et al. 2006 [10]	53/F	Porta hepatis (CBD)	Asymptomatic	EL + SR	DF (11 months)
9	Kamani et al. 2007 [11]	39/F	EHBD	Jaundice	SR	DF
10	Fenoglio et al. 2007 [12]	41/F	CBD	Pruritus, weight loss	EL + SR	DF (12 months)
11	Jung et al. 2007 [13]	64/F	EHBD	Asymptomatic	SR	DF
12	Madhusudan et al. 2009 [14]	46/F	IHBD & EHBD	Jaundice	No SR	-
13	Kulkarni et al. 2009 [15]	38/F	CBD	Abdominal pain and jaundice	SR	DF (3 months)
14	De Sena et al. 2009 [16]	58/F	EHBD	Jaundice	NA	NA
15	Parameshwarappa et al. 2010 [17]	38/F	CBD	Abdominal pain, jaundice	EL + SR	DF (12 months)
16	Panait et al. 2011 [18]	54/F	CHD	GERD	EL + SR	DF
17	Fonseca et al. 2012 [19]	64/F	EHBD	Incidental	Localized SR	DF (12 months)
18	Campos et al. 2016 [20]	62/M	IHBD	Abdominal pain, jaundice	CHDR	DF (18 months)
19	Xu et al. 2016 [21]	31/F	IHBD and EHBD, GB	Abdominal pain, abdominal distension	SR	DF (70 months)
20	Kolhe et al. 2019 [22]	46/F	CBD	Jaundice	NA	NA
21	Takami et al. 2021 [23]	78/M	EHBD	Incidental finding	EHBDR	DF
22	Ishimaru et al. 2021 [24]	68/M	Lower CBD	Abdominal pain	Local BDR with cholecystectomy	DF (30 months)
23	Present case	40/F	CBD	Abdominal pain	SR	DF (36 months)

CHDR, common hepatic duct resection; DF, disease free; EHBD, extrahepatic bile duct; EHBDR, extrahepatic bile duct resection; EL, exploratory laparotomy; SR, surgical resection.

Table 2. Discussion of common differential diagnoses of soft tissue masses in the biliary tract region

Differential diagnosis	Histomorphological features	Benign/ malignant	Immunohistochemistry
Neurofibroma	Less cellular, spindle cells with no significant nuclear pleomorphism, no mitosis or necrosis	Benign	S100+ (strong), SOX10+ (strong), CD34+ (fingerprint-like positivity)
Granular cell tumor	Cells with abundant granular cytoplasm in sheets	Benign	S100+
Leiomyoma	Spindle cells with blunt nuclear ends and cigar-shaped nuclei in fascicles, no significant nuclear pleomorphism, mitosis, or necrosis	Benign	SMA+, desmin+, h-caldesmon+, SMMHC+
GIST	Cellular tumors, mostly spindle cells in fascicles and sheets, sometimes epithelioid cells, mild to moderate nuclear pleomorphism, variable mitosis and necrosis	Benign/ malignant	CD117+, DOG1+, CD34+/−, SMA+/−, S100+/−
Leiomyosarcoma	Cellular tumors composed of spindle cells with blunt nuclear ends and cigar-shaped nuclei in fascicles, significant nuclear pleomorphism, mitoses, and necrosis	Malignant	SMA+, desmin+, h-caldesmon+, SMMHC+, high Ki67

SMA, smooth muscle actin; SMMHC, smooth muscle myosin heavy chain.

changes are uncommon in GI schwannomas, but if present can lead to error in diagnosis. Diagnosis in such cases can only be made on histology which requires excision of the mass. The most common differential diagnoses for schwannoma are other benign and malignant soft tissue tumors of the gastrointestinal tract such as neurofibroma, leiomyoma, GIST, and leiomyosarcoma, enumerated in Table 2.

Histologically, schwannomas show hypercellular areas (Antoni A) with Verocay bodies and hypocellular (Antoni B) areas. The tumor cells are predominantly spindle-shaped with hyperchromatic nuclei. Mitosis and necrosis are usually absent [10]. Schwannomas can show an array of degenerative changes such as hyalinization, calcification, hemorrhage, myxoid change, cyst formation, focal bizarre nuclear atypia. Multiple variants are seen, namely, ancient, plexiform, cellular, epithelioid, microcystic or reticular, and melanotic or pigmented [14].

