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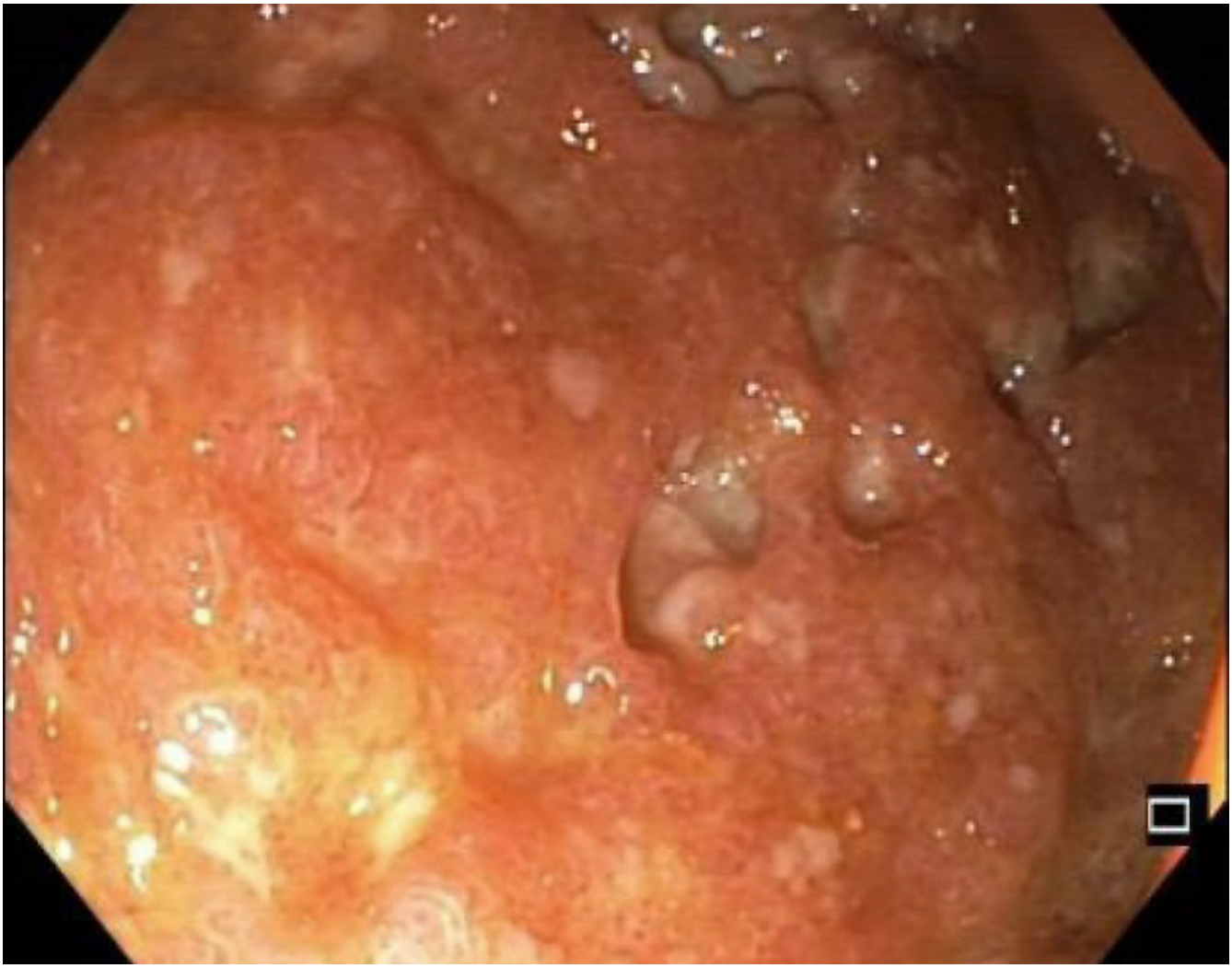

Highlights in this issue:

Review article: Future Perspectives in Liver Disease Associated with Alpha-1 Antitrypsin Deficiency

Research article: Narrow Band Imaging versus White Light for the Detection of Sessile Serrated Colorectal Lesions: A Randomized Clinical Trial

Research article: Impact of Percutaneous Endoscopic Gastrostomy Tube Feeding on Nutritional Status in Patients Undergoing Chemoradiotherapy for Oesophageal Cancer

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(Continued on next page)

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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).
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Contents

Cover illustration
Proctosigmoidoscopy showing deep mucosal ulceration in the sigmoid colon of a patient with refractory acute severe ulcerative colitis. From Antunes et al., pp. 390-397.

Karger

GE – Portuguese Journal of Gastroenterology

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Review Article

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Future Perspectives in the Diagnosis and Treatment of Liver Disease Associated with Alpha-1 Antitrypsin Deficiency

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Keywords
Alpha-1 antitrypsin · Liver disease · Treatment

Abstract
Alpha-1 antitrypsin deficiency (AATD) is one of the most common genetic diseases and is caused by mutations in the SERPINA1 gene. The homozygous Pi*Z variant is responsible for the majority of the classic severe form of alpha-1 antitrypsin deficiency, which is characterized by markedly decreased levels of serum alpha-1 antitrypsin (AAT) with a strong predisposition to lung and liver disease. The diagnosis and early treatment of AATD-associated liver disease are challenges in clinical practice. In this review, the authors aim to summarize the current evidence of the non-invasive methods in the assessment of liver fibrosis, as well as to elucidate the main therapeutic strategies under investigation that may emerge in the near future.

Perspetivas futuras no diagnóstico e tratamento da doença hepática na deficiência de alfa-1 antitripsina

Palavras Chave
Alfa-1 antitripsina · Doença hepática · Tratamento

Resumo
A deficiência de alfa-1 antitripsina é uma das doenças genéticas mais comuns e é causada por mutações no gene SERPINA1. A mutação Pi*Z em homozigotia é responsável pela maioria dos casos de apresentação clássica da deficiência de alfa-1-antripsina, que se caracteriza por uma diminuição significativa dos níveis séricos desta proteína com forte predisposição ao desenvolvimento de doença pulmonar e hepática. O diagnóstico precoce e tratamento da doença hepática representam importantes desafios na prática clínica. Nesta revisão, os autores têm como objetivo resumir a evidência atual dos métodos não invasivos na avaliação da fibrose hepática, bem como, elucidar as principais estratégias terapêuticas atualmente sob investigação e que poderão emergir num futuro próximo.

Introduction

Alpha-1-antitrypsin is the major inhibitor of multiple serine proteases in the serum, which is mainly synthesized by hepatocytes and then secreted into the bloodstream to protect tissues from proteolytic damage. The

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protein is encoded by the SERPINA1 gene, located in the chromosome 14q32.1 region [1, 2].

Most pathogenic mutations in SERPINA1 result in the aggregation of misfolded proteins in the hepatocytes, causing liver injury through a toxic "gain of function." On the other hand, the decrease in systemic AAT levels results in proteolytic lung damage by neutrophil elastase ("loss of function") that predisposes to the development of early-onset pan-lobular emphysema and chronic obstructive pulmonary disease [1, 3].

The alpha-1 antitrypsin deficiency (AATD) is an autosomal co-dominant condition and currently represents one of the most common and life-threatening genetic disorders. More than 150 variants of SERPINA1 have been reported, based on the migration speed of mutant AAT in an isoelectric field (e.g., medium-M, slow-S, and very slow-Z) [2, 4].

Pi*M constitutes the wild-type allele and is present in 85–90% of individuals [5]. Pi*Z (a substitution of lysine for glutamic acid at codon 342; rs28929474) and Pi*S (a substitution of valine for glutamic acid at codon 264; rs17580) are the most clinically relevant variants. Pi*Q0 alleles (null) represent a heterogeneous group of variants that yield no detectable protein in circulation.

The classic severe AATD is caused in 90% of the cases by the homozygous Pi*Z variant (Pi*ZZ genotype) and affects approximately 1:2,000 individuals in Europe (Table 1). It is characterized by markedly decreased levels of serum AAT and confers a strong predisposition to lung and liver disease. Epidemiological studies show that the Pi*Z allele is more prevalent in Northern Europe, up to 8%, and Pi*S is more common in Southern Europe (~20%) [6]. The compound heterozygous genotype Pi*SZ affects 1:500 Caucasians, with intermediate AAT serum concentrations, and moderately increases susceptibility to lung disease and liver fibrosis [3].

In Portugal, the true prevalence of AATD remains unclear. However, it is estimated that 1:5,249 individuals have a Pi*ZZ genotype and 1:281 individuals have a Pi*SZ genotype [7, 8]. Meira L. et al., [8] based on a retrospective analysis, evaluated a cohort of Portuguese individuals tested for AATD between the years 2006 and 2015. The data accessible for the study comprised only AAT phenotyping or genotyping results, patient age at the time of diagnosis, and the health entities requesting the AATD genetic diagnosis. Unfortunately, clinical information or AAT serum levels were unknown. Overall, 1,684 individuals were considered, covering almost every region in Portugal. Most subjects were distributed into more common genotypes: Pi*MZ (25.4%), Pi*MS (15.5%), Pi*SZ (11.2%), Pi*ZZ (9.4%), and Pi*SS (5.6%). Different types of rare deficiency and null alleles were also detected.

Liver Disease in AATD

AATD-mediated liver disease is associated with the retention of misfolded AAT protein within the endoplasmic reticulum (ER) of hepatocytes that may result in liver fibrosis, cirrhosis, and hepatocellular carcinoma. Seventy percent of misfolded AAT protein is degraded by ER, 15% is secreted, and 15% forms insoluble polymers, which mainly persist within the endoplasmic reticulum as inclusions that are positive on periodic acid-Schiff staining and resistant to diastase (PAS-D) – the histologic hallmark of liver disease on biopsy [1, 9]. The AATD variants linked to polymerization, such as SIiyama, MDuarte, MMalton, and particularly the Z allele, may all show signs of liver injury [9].

Hepatopathy in AATD has a bimodal distribution, with the first peak in early childhood and the second peak typically after 50 years of age [10]. In the neonatal period, prolonged cholestasis is the most common clinical manifestation of liver injury. A Swedish neonatal screening program identified 120 babies with the PI*ZZ genotype in a population of 200,000 newborns. In this cohort, 12% had prolonged jaundice, and 8% of the neonates had severe liver disease [11]. Biochemical abnormalities were present in more than 50% of the Pi*ZZ neonates with spontaneous resolution within months, and most of them remained healthy at follow-up at age 18 years. Only about 3% had progressed to severe, life-threatening liver disease [12]. In the pediatric population, the AATD represents 3.5% of the causes of liver transplantation [13].