Immunohistochemistry plays an important role in distinguishing schwannoma from close differentials such as GIST, leiomyomas, or neurofibromas. Schwannomas are strongly immunopositive for S100 protein and SOX10. GISTs are immunopositive for c-KIT and DOG1, while leiomyoma and leiomyosarcoma will show strong and diffuse smooth muscle actin positivity. CD34 and calretinin might help in differentiating these from neurofibroma as both are immunopositive for S100. Neurofibroma shows moderate CD34 positivity. Fine et al. [27] in their study compared calretinin positivity in schwannoma and neurofibroma and 96% of schwannomas displayed strong calretinin staining compared to only 7% in neurofibroma.

GI schwannomas show some histomorphological variations when compared to schwannomas at other regions in the form of predominance of hypercellular areas (Antoni A) and lack of nuclear palisading pattern as seen in conventional schwannoma [28]. Our case, although it showed both the areas, Lasota et al. [29] also reported lack of *NF-2* gene alterations in the GI schwannomas suggesting it to be a morphologically and genetically distinct group of nerve sheath tumors. However, more data needs to be incorporated to arrive successfully at this conclusion.

Being benign tumors, these have an excellent prognosis and complete surgical resection is the mainstay of treatment. Recurrence or malignant transformation is rarely seen [30].

Conclusion

CBD schwannomas are very rare and a surgeon's nightmare until the histopathological examination is done. The present case adds to the rare list of schwannomas arising from CBD and also enumerates the diagnostic challenges from a pathologist's perspective.

Acknowledgment

The authors thank Dr. Deepak Gunjan (gastroenterologist) for contributing the EUS image.

Statement of Ethics

Study approval from the institute's Ethics Committee (AIIMS, New Delhi) was not required. A written informed consent was obtained from the participant for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received for this study.

Author Contributions

Shilpi Thakur contributed to manuscript writing, editing, and data curation. Adarsh Barwad and Prasenjit Das contributed to review and editing. Nihar Ranjan Dash and Kumble S. Madhusudhan helped with clinical and radiological data curation. Rajni Yadav reviewed and edited the manuscript.

Data Availability Statement

No data were generated during this study. Further inquiries can be directed to the corresponding author.