In adulthood, two large cross-sectional studies demonstrated the presence of significant liver fibrosis in 20%–36% of Pi*ZZ carriers, and the advanced liver fibrosis was 10–20 times more common in "Pi*ZZ" subjects compared with individuals without a "Pi*Z" mutation (noncarriers) [14, 15]. Although not fully identified, there is a strong influence of genetic and environmental modifiers in the development of liver disease in AATD. Male sex, age ≥50 years, obesity, metabolic syndrome, and diabetes mellitus were associated with liver fibrosis and primary liver cancer in this group of patients [10, 15]. A study involving 335 homozygous Pi*ZZ identified a single nucleotide polymorphism (SNP) that confers a higher risk for liver disease [16].

Notably, only 10% of patients with AATD develop cirrhosis, and 14.7% of adults who presented with AATD-related liver disease required transplantation. The overall incidence of hepatocarcinoma is 1.3%, and it seems simi-

Table 1. Characterization of the most common genotypes associated with liver disease in AATD

	Pi*ZZ	Pi*SZ	Pi*MZ
Prevalence*	1:2,000	1:500	1:30
Serum AAT, mg/dL	10–45	50–120	66–210
Proportion of patients with elevated liver enzymes, %			
AST ≥ ULNALT ≥ ULN	15	5	5
ALT ≥ ULN	11	9	7
GGT ≥ ULN	22	18	17
Risk for liver cirrhosis (OR)	~20	3–5	1.7–3
HCC risk (OR)	45	6.6	1.4
Liver transplantation risk (OR)	20	–	3–4
Impact on liver disease	"disease-causing"	"disease-modifying"	"disease-modifying"

AAT, alpha-1 antitrypsin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HCC, hepatocellular carcinoma; Pi*MZ, AAT genotype with heterozygosity for the Pi*Z variant; Pi*SZ, AAT genotype with compound heterozygosity for the Pi*Z and Pi*S variants; Pi*ZZ, AAT genotype with homozygosity for the Pi*Z variant; ULN, upper limit of normal; OR, odds ratio. Adapted from [3, 7, 10, 14]. *Prevalence is estimated for European population.

lar to published data for aetiologies such as alcohol-related liver cirrhosis and primary biliary cholangitis [13]. A longitudinal study of Pi*ZZ individuals (n = 1,595) from the Swedish National AATD Register showed adjusted hazard ratios (HR) for hepatic and non-hepatic cancer of 23.4 and 1.3, respectively, in the Pi*ZZ individuals compared with the controls [17].

Regarding liver enzymes, as described in Table 1, only a small proportion of patients with AATD have abnormalities in liver parameters, which can fluctuate over time, even in patients with the Pi*ZZ genotype or with advanced liver fibrosis [18]. Schneider et al. [19] analyzed the liver phenotypes of a large cohort of patients with AATD (419 Pi*MZ; 309 Pi*ZZ; and 284 non-carriers). The authors concluded that gamma-glutamyl transferase (GGT) was the only parameter that clearly differed between the three genotypes, with the lowest values in non-carriers and the highest in Pi*ZZ subjects. This finding has been validated in another study [10]. Mean aspartate aminotransferase (AST) values were higher in Pi*ZZ versus Pi*MZ participants but were comparable between non-carriers and Pi*MZ individuals [19]. Accordingly, recent data from a large study showed that mean alanine aminotransferase (ALT) values were significantly higher in all AATD genotypes compared with non-carriers, and Pi*ZZ individuals had significantly higher AST values (adjusted odds ratio: 4.5) than any other assessed AATD subgroup [10].

Homozygous individuals for the Pi*S mutation (Pi*SS genotype) sheltered minimally elevated ALT values but no other hepatobiliary abnormality. However, Pi*SZ genotype displays higher liver enzymes and a clear predisposition to liver fibrosis/cirrhosis and primary liver cancer. This susceptibility is markedly lower than the one seen in Pi*ZZ carriers, which is consistent with the observed lower levels of intracellular polymers and a less pronounced lung disease [10, 19]. PI*MS genotype has not been consistently shown to increase the risk of liver disease [10].

On the other hand, the Pi*MZ genotype is primarily considered a disease-modifying factor in individuals with other liver diseases. Its relevance has been particularly well documented in individuals with cystic fibrosis as well as alcoholic/non-alcoholic fatty liver disease (ALD/NAFLD), in whom heterozygous Pi*Z presence greatly increased the odds to harbor cirrhosis. Pi*MZ was associated with a slightly elevation of liver enzymes and moderately increased odds for liver fibrosis/cirrhosis and cholelithiasis [3, 19]. Chen et al. [20] highlighted the role of Pi*MZ genotype as a risk factor for hepatic decompensation and the requirement for liver transplantation or liver-related death in a cohort of patients with compensated advanced chronic liver disease (576 patients with cirrhosis: 474 Pi*MM, 49 Pi*MZ, and 52 Pi*MS). Compared to the Pi*MM genotype, Pi*MZ was associated with increased rates of hepatic decompensation (hazard ratio 1.81) and liver transplant or liver-related death (hazard ratio 2.07). Moreover, a recent retrospective study identified the Pi*Z allele as an independent risk factor for liver transplantation and death in patients with advanced chronic liver disease (ACLD). In a population of 1,118 patients with ACLD, Pi*Z carriers (n = 42) had more se-

vere portal hypertension and hepatic dysfunction, compared to non-carriers [21].

These data provide evidence about the profoundly detrimental impact of the Pi*Z allele on the outcomes of ACLD and ALD/NAFLD. As a significant proportion of Pi*MZ patients can have normal AAT levels, dosing serum levels are insufficient to identify routinely these patients. Genotyping significantly increases the costs for the routine assessment of ALD/NAFLD and ACLD patients. An approach with phenotyping would permit identifying these patients at a significantly lower cost. As Pi*MZ patients have an increased OR of up to 3 for liver cirrhosis, up to 1.4 for hepatocellular carcinoma, and up to 4 for liver transplantation (as referred in Table 1), routine phenotyping for A1ATD would permit tailoring the follow-up of this large group of patients according to their risk stratification at a reasonable cost. However, further multicenter studies to validate these findings are warranted.

Diagnosis of Liver Disease in AATD

AATD is a widely underdiagnosed condition. When clinically suspected, the diagnosis should be confirmed by the AAT serum level and the determination of the AAT phenotype and/or genotype. If the serum levels, phenotype, or genotype do not agree with each other or with clinical manifestations, then a rare or null variant should be considered [7, 9, 22]. AAT is an acute phase protein, which is why its serum levels may be falsely elevated during inflammatory and infectious processes.

The evaluation of liver disease is particularly important in patients with AAT variants that lead to polymerization of misfolded AAT protein in the ER (mostly Pi*ZZ carriers). Liver biopsy is not recommended as a method of diagnosis and follow-up, given its invasive nature, and should be employed in individuals with inconclusive non-invasive results and/or additional investigation. Non-invasive assessment based on blood tests and various elastography methods has been proposed to estimate liver fibrosis. Liver stiffness measurement (LSM) has proven to be useful in the diagnosis of liver fibrosis, especially to rule out advanced fibrosis [23]. Several studies in AATD-related liver disease showed promising results using this approach [14, 15, 18, 24–28].

Clark et al. [14] evaluated 94 non-cirrhotic Pi*ZZ adults and demonstrated that LSM by transient elastography (TE) represented the best parameter to identify advanced liver fibrosis (AUROC 0.92), with the cut-off of 8.45 Kpa having the highest accuracy. Moreover, GGT was the best one to detect significant fibrosis (F ≥2 on a 0–4 METAVIR scale) with an AUROC of 0.77, while TE, Fibrosis-4 (FIB-4), and AST-to-platelet ratio indices (APRI) were less well suited (AUROC 0.70/0.66/0.69, respectively).

Unfortunately, this cohort contained only 6 individuals with advanced liver fibrosis, and patients with cirrhosis were initially excluded [14]. The superiority of LSM by TE compared to blood tests in ruling out advanced liver fibrosis was also reported by Kümpers et al. [24].

Another large multinational study including 554 Pi*ZZ patients without known liver disease compared against 234 adults not carrying any AAT mutation confirmed the high prevalence of significant liver fibrosis in Pi*ZZ individuals (20%–36%). In this cohort, significant fibrosis was defined as LSM ≥7.1 kPa and advanced liver fibrosis defined as LSM ≥10.0 kPa. The last one was 9–20 times more frequent in Pi*ZZ individuals [15]. Also, the parallel assessment of TE, APRI, and HepaScore (age, sex, alpha2-macroglobulin, hyaluronic acid, bilirubin, and gamma-glutamyl transferase) values revealed a moderate correlation between the former two, whereas the correlations with the HepaScore were less robust.

Kim et al. [28] suggested that magnetic resonance elastography (MRE) may be accurate for identifying fibrosis (AUROC 0.9) in patients with alpha-1 antitrypsin deficiency. A MRE threshold of ≥3.0 kPa provided 88.9% accuracy, with 80% sensitivity and 100% specificity to detect the presence of any fibrosis (stage ≥1).

To note, the cut-offs used for detection of the corresponding fibrosis stages were different in several studies. The cut-off of LSM ≥5.45 kPa for significant liver fibrosis suggested by Clark et al. [14] does not seem to be useful for risk stratification as these values are seen in >50% of Pi*ZZ patients [14, 24]. Since the etiology of liver disease has an important impact on LSM, further studies are needed to validate the best LSM cut-off for screening of liver disease in AATD.

The recently published studies revealed other interesting features of Pi*ZZ-related liver disease. Controlled attenuation parameter (CAP) ≥280 dB/m, suggesting severe steatosis (grade 3), was detected in 39% of Pi*ZZ carriers versus 31% of controls, and about 44% of Pi*ZZ carriers displayed histological liver steatosis [14, 15]. Alterations in lipid metabolism observed in Pi*ZZ individuals (e.g., lower serum levels of triglycerides, very low-density lipoproteins, and low-density lipoproteins compared with controls) indicate that impaired hepatic secretion of lipids might play a role. However, it is important to mention that the accuracy of CAP for predicting histological

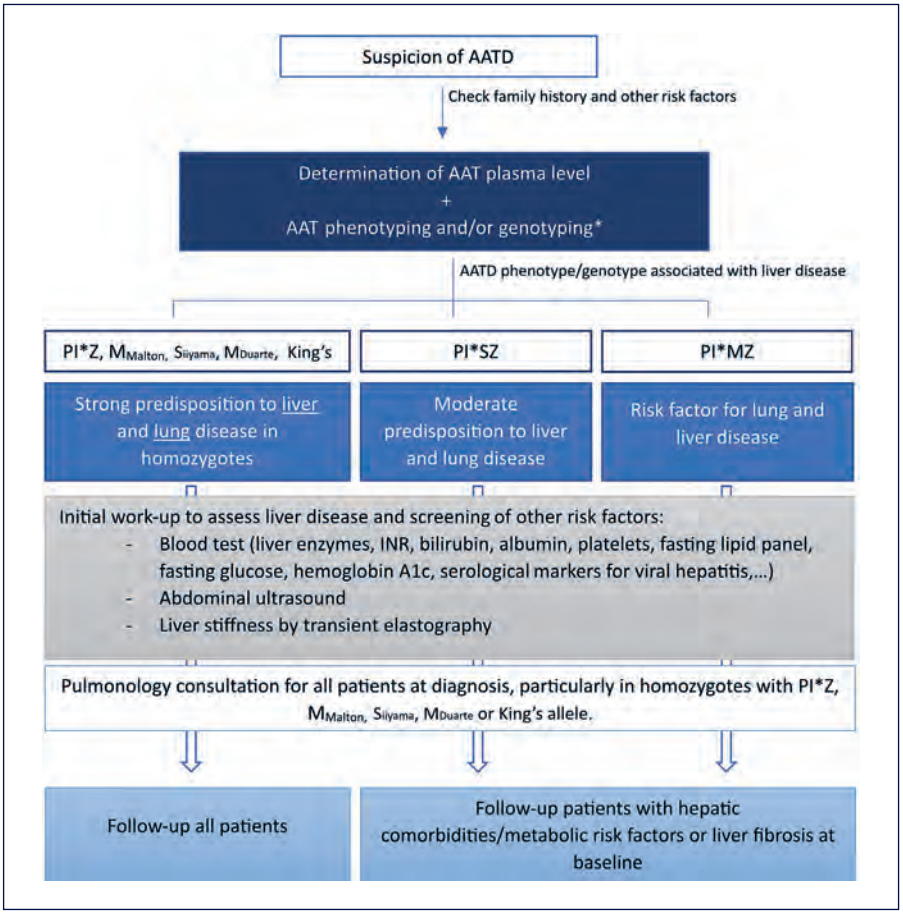

Fig. 1. The authors suggest the following diagnostic approach flowchart to assess liver disease in patients with AATD (*or whole gene sequencing depending on availability and/or the need for more detailed interpretation). The surveillance of Pi*MZ and Pi*SZ subjects needs to be adjusted to the overall clinical context that includes the presence of hepatic comorbidities/metabolic risk factors, other genetic factors as well as the presence/absence of baseline liver fibrosis as evaluated by non-invasive methods. AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; PI*MZ, AAT genotype with heterozygosity for the Pi*Z variant; Pi*SZ, AAT genotype with compound heterozygosity for the Pi*Z and Pi*S variants.

steatosis has not been validated in AATD. The authors suggest in Figure 1 a diagnosis approach flowchart for patients with suspicion AATD-liver disease.

Treatment of Liver Disease in AAT

For the treatment of AATD-related lung disease, the Food and Drug Association approved in 1987 the intravenous augmentation therapy with plasma-purified AAT, the first disease-specific therapy for AATD. In the last years, several trials showed a significant reduction in the annual rate of lung density and, thereby, a decrease in the progression of lung emphysema while on AAT augmentation [7, 22, 29, 30].

Unfortunately, for end-stage liver disease related to AATD, the liver transplantation is the only available curative treatment, with good survival and long-term outcomes for both children and adults [13, 31, 32]. Until the time of writing, there is no robust evidence of non-pharmacological interventions, such as smoking cessation or weight loss on liver outcomes. According to the known pathophysiology, it is expected that both of these behaviors would improve liver outcomes. Regarding this subject, previous data suggest that breast-feeding may have a protective effect in severe liver disease and early death in infants with alpha 1-antitrypsin deficiency [33].

Future Directions

The knowledge of pathological mechanisms of liver disease in AATD led to the investigation of several approaches for treating AATD-related liver disease. Some of these strategies are currently under evaluation in early-phase clinical trials and others in preclinical stages [1, 3, 34, 35]. Therapeutic targets address different steps of production, secretion, and elimination of misfolded AAT protein in the hepatocytes.

Silencing the production of mutated AAT constitutes a promising approach in the treatment of AATD-related liver disease. The small-interfering RNAs (siRNAs) and

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Table 2. Overview of the most important clinical studies listed in ClinicalTrial.gov for therapy of liver disease in AATD

Clinical trial	Phase	Therapeutic mechanism	Patients and methodology	Main findings
ARO-AAT in patients with alpha-1 antitrypsin deficiency associated liver disease; NCT03946449 [37]	Phase 2	Silencing of the Z-AAT mRNA using siRNA	16 Pi*ZZ patients. Dose of 200 mg (cohorts 1 [4 patients] and 2 [8 patients]). Dose of 100 mg (cohort 1b [4 patients]). Subcutaneous injections with ARO-AAT at weeks 0, 4, and 16 or at week 0, 4, 16, 28, and 40 and liver biopsies at week 0, 24, or 48, respectively	All patients showed a reduction of serum Z-AAT (~90%) and in accumulated total liver Z-AAT (median reduction 83.3%) and in histologic globule burden (69% reduction). All cohorts had reductions in liver enzyme concentrations 7 patients improved liver fibrosis, including 2 individuals with cirrhosis. The selected dose was 200 mg of Fazirsiran
Carbamazepine in severe liver disease due to alpha-1 antitrypsin deficiency; NCT01379469	Phase 2	Stimulation of the autophagy pathway	20 patients with AATD (Pi*ZZ or PI*SZ). 13 patients received carbamazepine. 7 patients received placebo	The effect of carbamazepine on hepatic Z-AAT load and fibrosis could not be assessed because the number of subjects with available pre- and post-biopsies was insufficient in subject number and sample quality to conduct the analyses
VX-864 in Pi*ZZ subjects; NCT04474197	Phase 2	Correction of misfolded protein in ER with chemical chaperones	44 Pi*ZZ patients 7 patients received placebo. 37 patients received VX-864 by oral administration (3 different doses)	First results were not published
Belcesiran in patients with AATD-associated liver disease (ESTRELLA); NCT04764448	Phase 2	Silencing of the Z-AA mRNA using siRNA	Recruiting	First results were not published
ADVM-043 gene therapy to treat alpha-1 antitrypsin (ADVANCE); NCT02168686	Phase 1/2	Gene therapy	6 Pi*ZZ patients	First results were not published
ARC-AAT in healthy volunteer subjects and patients with alpha-1 antitrypsin deficiency; NCT02363946 [36]	Phase 1	Silencing of the Z-AAT mRNA using siRNA	Healthy controls (54) versus Pi*ZZ patients (11). 36 healthy controls received ARC-AAT and 18 received placebo. 7 Pi*ZZ individuals received ARC-AAT and 4 received placebo	Serum AAT reduction was observed at doses ≥4 mg/kg with similar relative reductions in Pi*ZZ patients and healthy controls at 4 mg/kg and a maximum reduction of 76.1% (HVs) versus 78.8% (Pi*ZZ) at this dose. The study was terminated early because of toxicity findings related to the delivery vehicle (ARC-EX1) seen in a non-human primate study
ZF874 in healthy volunteers and Pi*MZ subjects; NCT04443192	Phase 1	Correction of misfolded protein in ER with chemical chaperones	Recruiting	First results were not published

ADVM-043, investigational gene therapy product expressing human AAT that is intended to deliver a functional gene to the liver of patients with AATD; ARC-AAT, RNA inter-ference-based, liver-targeted therapeutic; Pi*SZ, AAT genotype with compound heterozygosity for the Pi*Z and Pi*S variants; Pi*ZZ, AAT genotype with homozygosity for the Pi*Z variant; siRNA, small-interfering RNA; VX-864 and ZF874, novel chemical chaperones that are specifically designed to rescue the folding of the Z variant of AAT; Z-AAT, mutant alpha-1 antitrypsin associated with Pi*Z variant.

the antisense oligonucleotides (ASOs) are the most common strategies in this field that modulate gene expression by inducing enzymatic degradation of targeted mRNA and consequently interrupting the production of their corresponding proteins [34].

Turner et al. [36] showed the first evidence of siRNA therapeutic designed to silence expression of Z-AAT (the Z variant of AAT) mRNA (Table 2). His study demonstrated a deep and durable knockdown of hepatic AAT production based on an observed reduction in serum AAT concentrations with no occurrence of major adverse events or hepatotoxicity in patients with PI*ZZ and healthy volunteers. Despite the results, the study was terminated early because of toxicity findings related to the delivery vehicle (ARC-EX1) seen in a non-human primate study.

Recently, the ARO-AAT2002 open label trial (NCT03946449) evaluated the safety and efficacy of ARO-AAT injection (hepatocyte-targeted siRNA therapeutic against Z-AAT mRNA, Fazirsiran) administered subcutaneously to patients with alpha-1 antitrypsin deficiency. The Pi*ZZ patients received subcutaneous injections with ARO-AAT and underwent liver biopsies at weeks 0 and 24 or 48. The first results showed a reduced serum and liver Z-AAT and histologic globule burden in all patients and decreased serum ALT and GGT. Moreover, 7 individuals displayed an improvement in liver fibrosis, including 2 individuals with cirrhosis at baseline. These data demonstrate that removal of the causative factor, Z-AAT, in AATD liver disease ameliorates liver injury and can lead to an improvement in fibrosis [37]. This trial was followed by double-blindphase 2 clinical trial which results will be published soon. Phase 3 with this molecule (Fazirsiran) will begin recruiting in the end of 2022. Other trials based on siRNAs therapeutic that are currently ongoing are shown in Table 2. This approach seems to be a logical choice for individuals with isolated, advanced liver disease, but the long-term impact of the resulting decrease in serum AAT levels remains an important concern.