References

1 Salvati M, Polli FM, Caroli E, Frati A, Missori P, Delfini R. Radiation-induced schwannomas of the nervous system. Report of five cases and review of the literature. J Neurosurg Sci. 2003;47(2):113–6; discussion 6.
2 Sanei B, Kefayat A, Samadi M, Goli P, Sanei MH, Khodadustan M. Gastric schwannoma: a case report and review of the literature for gastric submucosal masses distinction. Case Rep Med. 2018;2018:1230285.
3 Oden B. Neurinoma of the common bile duct; report of a case. Acta Chir Scand. 1955; 108(5):393–7.
4 Whisnant JD Jr, Bennett SE, Huffman SR, Weiss DL, Parker JC, Griffen WO Jr. Common bile duct obstruction by granular cell tumor (schwannoma). Am J Dig Dis. 1974; 19(5):471–6.
5 Balart LA, Hines C Jr, Mitchell W. Granular cell schwannoma of the extrahepatic biliary system. Am J Gastroenterol. 1983;78(5): 297–300.
6 Honjo Y, Kobayashi Y, Nakamura T, Takehira Y, Kitagawa M, Ikematsu Y, et al. Extrahepatic biliary schwannoma. Dig Dis Sci. 2003;48(11):2221–6.
7 Jakobs R, Albert J, Schilling D, Nuesse T, Riemann JF. Schwannoma of the common bile duct: a rare cause of obstructive jaundice. Endoscopy. 2003;35(8):695–7.
8 Otani T, Shioiri T, Mishima H, Ishihara A, Maeshiro T, Matsuo A, et al. Bile duct schwannoma developed in the remnant choledochal cyst-a case associated with total agenesis of the dorsal pancreas. Dig Liver Dis. 2005;37(9):705–8.
9 Vyas FL, Jesudason MR, Samuel R, Govil S, Jesudason SRB. Schwannoma of bile duct--a case report. Trop Gastroenterol. 2006; 27:50–1.
10 Park MK, Lee KT, Choi YS, Shin DH, Lee JY, Lee JK, et al. [A case of benign schwannoma in the porta hepatis]. Korean J Gastroenterol. 2006;47(2):164–7.
11 Kamani F, Dorudinia A, Goravanchi F, Rahimi F. Extrahepatic bile duct neurilemmoma mimicking Klatskin tumor. Arch Iran Med. 2007;10(2):264–7.
12 Fenoglio L, Severini S, Cena P, Migliore E, Bracco C, Pomero F, et al. Common bile duct schwannoma: a case report and review of literature. World J Gastroenterol. 2007;13: 1275–8.
13 Jung JH, Joo KR, Chae MJ, Jang JY, Lee SG, Dong SH, et al. Extrahepatic biliary schwannomas: a case report. J Korean Med Sci. 2007;22(3):549–52.
14 Madhusudhan KS, Srivastava DN, Dash NR, Gupta C, Gupta SD. Case report. Schwannoma of both intrahepatic and extrahepatic bile ducts: a rare case. Br J Radiol. 2009; 82(982):e212–5.
15 Kulkarni N, Andrews SJ, Rao V, Rajagopal KV. Case report: benign porta hepatic schwannoma. Indian J Radiol Imaging. 2009; 19(3):213–5.
16 De Sena G, Molino C, De Riitis MR, Candela S, Cifarelli V, Di Maio V, et al. [Surgical management of schwannoma of biliary tract]. Chir Ital. 2009;61(1):119–21.
17 Parameshwarappa S, Rodrigues G, Kumar S, Patil B, Valliathan M. Schwannoma of common bile duct causing obstructive jaundice. Indian J Surg. 2010;72(Suppl 1): 333–5.
18 Panait L, Learn P, Dimaio C, Klimstra D, Do KG, Schwarz T, et al. Resection of perihilar biliary schwannoma. Surg Oncol. 2011;20(4): e157–9.
19 Fonseca GM, Montagnini AL, Rocha Md S, Patzina RA, Bernardes MVAA, Cecconello I, et al. Biliary tract schwannoma: a rare cause of obstructive jaundice in a young patient. World J Gastroenterol. 2012;18(37):5305–8.
20 Marin Campos C, Garcia Sanz I, Munoz de Nova JL, Valdés de Anca A, Martín Pérez ME. Schwannoma of the biliary tract resembling cholangiocarcinoma: a case report and review. Ann R Coll Surg Engl. 2016;98(7): e143–6.
21 Xu SY, Guo H, Shen Y, Sun K, Xie HY, Zhou L, et al. Multiple schwannomas synchronously occurring in the porta hepatis, liver, and gallbladder: first case report. Medicine. 2016;95(33):e4378.
22 Kolhe KM, Amarapurkar A, Ingle M, Pandey V, Amonkar M, Khairnar H, et al. Jack in the duct: a case of common biliary duct schwannoma. ACG Case Rep J. 2019;6(10): e00223.
23 Takami K, Yamamoto K, Sakurai H, Kondo N, Shibata C, Katayose Y. Biliary schwannoma that required differentiation from bile duct cancer. Case Rep Gastroenterol. 2021; 15(2):578–86.
24 Ishimaru N, Fujikawa H, Kobayashi Y. Successful preoperative diagnosis and minimally invasive surgery of bile duct schwannoma. Clin J Gastroenterol. 2021;14(1):336–40.
25 Bilgin M, Shaikh F, Semelka RC, Bilgin SS, Balci NC, Erdogan A. Magnetic resonance imaging of gallbladder and biliary system. Top Magn Reson Imaging. 2009;20(1):31–42.
26 Rha SE, Byun JY, Jung SE, Chun HJ, Lee HG, Lee JM. Neurogenic tumors in the abdomen: tumor types and imaging characteristics. Radiographics. 2003;23(1):29–43.
27 Fine SW, McClain SA, Li M. Immunohistochemical staining for calretinin is useful for differentiating schwannomas from neurofibromas. Am J Clin Pathol. 2004;122(4): 552–9.

28 Daimaru Y, Kido H, Hashimoto H, Enjoji M. Benign schwannoma of the gastrointestinal tract: a clinicopathologic and immunohistochemical study. Hum Pathol. 1988;19(3):257–64.

29 Lasota J, Wasag B, Dansonka-Mieszkowska A, Karcz D, Millward CL, Ryś J, et al. Evaluation of NF2 and NF1 tumor suppressor genes in distinctive gastrointestinal nerve sheath tumors traditionally diagnosed as benign schwannomas: s study of 20 cases. Lab Invest. 2003;83(9):1361–71.