The administration of ASO can also represent a possible future direction in the treatment of liver disease [38, 39]. Some data from studies in preclinical stages showed that administration of ASO in Pi*ZZ transgenic mice led to an approximately 80% reduction in levels of circulating normal AAT and ameliorates liver fibrosis [38].

The correction of misfolded proteins in the ER with chemical chaperones is one of the approaches that have been studied. Burrows et al. [40] demonstrated in experimental models that phenylbutyrate (PBA), a substance used for treatment of urea cycle disorders, increased fivefold the secretion of functionally mutant AAT in Pi*ZZ mice. However, in a preliminary study of a small number of patients with AATD (9 Pi*ZZ individuals and 1 with a homozygous null genotype), the oral administration of PBA during 14 days was not effective in increasing AAT blood levels, and metabolic side effects were noted [41]. As shown in Table 2, other folding correctors are the object of study in current trials, such as VX-864 and ZF874.

Some studies have identified small molecules that are effective in reducing the polymerization of Z-AAT in vitro [34, 35, 42]. Recently, Lomas et al. [43] described a small molecule termed "GSK716" that blocked intracellular polymerization of Z-AAT and increased the circulating levels of monomeric protein by sevenfold in a transgenic mouse model of AATD.

On the other way, intracellularly expressed antibody fragments ("intrabodies"), particularly ones that consist of one heavy and one light variable domain linked by a synthetic flexible peptide, were also used to block the polymerization in the ER. scFv is capable of preserving antigen-binding specificity and can be targeted to subcellular compartments by incorporating trafficking signals specific for the ER [34, 35]. In vitro, the scFv4B12 intrabody reduced the intracellular polymerization of Z-AAT up to 60% and increased its secretion, keeping the functional activity of AAT against neutrophil elastase [44].

Another pathway in decreasing the hepatic burden of AAT is autophagy, which is able to degrade structures that are too large to be processed via the proteosome, namely the misfolded proteins. Drugs approved and used for other diseases, such as carbamazepine and rapamycin, have been found to be promoters of autophagy and thereby reduce the number of intra-hepatic Z-AAT inclusions and hepatic fibrosis in a mouse model of AATD-associated liver disease [45, 46]. A recent randomized, double-blind, and placebo-controlled trial (NCT01379469) evaluated the effect on hepatic Z-AAT load and liver fibrosis of a 52-week treatment with carbamazepine in individuals with Pi*MZ/Pi*ZZ and severe liver disease. However, the main outcomes could not be assessed because the number of subjects with available pre- and post-biopsies was insufficient in subject number and sample quality to conduct the analyses (Table 2).

The advance of stem cells and molecular biology techniques allowed the development of promising therapeutics for liver disease in AATD. The recent study of Baligar et al. [47] showed that the transplantation of human mesenchymal stem cells and bone marrow-derived stem cells in trans-

genic mice expressing human Z-AAT confer some competitive advantages compared to host cells that could lead to pathological improvement. Transplantation of these cells resulted in the decline of globule-containing hepatocytes and partially improved liver pathology as reflected by inflammatory response, fibrosis, and apoptotic death of hepatocytes. Previously, Yusa et al. [48] accomplished the biallelic correction of the underlying mutation causing the expression of Z-AAT in the genome of human induced pluripotent stem cells derived from Pi*ZZ patients via a combination of piggyBac technology and zinc finger nucleases. This gene correction was sustained in subsequently differentiated hepatocyte-like cells and led to a restored structure and enzymatic function of native AAT.

Viral vector-mediated expression of short hairpin RNAs can be efficiently used to knockdown and functionally evaluate disease-related genes in patient-specific pluripotent stem cells. These methodologies can achieve a relevant reduction (−66%) of intracellular Pi*Z protein in hepatic cells after differentiation of patient-specific pluripotent stem cells [49].

Conclusion

Liver involvement constitutes the second most common clinical manifestation and cause of death in patients with AATD [3]. The assessment of liver fibrosis is a crucial step in the evaluation and follow-up of these patients. Among the non-invasive methods, the LSM by TE has particular interest and is useful to identify advanced liver fibrosis. Currently, liver transplantation is the only curative therapy for AATD-related liver disease. However, several promising strategies are currently under investigation and may emerge in the near future. In the light of clinical studies, silencing the production of mutated AAT using small-interfering RNAs seems to take advantage when compared with others strategies.

Statement of Ethics

Due to the nature of the article (review article), ethical approval was not required.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

The four authors contributed equally to the planning and organization of the article. Nélia Abreu was in charge of bibliographic research and first draft. Vítor Magno Pereira, Madalena Pestana, and Luís Jasmins contributed to the improvement of the final draft and overall critical review.

Data Availability Statement

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

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Small-Bowel Angioectasias: Are They Responsible for a Real Impact on Survival?

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Keywords
Angiectasia · Capsule endoscopy · Survival

Abstract

Introduction: This study aimed to evaluate the effect of small-bowel angioectasia on survival, given the hypothesis that angioectasia might be an independent risk factor of frailty and poor outcomes. ***Methods:*** In this retrospective cohort study, all patients undergoing small-bowel capsule endoscopy between 2010 and 2013 for obscure gastrointestinal bleeding from a Portuguese tertiary centre were included. Follow-up started after capsule endoscopy and ended upon death or end of the study (November 2020). Survival analysis was performed using a Cox proportional-hazards model, in order to analyse the effect of small-bowel angioectasia on survival as well as potentially confounding factors (age, vascular diseases and chronic kidney disease). ***Results:*** A total of 176 patients were included in this study (50.6% male), with a median age of 68.5 years (IQR 24). The median follow-up was 7 years (IQR 4), during which 67 (38.1%) patients died. Seventy-three (41.5%) patients had at least one small-bowel angioectasia on capsule endoscopy. On multivariate Cox regression analysis, only age, peripheral arterial disease, history of previous mesenteric ischaemia and chronic kidney disease were independent risk factors of death. The presence of small-bowel angioectasia did not affect survival in this analysis (HR 1.30; 95% CI 0.75–2.23; $p = 0.35$). ***Conclusion:*** In this retrospective cohort study, some comorbidities and age were independent predictors of poor survival. The presence of small-bowel angioectasia per se did not affect survival.

Angiectasias intestinais: existe um verdadeiro impacto na sobrevida?

Palavras Chave
Angiectasia · Cápsula endoscópica · Sobrevida

Resumo

Introdução: Este estudo pretendeu avaliar a influência das angiectasias do intestino delgado na sobrevida, dada a hipótese de que as angiectasias pudessem constituir um fator de risco independente para fragilidade e *outcomes* adversos. ***Métodos:*** Os autores incluíram neste estudo de coorte retrospetivo todos os doentes submetidos a cápsula endoscópica entre 2010 e 2013 por hemorragia di-

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gestiva obscura num centro português terciário. O *follow-up* iniciou-se após a realização da cápsula e terminou aquando da morte ou fim do estudo (Novembro de 2020). A análise da sobrevida foi realizada através de um modelo de regressão de Cox, no sentido de analisar o efeito na sobrevida das angiectasias do intestino delgado e de potenciais fatores confundidores (idade, doenças vasculares e doença renal crónica). ***Resultados:*** Neste estudo foram incluídos 176 doentes (50.6% do sexo masculino), com uma idade mediana de 68.5 anos (IQR 24). O tempo de *follow-up* mediano foi de 7 anos (IQR 4), durante o qual se verificaram 67 (38.1%) óbitos. 73 (41.5%) dos doentes apresentavam pelo menos uma angiectasia no intestino delgado. Na análise de sobrevida, apenas a idade, doença arterial periférica, história prévia de isquemia mesentérica e doença renal crónica foram fatores de risco independentes de mortalidade. A presença de angiectasias no intestino delgado não afetou a sobrevida nesta amostra (HR 1,30; 95% CI 0,75–2,23; $p = 0.35$). ***Conclusão:*** Neste estudo de coorte retrospetivo, algumas co-morbilidades e a idade foram fatores de risco independentes de mortalidade. A presença de angiectasias no intestino delgado, *per se*, não afetou a sobrevida.

Introduction

In the diagnostic workup of obscure gastrointestinal bleeding (OGIB), defined as bleeding from the digestive tract with negative findings on upper endoscopy and colonoscopy, small-bowel capsule endoscopy (SBCE) remains the first-line diagnostic tool in haemodynamically stable patients [1, 2]. SBCE has a well-documented diagnostic yield and positive impact in the management of these patients [3, 4].

Small-bowel vascular lesions, including angioectasia (AE), Dieulafoy's lesion and arteriovenous malformation are the most common causes of OGIB [5]. AE are found in 30–40% of patients presenting with OGIB [6]. Since these vascular lesions are considered to be venous [7], they usually manifest as iron deficiency anaemia (IDA) due to chronic bleeding. However, these lesions may also result in overt bleeding episodes (OBE) [8].

Although being incompletely understood, the pathophysiology of AE includes high intestinal wall tension causing chronic obstruction of the submucosal veins with consecutive precapillary dilation, mucosal ischaemia from chronic hypoxia and vascular endothelial growth factor (VEGF)-related disorders of angiogenesis [9].

As such, numerous conditions have been associated with the presence of these lesions, including vascular comorbidities and ageing [10–12]. In a systematic review conducted by Grooteman et al. [13], which included 92,634 participants from 23 studies, age, chronic kidney disease (CKD) and cardiovascular disease were the most important risk factors for the presence of AE on endoscopy.

The clinical significance of these gastrointestinal lesions is incompletely understood [6], with some studies questioning their impact on survival [14]. In fact, most of these lesions do not require treatment, unless they become symptomatic [15]. In this study, the authors aimed to evaluate the independent effect of small-bowel AE on survival of patients with OGIB.

Methods

Study Design

This was a single-centre, retrospective cohort study.

Patient Population

All adult patients undergoing SBCE between 2010 and 2013 for OGIB, presenting as OBE or IDA, from Centro Hospitalar de Vila Nova de Gaia/Espinho, EPE, were included in this study. The CE system used was Mirocam (IntroMedic, Seoul, Korea). All CE studies were analysed by an expert gastroenterologist with extensive experience in CE (more than 300 CE examinations).

The authors recorded the presence or absence of small-bowel AE (P2 lesions according to the Saurin Classification [16]), number of AE, maximum size of AE and referral for argon plasma coagulation (APC).

Exclusion Criteria

Inadequate small-bowel cleansing and incomplete exams were exclusion criteria from the study. Using the Brotz preparation scale, an exam was considered inadequately prepared if a quantitative index lower than 7 was described [17].

An exam was considered incomplete if the capsule did not reach the cecum/colon or stoma bag (in patients who had had ileocolonic resection or other relevant surgery) during recording time.

Bowel Cleansing Protocol

All patients took the same bowel cleansing procedure: clear liquids diet on the day prior to the procedure and 2L polyethylene glycol solution the night before the exam. Four hours after the capsule was swallowed, they were instructed to take a small meal.

Population Characteristics

On the date of SBCE performance, gender and age were recorded, as well as the presence or absence of the following vascular comorbidities (diagnosed before SBCE performance or during fol-

Table 1. Comparison of demographical data and comorbidities between patients with small-bowel AE and patients without this finding on small-bowel capsule endoscopy

Variable	Small-bowel AE (n = 73)	No AE (n = 103)	p value
Median age (IQR), years	**73 (17)**	**65 (24)**	**0.03**
Congestive heart failure, *n* (%)	**29 (39.7)**	**23 (22.3)**	**0.01**
Heart valve disease, *n* (%)	**22 (30.1)**	**13 (12.6)**	**<0.01**
Ischaemic heart disease, *n* (%)	18 (24.7)	14 (13.6)	0.06
Atrial fibrillation, *n* (%)	14 (19.2)	13 (12.6)	0.23
Previous Stroke, *n* (%)	9 (12.3)	12 (11.7)	0.89
Abdominal aorta aneurism, *n* (%)	1 (1.4)	0 (0)	0.23
Peripheral arterial disease, *n* (%)	2 (2.7)	2 (1.9)	0.72
Previous mesenteric ischaemia, *n* (%)	1 (1.4)	2 (1.9)	0.77
Chronic kidney disease, *n* (%)	15 (20.5)	18 (17.5)	0.61

Bold values indicate statistical significance. AE, angioectasia.

low-up): congestive heart failure (CHF), heart valve disease, ischaemic heart disease, atrial fibrillation, history of previous stroke, abdominal aorta aneurism, peripheral artery disease, history of previous mesenteric ischaemia and CKD.

Referral for APC

In the study centre, a conservative approach for APC treatment of small-bowel AE was used; it is generally reserved for patients who present with a low haemoglobin level and with relapsing anaemia despite iron supplementation.

Follow-Up

Follow-up started after SBCE and ended upon death or end of the study (November 2020). The primary endpoint of the study was mortality. The date of death was electronically available in all patients who died during follow-up. The cause of death when know (only in patients who died in the study centre facilities) was also reported.

Statistical Analysis

Data was reported as median (interquartile range [IQR]) or mean (standard deviation [SD]), when appropriate, for numerical variables and as absolute and relative frequencies for categorical variables.

The Student t test and the Mann-Whitney test, when suitable, were used to compare numerical variables, and the χ^2 test and Fisher's exact test, when suitable, were used to compare categorical variables.

The Kaplan-Meier method was used to estimate 1-year and 5-year cumulative survival in both groups, and the log-rank test was used to assess differences in overall survival.

Survival analysis was performed using a Cox proportional-hazards model to analyse the effect of small-bowel AE on survival as well as potentially confounding factors, including age and the comorbidities under evaluation. We initially performed a univariate analysis. Variables with a p value less than 0.1 were included in the multivariate analysis.

We also performed a survival analysis, again using a Cox proportional-hazards model, in patients with AE on SBCE, to assess the effect of age, clinical presentation (OBE vs. IDA), number of AE, AE maximum size and treatment with APC by balloon-assisted enteroscopy on survival.

In order to assess the effectiveness of AE endoscopic treatment, a 2-year follow-up of the patients submitted to APC was carried out. The authors assessed the lowest haemoglobin level, the transfusion support rate and the rebleeding rate (defined as the need for a blood transfusion, the presence of OBE or a decrease in haemoglobin ≥2 g/dL).

The IBM Statistical Package for the Social Sciences (SPSS) version 26 was used for statistical analysis. A p value less than 0.05 was considered as statistically significant.

Results

Between 2010 and 2013, 196 SBCE due to OGIB were performed. The authors excluded 20 of the exams due to inadequate bowel cleansing (n = 13) and incomplete examination (n = 7).

The authors included 176 patients in this study (50.6% male), with a median age of 68.5 years (IQR 24). Regarding exam indication, in 149 (84.7%) of these patients SBCE was performed due to IDA and in the remaining 27 (15.3%) patients due to OBE.

Concerning findings on SBCE, in 122 (69.3%) of SBCE at least one relevant finding was identified: small-bowel AE, 73 (41.5%) exams; erosions/ulcers, 29 (16.5%); mucosal erythema, 10 (5.7%); subepithelial lesions, 5 (2.8%); polyps, 2 (1.1%); haemangioma, 1 (0.6%); Meckel's diverticulum, 1 (0.6%) and small-bowel tumour, 1 (0.6%).

Age and comorbidities were compared between patients with AE and patients without these findings (Table 1). Patients with small-bowel AE were older (73 [IQR 17] vs. 65 [IQR 24] years, p = 0.03) and were more likely to have CHF (29 [39.7%] vs. 23 [22.3%], p = 0.01) and HVD (22 [30.1%] vs. 13 [12.6%], p < 0.01). There were no statistically significant associations concerning the remaining factors analysed.

Table 2. Causes of death of the study population

Cause of death	*N* (%)
Unknown	28 (41.8)
Respiratory infection	12 (17.9)
Decompensated heart failure	6 (9.0)
Septic shock	4 (6.0)
Acute limb ischaemia	2 (3.0)
Central venous catheter infection	2 (3.0)
Cerebral stroke	2 (3.0)
Decompensated liver disease	2 (3.0)
Pulmonary thromboembolism	2 (3.0)
Skin and soft tissue infection	2 (3.0)
Endocarditis	1 (1.5)
Urinary infection	1 (1.5)
Acute kidney failure	1 (1.5)
Acute pancreatitis	1 (1.5)
Pancreatic cancer	1 (1.5)

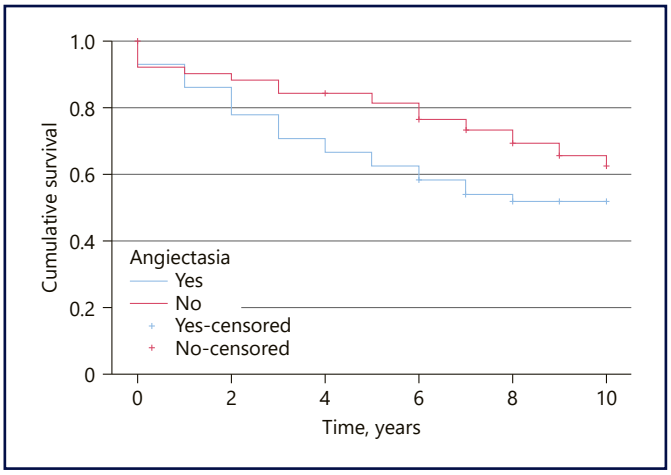

Fig. 1. Kaplan-Meier curve for the presence of angioectasia.

Survival Analysis

The median follow-up was 7 years (IQR 4), during which 67 (38.1%) patients died. Causes of death are reported in Table 2. In 41.8% of the patients, the cause of death was unknown or not reported on the available medical records. In all of the cases of death with known cause, overt small-bowel gastrointestinal bleeding was not reported.

The 1-year and 5-year cumulative survival in patients with AE was 93.2% and 66.7%, respectively, and 92.2% and 84.4% in patients without AE. Overall survival was inferior in the group of patients with AE ($p = 0.03$) (Fig. 1).

On univariate Cox proportional-hazards analysis, age, the presence of AE and all the analysed comorbidities (except for ischaemic heart disease) were significant risk factors for death. However, on multivariate analysis, only age, peripheral artery disease, history of previous mesenteric ischaemia and CKD were independent risk factors for death. The presence of small-bowel AE per se did not affect survival in this analysis (Table 3).

Subanalysis of Patients with AE on CE

As mentioned before, 73 patients had small-bowel AE. 50.7% of these patients were male and the median age was 73 years (IQR 17). The median follow-up was 7 years (IQR 6), during which 33 patients (45.2%) died.

Regarding indication, 62 (85.3%) of the SBCE were performed due to IDA, whereas the remainder were due to OBE. Concerning AE features, the median number of AE was 3 (IQR 3), the median maximum size was 4 mm (IQR 4), and 28 (38.4%) were submitted to APC.

Multivariate Cox regression analysis revealed that age and AE maximum size were independent predictors of poor survival, whereas indication for SBCE, number of AE and APC treatment were not (Table 4).

However, when comparing patients who were submitted to APC with those who were not, the first group had a lower haemoglobin level upon OGIB diagnosis. Furthermore, these patients had a higher need for transfusion support and a higher rate of relapsing anaemia despite iron supplementation (Table 5).

Subanalysis of Patients with AE Who Underwent Endoscopic Treatment

On a 2-year follow-up, 4 from the 28 patients submitted to APC died; none of these reached the endpoint of rebleeding. Concerning the remaining 24 patients, the rebleeding rate was 37.5%. However, the mean lowest haemoglobin level was significantly higher than the value upon OGIB diagnosis (10.2 [0.4] g/dL vs. 7.5 [1.6] g/dL, $p < 0.01$), and the transfusion need was significantly lower (5 [20.8%] vs. 20 [71.4%], $p < 0.01$). Furthermore, there were no OBE reported during this period.

Discussion

IDA and OBE, two possible clinical presentations of small-bowel AE, are factors which may decompensate underlying comorbidities. In fact, the presence of anaemia in patients with CHF increases overall mortality and hospitalization rate according to a recent meta-analysis [18].