30 Yin SY, Zhai ZL, Ren KW, Yang YC, Wan DL, Liu XY, et al. Porta hepatic schwannoma: case report and a 30-year review of the literature yielding 15 cases. World J Surg Oncol. 2016;14:103.

GE – Portuguese Journal of Gastroenterology

Endoscopic Snapshot

GE Port J Gastroenterol 2024;31:296–298
DOI: 10.1159/000534420

Received: August 4, 2023
Accepted: September 25, 2023
Published online: October 25, 2023

Endoscopic Mucosal Resection Using Band Ligation of a Duodenal Neuroendocrine Tumor

Isabel Garrido[a, b] Gany Mussagi[a, c] Rui Morais[a, b] Guilherme Macedo[a, b]

[a]Gastroenterology Department, Centro Hospitalar Universitário de São João, Porto, Portugal; [b]World Gastroenterology Organization (WGO) Porto Training Center, Porto, Portugal; [c]Gastroenterology Department, Maputo Central Hospital, Maputo, Mozambique

Keywords
Duodenal neuroendocrine tumor · Endoscopic submucosal resection · Band ligation

Mucosectomia em banda de tumor neuroendócrino duodenal

Palavras Chave
Tumor neuroendócrino duodenal · Mucosectomia endoscópica · Laqueação por banda

A 67-year-old female, with no relevant past medical history, underwent a screening upper endoscopy that revealed a 12 mm subepithelial lesion in the anterior face of the duodenal bulb (Fig. 1a). Biopsies were performed and revealed a well-differentiated neuroendocrine tumor (NET G1). Endoscopic ultrasound confirmed the presence of a hypoechoic lesion with 13 × 7 mm in the submucosa and no lymph node metastasis was detected. Abdominal computerized tomography and somatostatin receptor scintigraphy revealed no evidence of extraduodenal disease. After a multidisciplinary discussion, endoscopic mucosal resection (EMR) using band ligation was decided.

A conventional single-channel endoscope (GIF-HQ190; Olympus Medical Systems, Tokyo, Japan) was used for the procedure. Marking of the borders of the lesion was performed with argon plasma coagulation, followed by submucosal injection with saline, diluted adrenaline, blue methylene, and colloid solution (Fig. 1b). This was performed to reduce the risk of muscle injury during resection. The Captivator^{TM} EMR Device (Boston Scientific) was used to perform band ligation. Several attempts of suction of the lesion into the distal cap were done to create a pseudopolyp and to achieve an adequate aspiration of the lesion. The band was correctly deployed (Fig. 1c). Then, the underwater technique was used to assist in the correct positioning of the snare. The snare was placed below the band, and hot snare resection was performed using a blended electrosurgical current (Fig. 1d). The lesion was removed by aspirating it into a cap. Inspection of the resection bed revealed no signs of muscular injury or other complications (Fig. 1e). The mucosal defect was closed using 4 through-the-scope clips (Fig. 1f). The histopathology report confirmed complete curative resection of the lesion (NET G1, pT1NxR0). The patient remains well in the follow-up, with no evidence of disease recurrence.

Duodenal NETs comprise 15% of all gastrointestinal NETs [1]. They are generally small, with a mean size of 1.2–1.5 cm, and usually limited to the submucosa or mucosa. All duodenal NETs should be removed, unless in the presence of distant metastases or of medical conditions that markedly limit life expectancy [2]. Small tumors can be locally resected by endoscopy, and en bloc resection is recommended [3]. However, studies on the best resection