GE Port J Gastroenterol 2023;30:336–342
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Table 3. Survival analysis using a proportional-hazards Cox regression model

Variables	Univariate analysis		Multivariate analysis	
	hazard ratio (95% CI)	*p* value	hazard ratio (95% CI)	*p* value
Small-bowel angioectasia	1.68 (1.04–2.71)	0.04	1.23 (0.72–2.10)	0.45
Age	**1.08 (1.05–1.10)**	**<0.01**	**1.06 (1.03–1.08)**	**<0.01**
Congestive heart failure	3.69 (2.27–6.00)	<0.01	1.97 (0.99–3.93)	0.05
Ischaemic heart disease	1.46 (0.81–2.63)	0.21		
Heart valve disease	2.98 (1.80–4.95)	<0.01	0.90 (0.43–1.85)	0.77
Atrial fibrillation	4.90 (2.89–8.29)	<0.01	1.68 (0.88–3.19)	0.12
Previous stroke	2.40 (1.28–4.50)	0.01	1.47 (0.73–2.97)	0.29
Abdominal aorta aneurism	14.62 (1.91–112.19)	0.01	2.42 (0.19–30.55)	0.49
Peripheral arterial disease	**4.46 (1.61–12.35)**	**0.01**	**6.08 (2.09–17.72)**	**0.01**
Previous mesenteric ischaemia	**13.44 (3.89–46.51)**	**<0.01**	**9.60 (2.10–43.94)**	**0.04**
Chronic kidney disease	**3.50 (2.09–5.85)**	**<0.01**	**2.02 (1.18–3.48)**	**0.01**

Bold values indicate statistical significance.

Table 4. Survival analysis of the patients with small-bowel AE using a multivariate Cox regression model

Variables	Univariate analysis		Multivariate analysis	
	hazard ratio (95% CI)	*p* value	hazard ratio (95% CI)	*p* value
Age	**1.05 (1.02–1.09)**	**<0.01**	**1.05 (1.01–1.08)**	**0.01**
Overt gastrointestinal bleeding	0.54 (0.22–1.31)	0.18		
Number of AE	1.01 (0.89–1.16)	0.86		
AE maximum size	**1.23 (1.07–1.41)**	**<0.01**	**1.17 (1.01–1.35)**	**0.04**
APC treatment	1.39 (0.71–2.74)	0.34		

Bold values indicate statistical significance. AE, angioectasia; APC, argon plasma coagulation.

Table 5. Comparison of clinical features of patients with AE submitted to argon plasma treatment and patients managed conservatively

Variables	Argon plasma treatment (*n* = 28)	Conservative approach (*n* = 45)	*p* value
Mean haemoglobin level (SD), g/dL	**7.5 (1.6)**	**8.6 (2.0)**	**0.01**
Transfusion need, *n* (%)	**20 (71.4)**	**21 (46.7)**	**0.04**
Relapsing anaemia despite iron supplementation, *n* (%)	**17 (60.7)**	**15 (33.3)**	**0.02**

Bold values indicate statistical significance. AE, angioectasia.

However, when analysing the independent effect of AE on survival, the authors did not find a significant association. The authors also did not find any recorded death directly associated with AE. These findings are similar to a recent study published by Robertson et al. [14], in which small-bowel AE did not cause any death in a 5-year cohort, but survival was poor in the AE group due to the higher frequency of vascular comorbidities.

Concerning the subanalysis of factors impacting survival in patients with AE, besides age, only AE size had an independent effect on survival. It is plausible to affirm that a larger number of participants would be necessary

to strengthen the conclusion of this subanalysis, given that multiple lesions, for instance, increase the risk of rebleeding and, therefore, there is an expected benefit of treating these patients [13, 19, 20].

Although APC treatment was not identified as an independent predictor of survival, it is important to consider that in the study centre, there is a conservative approach for endoscopic referral. In fact, the group of patients submitted to APC had a lower haemoglobin level upon OBE diagnosis, a higher need for transfusion support and a higher rate of relapsing anaemia. These considerations may explain the absence of survival impact of APC treatment in the study analysis, given that a conservative approach was taken in patients with a better prognosis and the invasive approach was reserved for patients with more adverse clinical features upon OBE presentation.

Concerning the effectiveness of the procedure, although more than one-third of the patients fulfilled the criteria of rebleeding, the haemoglobin level significantly improved, as well as the transfusion need, and no OBE were reported. Moreover, the increase in the mean haemoglobin level and the decrease in transfusion support achieved with endoscopic treatment are indirect markers of quality of life improvement and reduced utilisation of healthcare services [21].

The authors present a real-world analysis of a population with multiple comorbidities, which have a stronger impact on survival than the presence of AE. Despite the neutral effect on survival, it is important to keep the high rebleeding rate of these lesions after endoscopic treatment in mind (especially in patients with high-risk comorbidities), as well as the eventual need for a second or even third enteroscopy [22, 23].

Nevertheless, with these considerations, the authors do not aim to discourage the treatment of these lesions, but rather to alert for the need to outweigh its risks and benefits, especially in older and frail patients with IDA compensated with iron supplementation. This study has several strong points. Firstly, the median follow-up of this study is quite large: 7 years (IQR 4). Secondly, to our knowledge, this is the first study which analyses the independent effect of small-bowel AE, adjusted for age and vascular comorbidities, using a multivariate Cox regression model. Thirdly, the authors only included P2 AE according to the Saurin classification, excluding red spots (P1 lesions), which do not have a significant impact in this setting [24].

This study has, however, two important limitations. Firstly, data was collected retrospectively through the medical records of the study centre; therefore, the authors were only able to know the cause of death of patients who died in the hospital facilities. Secondly, other potential risk factors for the presence of AE, which might affect survival, were not analysed, including obesity and chronic liver disease [9, 25].

Conclusion

Some vascular comorbidities and age were predictors of poor survival. The presence of small-bowel AE per se did not affect survival.

Statement of Ethics

This retrospective study was approved by the local ethics committee. The research was conducted ethically in accordance with the Declaration of Helsinki, 2014.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Data Availability Statement

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

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Alcohol Consumption Post-Liver Transplantation: A Cross-Sectional Study

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Keywords
Alcoholism · Relapse · Recidivism · Liver transplant

Abstract

Background: Listing patients with alcohol-associated liver disease (ALD) for liver transplant (LT) remains challenging especially due to the risk of alcohol resumption post-LT. We aimed to evaluate post-LT alcohol consumption at a Portuguese transplant center. ***Methods:*** We conducted a cross-sectional study including LT recipients from 2019 at Curry Cabral Hospital, Lisbon, Portugal. A pretested survey and a validated Portuguese translation of the Alcohol Use Disorder Identification Test (AUDIT) were applied via a telephone call. Alcohol consumption was defined by patients' self-reports or a positive AUDIT. ***Results:*** In 2019, 122 patients underwent LT, and 99 patients answered the survey (June 2021). The mean (SD) age was 57 (10) years, 70 patients (70.7%) were males, and 49 (49.5%) underwent ALD-related LT. During a median (IQR) follow-up of 24 (20–26) months post-index LT, 22 (22.2%) recipients consumed any amount of alcohol: 14 had a drink monthly or less and 8 drank 2–4 times/month. On drinking days, 18 patients usually consumed 1–2 drinks and the remainder no more than 3–4 drinks. One patient reported having drunk ≥6 drinks on one occasion. All post-LT drinking recipients were considered low risk (score <8) as per the AUDIT score (median [IQR] of 1 [1–2]). No patient reported alcohol-related problems, whether self-inflicted or toward others. Drinking recipients were younger (53 vs. 59 years, $p = 0.020$), had more non-ALD-related LT (72.7 vs. 44.2%, $p = 0.018$) and active smoking (31.8 vs. 10.4%, $p = 0.037$) than abstinent ones. ***Conclusion:*** In our cohort, about a quarter of LT recipients consumed alcohol early posttransplant, all with a low-risk pattern according to the AUDIT score.

Consumo de álcool pós-transplante hepático: um estudo transversal

Palavras Chave
Alcoolismo · Recaída · Recidiva · Transplante hepático

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Resumo

Introdução: Incluir doentes com doença hepática associada ao álcool (DHA) em lista ativa de transplante hepático (TH) é desafiante, especialmente pelo risco de recidiva de consumo de álcool pós-TH. O objetivo foi avaliar o consumo de álcool pós-TH num centro de transplantação português. ***Métodos:*** Realizamos um estudo transversal incluindo doentes submetidos a TH em 2019 no Hospital Curry Cabral, Lisboa, Portugal. Foi realizado um questionário previamente testado e uma tradução validada para o português do *Alcohol Use Disorder Identification Test* (AUDIT), através de uma chamada telefónica. O consumo de álcool foi definido pelo autorrelato do doente ou por um AUDIT positivo. ***Resultados:*** Durante 2019, 122 doentes foram submetidos a TH e 99 responderam ao questionário (junho de 2021). A idade média (SD) foi de 57 (10) anos, 70 doentes (70,7%) eram do sexo masculino e 49 (49,5%) foram submetidos a TH relacionado com DHA. Com uma mediana (IQR) de *follow-up* de 24 (20–26) meses após o TH-índex, 22 (22,2%) doentes admitiram algum consumo de álcool: 14 beberam mensalmente ou menos e oito beberam 2–4 vezes/mês. Nos dias em que bebiam, 18 consumiam normalmente 1–2 bebidas e os restantes não mais do que 3–4 bebidas. Um doente reportou o consumo de ≥6 bebidas em uma ocasião. Todos os doentes transplantados com consumo alcoólico pós-TH foram considerados de baixo risco (pontuação <8) de acordo com o AUDIT (mediana [IQR] de 1 [1–2]). Nenhum doente reportou problemas relacionados com o álcool, tanto autoinfligido como a terceiros. Os indivíduos transplantados com consumo alcoólico eram mais jovens (53 vs. 59 anos, $p = 0{,}020$), o motivo de TH era mais frequentemente não relacionado com DHA (72,7 vs. 44,2%, $p = 0{,}018$) e apresentavam mais tabagismo ativo (31,8 vs. 10,4%, $p = 0{,}037$) quando comparado com os abstinentes. ***Conclusão:*** Na nossa coorte, cerca de um quarto dos doentes transplantados hepáticos consumiram álcool no período pós-transplante precoce, todos com um padrão de baixo risco, de acordo com o AUDIT.

Introduction

Alcohol use disorder is one of the most common causes of cirrhosis in the world, affecting around 10% of the general population in both the USA and Europe [1, 2]. Alcohol-associated liver disease (ALD) is one of the leading causes of liver transplant (LT), currently representing the second indication for LT in Europe [3]. However, the overall access of patients with ALD to liver transplantation remains low [3].