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

Correspondence to:
Isabel Garrido, isabelmng@hotmail.com

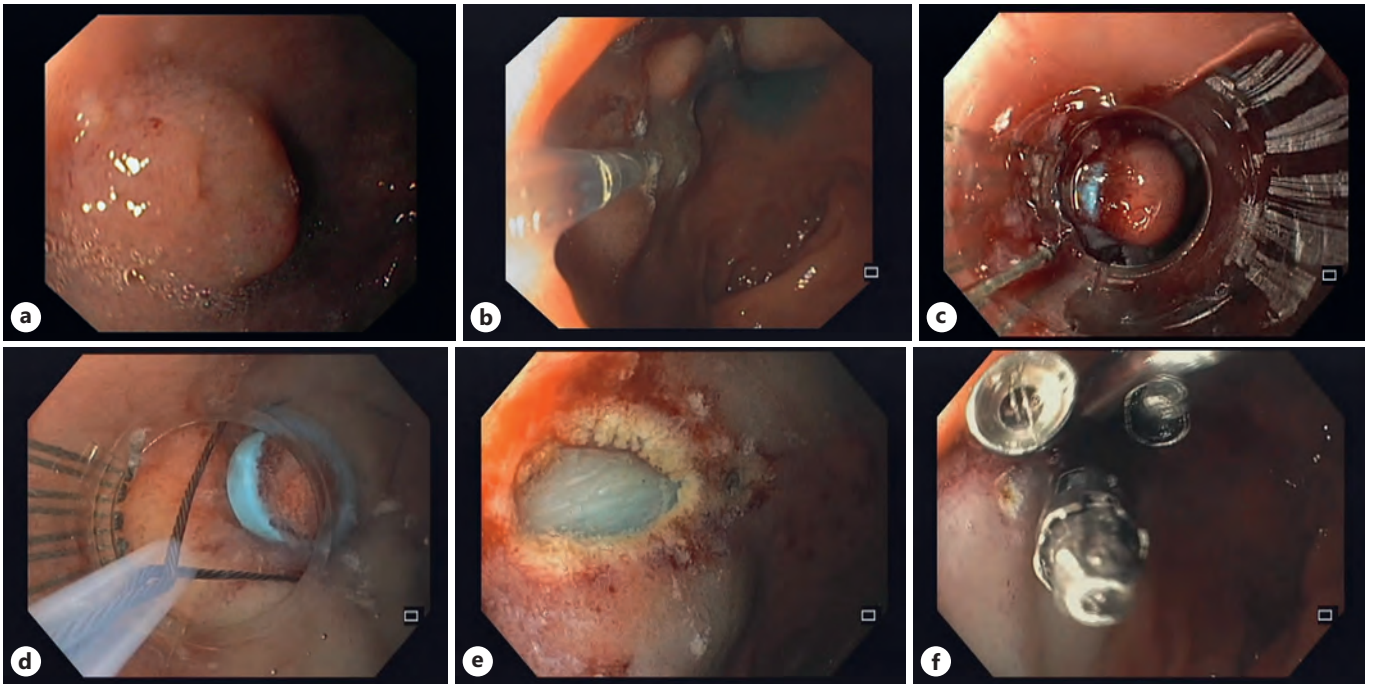


Fig. 1. a Duodenal NET. **b** Saline solution was injected in the submucosal layer. **c** The tumor was aspirated into the ligator device, followed by deployment of the elastic band. **d** Hot snare resection was performed below the band, using the underwater technique. **e** The lesion was completely removed. **f** The mucosal defect was closed using through-the-scope clips.

methods are lacking. Conventional EMR is occasionally associated with margin involvement and crush injury of the resected specimens, which leads to difficulty in pathological evaluation [4]. On the other hand, endoscopic submucosal dissection is technically difficult and carries a high risk of complications [5]. Endoscopic full-thickness resection (EFTR) is a minimally invasive procedure that allows for potentially curative treatment in local disease. Although several studies have reported consistent negative margins, there are limited data regarding the use of EFTR for duodenal NETs [6]. Recently, underwater EMR has also been applied for the management of these lesions, with some authors describing an en bloc resection and complete resection rates of 100%, and no complications [7]. Although the efficacy of underwater-assisted resection cannot be fully demonstrated with just a few case reports, it may represent a potential alternative endoscopic approach.

This case highlights the role of EMR using band ligation as an effective, safer, and faster technique compared with conventional EMR, endoscopic submucosal dissection, and EFTR for the treatment of duodenal NETs that are confined to the submucosal layer without metastasis. In fact, this is a simple procedure that enables easy and complete resection of these tumors, without complications [8].

Statement of Ethics

Written informed consent was obtained from the participant for publication of the details of his medical case and any accompanying images.

Conflict of Interest Statement

The authors have no disclosures to report.

Funding Sources

The authors have no funding sources to declare.

Author Contributions

Isabel Garrido did literature review and drafted the manuscript. Isabel Garrido, Gany Mussagi, Rui Morais, and Guilherme Macedo have critically revised and finalized the manuscript. All authors have approved the final version of the manuscript.