Alcohol relapse after LT has been reported in 7–95% of individuals, with harmful drinking reported to be between 10 and 26% [4–8]. This broad range is mainly due to the lack of standardized definitions for alcohol consumption post-LT [4–6]. There are known risk factors associated with alcohol relapse after LT, being the most consistently proven younger age, active smoking, poor social support, unemployment, and a family environment with alcohol use [9–16]. Resumed alcohol consumption post-LT has been associated with accelerated cirrhosis development and lower graft and patient survival rates [10, 17–20].

Several scores have been used to access the risk of alcohol resumption after LT, for example, the Alcohol Relapse Risk Assessment, the High-Risk Alcoholism Relapse, and the Sustained Alcohol Use Post-LT scores [20–22]. However, challenges remain in predicting alcohol use following LT based on pre-LT characteristics [23].

The Alcohol Use Disorders Inventory Test (AUDIT) was developed by the World Health Organization (WHO) decades ago, and it has been proven to have good sensitivity and specificity as a screening tool to detect hazardous alcohol drinking in diverse clinical settings across different countries [24, 25]. The AUDIT includes 10 questions that explore alcohol consumption (questions 1–3; also called the AUDIT-Consumption [AUDIT-C]), drinking behavior (questions 4–6), and alcohol-related problems (questions 7–10). Although the AUDIT or AUDIT-C were not designed to specifically assess alcohol use post-LT, they have been used in several studies in the post-LT setting [26–28].

Most reports have only analyzed alcohol consumption in ALD-related LT recipients resulting in limited data regarding alcohol consumption in non-ALD-related patients. A few studies reported similar overall alcohol use rates between ALD-related and non-ALD-related LT patients [29, 30]. Nevertheless, ALD-related LT recipients tended to drink in greater quantities than non-ALD-related ones [29, 30].

Accordingly, we hypothesized that alcohol consumption following LT would be frequent but non-severe in our cohort [1, 4–6]. Therefore, the objectives of our study were the following: (1) to assess the prevalence of alcohol use post-LT based on the AUDIT score in a Portuguese sample of LT recipients and (2) to try to further characterize patients that more likely drank alcohol following LT.

Materials and Methods

Ethics

The study was approved by the Ethics Committee at Central Lisbon University Hospital Center (CHULC), and it was performed in accordance with the Declaration of Helsinki [31]. Participation in this study was voluntary, and all patients provided consent before enrollment. The reporting of this study followed the Strobe statement [32].

Study Design, Setting, and Participants

We conducted a cross-sectional study including all patients who underwent LT between January and December 2019 at Curry Cabral Hospital (CCH), CHULC, Lisbon, Portugal. Patients who had died, were not within reach by telephone or other means of contact, or who declined to participate in the interview were excluded.

Survey Development and Implementation

The survey content was based on the up-to-date literature about alcohol consumption post-LT and comprised questions on demography (date of birth and sex), liver transplantation (etiology and date of index LT, i.e., the first transplant in 2019), actual employment, marital status, actual smoking status, alcohol consumption of housemates, and a validated Portuguese translation of the AUDIT (online suppl. File 1; for all online suppl. material, see www.karger.com/doi/10.1159/000525808) [33]. All closed-model questions were given specific options for answers.

The survey was reviewed by the authors and underwent pilot testing in the Transplant Unit at CCH to assess comprehension, feasibility, redundancy, and consistency. Necessary changes were made, and surveys were conducted via a telephone call between 8 and 14 June 2021, by 2 senior gastroenterology residents (C.F. and C.C.R.). One patient was an English native speaker and answered the original AUDIT. All the other patients were native Portuguese speakers and answered the translated version of the AUDIT.

Operational Definitions and Endpoints

LT etiology was defined according to the patients' medical charts. Diagnosis of ALD was based on a history of alcohol consumption, along with compatible clinical, laboratory, or histological findings. At our center, ALD-related LT recipients generally had a minimum of 6 months of alcohol abstinence before LT and a commitment to a lifelong alcohol abstinent behavior. All LT recipients had a favorable psychological or psychiatric evaluation, with screening for any substance abuse disorder. At our center, no LT was performed due to alcoholic hepatitis in 2019 [34].

Employment was defined as working or non-working (the latter including unemployed or retired patients and patients on sick leave). Marital status was defined as married (including cohabiting unmarried couples) or non-married. Alcohol consumption of housemates was defined as yes or no, whether they consumed or not any amount of alcohol, respectively.

The Portuguese AUDIT application targeted only the post-LT period. We defined alcohol consumption (drinking vs. nondrinking recipients) by the patients' positive AUDIT response to question 1: "How often do you have a drink containing alcohol"? The AUDIT was also used to characterize the pattern of alcohol consumption. The total AUDIT score (0–40) was calculated based on participants' responses and classified as low risk (<8), low or moderate risk (8–15), moderate or high risk (16–19), or high risk (20–40) [35]. The length of follow-up was calculated from the date of index LT until the date of the survey implementation. The primary endpoint was any alcohol use following index LT.

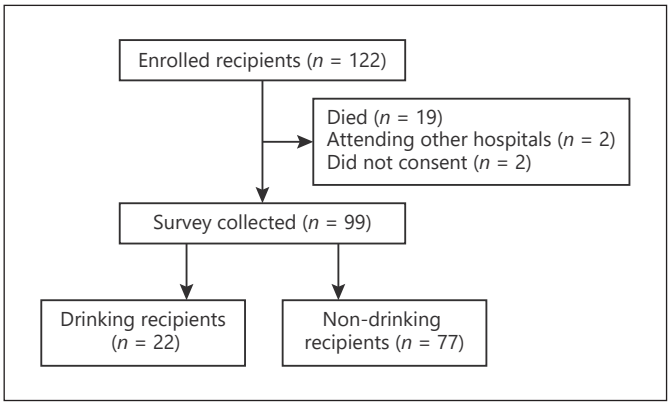

Fig. 1. Flowchart of patients' selection.

Statistical Analysis

Categorical variables were presented as frequencies and percentages, whereas continuous variables as mean and standard deviation (SD), for normal distribution, or median and interquartile range (IQR), for non-normal distribution. No missing data were found, so no imputation was performed.

Continuous variables were compared using Student's t or Mann-Whitney tests, whereas categorical variables were compared using χ^2 or Fisher's exact tests, as appropriate. Multivariable analysis was performed using logistic regression. Variables clinically and statistically significant on univariable comparisons were included in this analysis. Final models were selected based on a backward stepwise approach.

A p value of 0.05 indicated statistical significance (2-tailed). Analyses were performed with SPSS software, version 23 (IBM Corp., Armonk, NY, USA).

Results

Baseline Characteristics

In 2019, 122 patients who received an orthotopic LT at CCH were considered. After the exclusion of recipients who had died (n = 19) or were followed up at an institution abroad (n = 2), a total of 101 patients were asked to participate in the study. Among these 101 patients, only 99 (81.1% of all) patients freely agreed to participate in the telephone interview and were therefore included in the study (shown in Fig. 1).

Overall, the mean (SD) age was 57 (10) years, and 70 (70.7%) patients were males. Forty-nine (49.5%) patients

Table 1. Baseline characteristics

Characteristics	Recipients (*n* = 99)
Male sex, *n* (%)	70 (70.7)
Age, mean (SD), years	57 (10)
Duration after index LT, median (IQR), months	24 (20–26)
Etiology and indication for index LT, *n* (%)	
ALD	28 (28.4)
ALD and HCV	18 (18.2)
HCV	4 (4.0)
HBV	4 (4.0)
AIH	3 (3.0)
PBC/PSC	5 (5.1)
FAP	6 (6.1)
Acute liver failure	4 (4.0)
Cryptogenic	2 (2.0)
NASH	3 (3.0)
Retransplant	12 (12.1)
Others	10 (10.1)
Patients with hepatocellular carcinoma, *n* (%)	37 (37.4)
Married, *n* (%)	71 (71.7)
Working, *n* (%)	34 (34.3)
Active smoking, *n* (%)	15 (15.2)
Housemate alcohol consumption, *n* (%)	28 (28.3)

SD, standard deviation; LT, liver transplant; IQR, interquartile range; ALD, alcohol-associated liver disease; HCV, hepatitis C virus; HBV, hepatitis B virus; AIH, autoimmune hepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; FAP, familial amyloid polyneuropathy; NASH, nonalcoholic steatohepatitis.

underwent ALD-related LT, and 12 (12.1%) index LT procedures were retransplants (3 originally transplanted due to ALD). Median (IQR) follow-up time after index LT was 24 (20–26) months (minimum of 18 months). All baseline characteristics are summarized in Table 1.

Characterization of Alcohol Consumption Post-LT

Among all responders (*n* = 99), alcohol consumption after LT was reported in 22 (22.2%) recipients. Of these, 6 (6.1%) had ALD-related LT and 16 (16.2%) did not have ALD prior to LT. Regarding the patterns of alcohol consumption post-LT, 14 (14.1%) patients had a drink monthly or less and 8 (8.1%) drank 2 to 4 times a month. On a typical drinking day, 18 (18.2%) patients described consuming one or 2 drinks and the remainder no more than 3 or 4 drinks. One (1.0%) patient reported having drunk at least 6 drinks on one occasion. When asked about the type of alcoholic beverage usually consumed, 12 (12.1%) patients reported wine consumption preferably, 9 (9.1%) beer, and one (1.0%) liquor instead. No patients reported alcohol-related injuries whether self or toward others. All post-LT drinking recipients were considered low risk (score <8) as per AUDIT score (median [IQR] of 1 [1–2] and maximum of 4). All drinking recipients with ALD-related LT reported that they drank less after LT.

Risk Factors for Alcohol Consumption Post-LT: Study of Associations

Younger age (53 vs. 59 years, p = 0.020), non-ALD-related LT (72.7 vs. 44.2%, p = 0.018), and active smoking (31.8 vs. 10.4%, p = 0.037) were all significantly more prevalent in drinking LT recipients than in abstinent ones (Table 2). Male sex (72.7 vs. 70.1%), married status (72.7 vs. 71.4%), working status (45.5 vs. 31.2%), and living with a housemate who consumed alcohol (40.9 vs. 24.7%) were all more common in drinking LT recipients than in abstinent ones, but those differences did not reach statistical significance. Among drinking LT recipients, the median (IQR) AUDIT score was similar between ALD-related LT and non-ALD-related LT (1 vs. 1, p = 0.914).