Data Availability Statement

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

References

1 Delle Fave G, Kwekkeboom DJ, Van Cutsem E, Rindi G, Kos-Kudla B, Knigge U, et al. ENETS Consensus Guidelines for the management of patients with gastroduodenal neoplasms. Neuroendocrinology. 2012;95(2):74–87.

2 Wang R, Zheng-Pywell R, Chen HA, Bibb JA, Chen H, Rose JB. Management of gastrointestinal neuroendocrine tumors. Clin Med Insights Endocrinol Diabetes. 2019;12:1179551419884058.

3 Bourke MJ. Endoscopic resection in the duodenum: current limitations and future directions. Endoscopy. 2013;45(2):127–32.

4 Shroff SR, Kushnir VM, Wani SB, Gupta N, Jonnalagadda SS, Murad F, et al. Efficacy of endoscopic mucosal resection for management of small duodenal neuroendocrine tumors. Surg Laparosc Endosc Percutan Tech. 2015;25(5):e134–9.

5 Matsumoto S, Miyatani H, Yoshida Y, Nokubi M. Duodenal carcinoid tumors: 5 cases treated by endoscopic submucosal dissection. Gastrointest Endosc. 2011;74(5):1152–6.

6 Dwyer S, Mok S. Endoscopic full-thickness resection of well-differentiated T2 neuroendocrine tumors in the duodenal bulb: a case series. VideoGIE. 2022;7(5):196–9.

7 Kim SJ, Kim TU, Choi CW, Kim HW, Park SB, Ryu DG. Underwater endoscopic mucosal resection of upper gastrointestinal subepithelial tumors: a case series pilot study (with video). Medicine. 2022;101(41):e31072.

8 Inokuchi Y, Hayashi K, Kaneta Y, Okubo Y, Watanabe M, Furuta M, et al. Endoscopic mucosal resection using a ligation device for duodenal neuroendocrine tumors: a simple method. Ther Adv Gastrointest Endosc. 2022;15:26317745221103735.

GE – Portuguese Journal of Gastroenterology

Endoscopic Snapshot

GE Port J Gastroenterol 2024;31:299–301
DOI: 10.1159/000535225

Received: September 21, 2023
Accepted: October 30, 2023
Published online: December 4, 2023

Lower Gastrointestinal Bleeding after Gynecological Surgery: An Atypical Endoscopic Diagnosis

Vítor Macedo Silva[a, b, c] Tiago Lima Capela[a, b, c] Pedro Boal Carvalho[a, b, c] Bruno Rosa[a, b, c] José Cotter[a, b, c]

[a]Gastroenterology Department, Hospital da Senhora da Oliveira, Guimaraes, Portugal; [b]Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal; [c]ICVS/3B's – PT Government Associate Laboratory, Guimaraes, Portugal

Keywords
Lower gastrointestinal bleeding · Surgical trauma · Rectum

Hemorragia Digestiva Baixa Após Cirurgia Ginecológica: Um Diagnóstico Endoscópico Atípico

Palavras Chave
Hemorragia digestiva baixa · Trauma cirúrgico · Recto

A 75-year-old woman with arterial hypertension and dyslipidemia was hospitalized in the Gynecology Department after transvaginal hysterectomy with anterior colporrhaphy due to grade IV hysterocele and cystocele. One week after the surgical procedure, the patient developed constipation, associated with abundant rectal bleeding and hypotension (90/55 mm Hg), without associated tachycardia. The patient reported no abdominal pain. There was no history of antiplatelet or anticoagulant agents' usage.

Analytically, a de novo microcytic anemia was detected, with hemoglobin levels of 8.4 g/dL (previously available value was 12.2 g/dL). Coagulation tests were normal.

In the setting of an acute lower gastrointestinal bleeding, an urgent colonoscopy after bowel preparation was conducted. Proctologic examination was normal. On digital rectal examination, a soft bulge was felt on the distal rectum, with bright blood being detected.

On colonoscopy, a voluminous bulge (approximately 60 × 55 mm) with a congestive appearance was seen in the distal rectum, with a 10-mm orifice being evident on its surface (Fig. 1). Inside this orifice, there was abundant coagulated hematic content, which could not be aspirated. This bulge was passable by the

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

Correspondence to:
Vitor Macedo Silva, vitorbmacedo@gmail.com

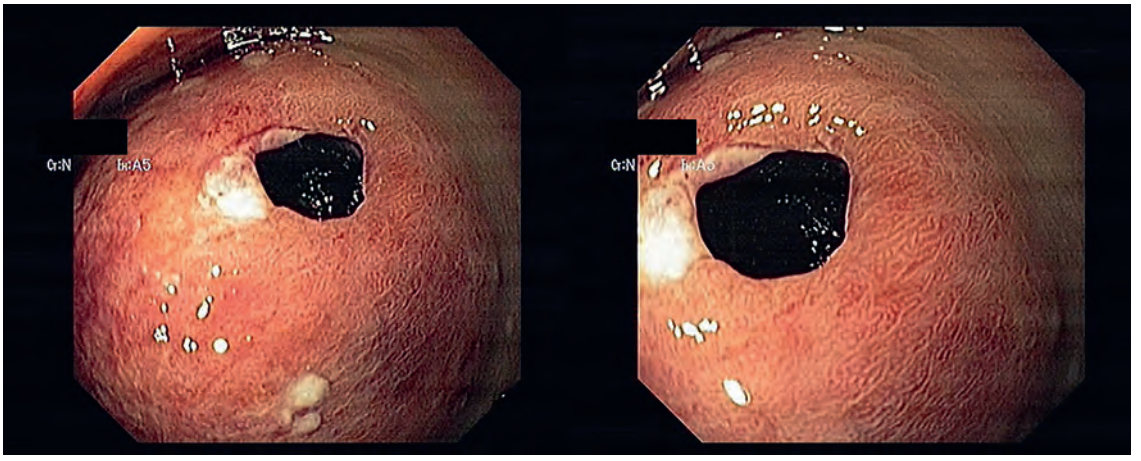


Fig. 1. Endoscopic images showing a voluminous bulge (approximately 60 × 55 mm) with a congestive appearance seen in the distal rectum, with a 10-mm orifice being evident on its surface, compatible with a rectal hematoma.

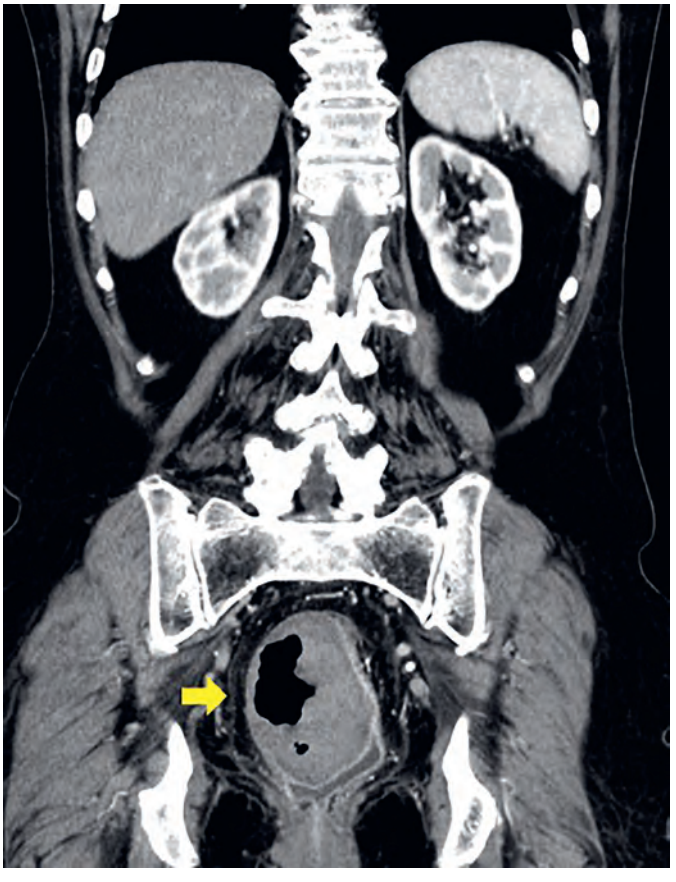


Fig. 2. Abdominal and pelvic computerized tomography revealing an intramural collection containing hydro-aeric levels in the right rectal wall, with a maximum diameter of 7 cm, compressing the rectal lumen.

conventional colonoscope, without resistance. There were no other relevant endoscopic findings throughout the colon.

An abdominal and pelvic computerized tomography was performed, revealing an intramural collection containing hydro-aeric levels in the right rectal wall, with a maximum diameter of 7 cm, compressing the rectal lumen (Fig. 2). The lower gastrointestinal bleeding and endoscopic findings were thus interpreted in the context of a rectal mural hematoma, communicating with the rectal lumen. The patient underwent conservative treatment, with complete reabsorption of the hematoma 2 months after surgery, which was confirmed by cross-sectional imaging and colonoscopy (Fig. 3).

Small pelvic hematomas are a common finding after transvaginal hysterectomy, occurring in more than 25% of the performed surgeries [1]. Nevertheless, most of these are asymptomatic, being accidentally detected in scheduled follow-up ultrasounds. Furthermore, hematomas most frequently form in dependent areas, such as the pouch of Douglas, sub-vesical space, or ischium-rectal fossa [2]. Treatment consists of antibiotics if infected, with or without percutaneous or surgical drainage according to clinical evolution [1].

To our knowledge, this is the first case reporting a symptomatic rectal hematoma after gynecological surgery. With this clinical case, we aim to highlight an unusual etiology of lower gastrointestinal bleeding, associated with unique endoscopic findings, as well as to emphasize the importance of investigating medical and surgical history in patients with acute rectal bleeding.

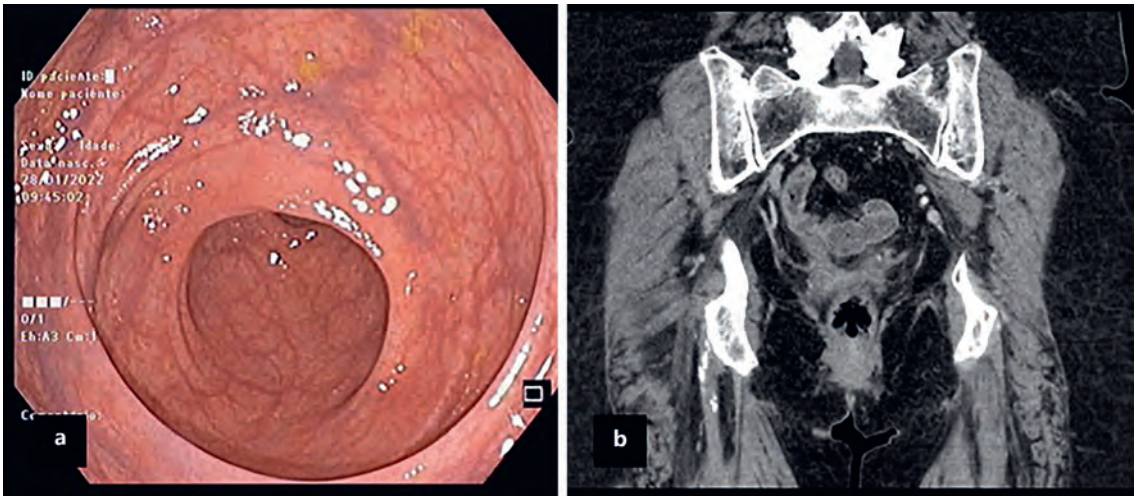


Fig. 3. Colonoscopy (**a**) and computed tomography (**b**) images confirming complete rectal hematoma resolution.

Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. Ethical Committee approval was not required for this study, in accordance with local/national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There was no funding for this work.

Author Contributions

Vítor Macedo Silva, Tiago Lima Capela, and Bruno Rosa were involved in the endoscopic procedure and in manuscript drafting. Pedro Boal Carvalho and Bruno Rosa were involved in manuscript drafting and critical revision. José Cotter reviewed the manuscript and gave final approval. All authors approved the final version.

Data Availability Statement

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

References

1 Chill HH, Amsalem I, Karavani G, Amit S, Benshushan A, Shveiky D. Symptomatic pelvic hematoma following hysterectomy: risk factors, bacterial pathogens and clinical outcome. BMC Womens Health. 2020;20(1):272.

2 Alhubaishi L, Fazari A. Vault hematoma after vaginal hysterectomy: an invariable complication. Open J Obstet Gynecol. 2019;09(05):578–81.

Explore our products and services

FOR RESEARCHERS

Supporting the Scientific Community at Each Step

IA23008_280

Karger