To avoid overfitting the models, we included up to 3 variables in the final models of the multivariable analysis (Table 3). Using logistic regression, while ALD-related LT was associated with lower odds of alcohol intake post-LT (adjusted odds ratio [aOR] [95% CI] 0.17 [0.04–0.72]), active smoking was associated with higher odds of alcohol use following transplant (aOR [95% CI] 8.12 [1.72–38.24]).

Discussion

Main Findings and Comparisons with Previous Studies

The main finding of our cross-sectional study was that less than a quarter of LT recipients consumed alcohol following a median of 2 years after transplant. Additionally, all drinkers post-LT had a low-risk pattern as per AUDIT. Finally, alcohol consumption was more prevalent in patients transplanted for non-ALD than those who had ALD prior to LT. In fact, ALD-related LT was independently associated with lower odds of drinking alcohol following transplant.

Up to 2 years after LT, alcohol consumption in our cohort was within the range described in the literature [11, 23]. However, when considering heavy alcohol consumption, according to the AUDIT-C score, we found a lower relapse rate than previously reported. Actually, we found no heavy alcohol consumption after LT (median AUDIT score of 1). This finding is especially important as it has been established that the higher the quantity of alcohol

Table 2. Baseline characteristics stratified by drinking behavior following liver transplant

Characteristics	Drinking recipients (*n* = 22)	Nondrinking recipients (*n* = 77)	*p* value
Male sex, *n* (%)	16 (72.7)	54 (70.1)	0.813
Age, mean (SD), years	53±12	59±10	0.020
ALD-related LT, *n* (%)	6 (27.3)	43 (55.8)	0.018
Married, *n* (%)	16 (72.7)	55 (71.4)	0.905
Working, *n* (%)	10 (45.5)	24 (31.2)	0.213
Active smoking, *n* (%)	7 (31.8)	8 (10.4)	0.037
Housemate alcohol consumption, *n* (%)	9 (40.9)	19 (24.7)	0.136

SD, standard deviation; ALD, alcohol-associated liver disease; LT, liver transplant.

Table 3. Multivariable analysis for the study of the associations between baseline characteristics and drinking following liver transplant

Characteristics	Adjusted odds ratio	95% confidence interval	*p* value
Age, mean (SD), years	0.99	0.94–1.04	0.597
ALD-related LT, *n* (%)	0.17	0.04–0.72	0.016
Active smoking, *n* (%)	8.12	1.72–38.24	0.008

N included = 99, *N* events = 22, χ^2 test = 16, $p = 0.001$. SD, standard deviation; ALD, alcohol-associated liver disease; LT, liver transplant.

consumed, the worse the effect on graft function [24, 34]. While our median follow-up time post-LT was higher than in previous studies (24 vs. 19 months), that may not be such a substantial difference, especially because it has been suggested that the longer the time since LT, the higher the alcohol consumption risk [4, 36, 37].

In our study, the most prevalent variables associated with alcohol consumption were younger age, non-ALD-related LT, and active smoking. Alcohol consumption post-LT has been reported to be more common in younger patients, much like in our cohort [13–16]. Active smoking has also been a well-established risk factor associated with alcohol consumption [11]. According to Ehlers et al. [12], those who resumed smoking after LT were 1.79 times more likely to also drink alcohol.

Interestingly, in our cohort, there was a higher prevalence of alcohol consumption in non-ALD-related LT recipients in comparison to those with previous ALD. There are few studies addressing alcohol consumption in non-ALD-related LT recipients. According to those, there seems to be similar alcohol use between these subgroups or a higher prevalence in the ALD subgroup [30, 38, 39]. A study by Faure et al. [30], wherein 46.7% of patients were transplanted with ALD as a primary indication (comparable to our cohort with ALD-related LT in 49.5%), showed that among the drinking patients after LT, 57.6% of those had non-ALD as the primary indication for transplant but with previous excessive alcohol consumption. In the present study, we did not address previous excessive alcohol consumption, irrespective of LT indication.

In our study, there was no quantification of alcohol consumption before LT. After LT, only qualitative categories from AUDIT were used. Moreover, there seems to be an underestimation of the drinking behavior prior to LT in patients diagnosed with liver diseases other than ALD [40]. Using a screening protocol, Ursic-Bedoya et al. [40] identified, in a timeframe of 6 years, that 72% of the LT candidates experienced excessive alcohol use at some time in their life and only 40% of them were labeled as ALD as the primary indication.

In Portugal, alcohol has been the psychoactive substance with the highest experimental prevalence of consumption, estimated as 86.4% of the general population at any time during life according to a 2017 report [41]. In Portugal, alcohol consumption is generally socially accepted, affordable, and easily accessible, which has led to an onset of alcohol consumption at progressively younger ages [42]. Such wide availability of alcohol remains a challenge in the management of all post-LT patients too.

In our cohort, all drinking recipients with ALD-related LT reported that they drank less after LT. This finding is in line with other studies suggesting that a substantial reduction in alcohol intake following LT may be a relevant endpoint, besides total abstinence. Such reduction in alcohol consumption has been associated with a decrease in overall morbidity, mortality, and health costs, and an improvement in psychosocial status [34].

Some limitations should be considered when interpreting our results. First, drinking behavior was self-reported, and only during the first-year post-LT therefore recall bias may have played a role. Although the questionnaire was conducted telephonically by an unfamiliar physician and confidentiality was ensured, it is known that patients tend to underreport their alcohol consumption [43]. Second, no biochemical screening tools were used to further assess alcohol intake, even if they lack often sensitivity and specificity. Third, the study included only one transplant center, thus caution should be taken when extrapolating these results to other settings. Fourth, at our center, there was no formal surveillance protocol to assess the risk of alcohol intake post-LT, and no addiction experts to help us monitor that risk. Therefore, alcohol intake could have gone unnoticed and underreported in medical charts.

Despite these limitations, we think that our study adds to the literature as it reports on the prevalence and severity of alcohol use post-LT, based on an easy-to-use and widely accepted validated tool (AUDIT), and using a reasonably large cohort from Portugal. Moreover, it describes possible characteristics that clinicians may need to consider as possible drivers of the risk of alcohol resumption post-LT. Finally, these data raised awareness of the need of taking detailed alcohol use history, irrespective of LT indication, and to adopt a standardized approach to screen alcohol consumption post-LT in all patients, during each visit. This could also include scheduled formal assessments by addiction experts. Future large and multicenter studies, with further tools for alcohol intake surveillance and a longer follow-up period, are needed to improve our knowledge of the alcohol-related behavior of candidates and recipients of LT.

Conclusions

In our cohort, about a quarter of LT recipients consumed alcohol early posttransplant, all with a low-risk pattern according to the AUDIT score.

Statement of Ethics

The study was approved by the Ethics Committee at Central Lisbon University Hospital Center (CHULC), and it was performed in accordance with the Declaration of Helsinki. Participation in this study was voluntary, and all patients provided consent before enrollment.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

None to declare.

Author Contributions

C.F., C.C.R., F.S.C., and R.P. conceived the idea of the study. C.F. and C.C.R. retrieved data. C.F., C.C.R., and F.S.C. performed the statistical analysis. C.F. and C.C.R. drafted the manuscript. F.S.C. and R.P. revised extensively the manuscript. All the authors read and approved the final version of the manuscript.

Data Availability Statement

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

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Impact of Percutaneous Endoscopic Gastrostomy Tube Feeding on Nutritional Status in Patients Undergoing Chemoradiotherapy for Oesophageal Cancer

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Keywords

Nutritional status · Esophageal neoplasms · Gastrostomy · Neoadjuvant therapy

Abstract

Introduction: Oesophageal cancer causes dysphagia and weight loss. Malnutrition further worsens with multimodal treatment. ***Aim:*** The aim of the study was to evaluate the impact of percutaneous endoscopic gastrostomy (PEG) placement in the nutritional status of patients with oesophageal cancer requiring chemoradiotherapy (CRT). ***Methods:*** A comparative study with a prospective arm and a historical cohort was conducted. Oesophageal cancer patients undergoing CRT with dysphagia grade >2 and/or weight loss >10% were submitted to PEG-tube placement (pull method) before CRT. Stoma seeding was evaluated through a swab obtained after placement and, in surgical patients, the resected stoma. A matched historical cohort without PEG placement was used as control (trial ACTRN12616000697482). ***Results:*** Twenty-nine patients (intervention group, IG) were compared to 30 patients (control group, CG). Main outcomes did not differ in the IG and CG: weight loss during CRT 8.1 ± 5.5 kg versus 9.1 ± 4.2 kg ($p = 0.503$); 6-month mortality after CRT or surgery 17.2% versus 26.7% ($p = 0.383$); perioperative complication rate 54.5% versus 55.6% ($p = 1.000$); unplanned hospital admissions 34.5% versus 40.0% ($p = 0.661$). In the CG, during CRT, 14 (46.7%) patients presented with dysphagia grade 3–4, of whom 12 required nasogastric tube feeding ($n = 10$), surgical gastrostomy ($n = 1$), and oesophageal dilation ($n = 1$). In the IG, 89.7% used the PEG tube during CRT, sometimes exclusively in 51.7%. Adverse events were mainly minor ($n = 12$, 41.4%), mostly late peristomal infections, 1 major complication (exploratory laparotomy due to suspected colonic interposition, not confirmed). There was no cytological or histological evidence of stomal tumour seeding. ***Conclusion:*** Weight loss, hospital admissions, surgical complications, and mortality were identical in oesophageal cancer patients referred for CRT, regardless of prophylactic PEG. However, half of the patients required exclusive enteral nutritional support, making PEG-tube placement an alternative to consider.

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Impacto da colocação de gastrostomia percutânea endoscópica (PEG) no status nutricional de doentes submetidos a quimiorradioterapia para cancro do esófago

Palavras Chave
Estado nutricional · Neoplasia do esófago · Gastrostomia · Terapêuica neoadjuvante

Resumo
Introdução: A neoplasia do esófago associa-se a disfagia e perda ponderal, sendo a desnutrição agravada pelo tratamento multimodal. ***Objetivo:*** Avaliar o impacto da colocação de gastrostomia percutânea endoscópica (PEG) no estado nutricional de doentes com neoplasia do esófago propostos para quimiorradioterapia (QRT). ***Métodos:*** Estudo comparativo com braço prospetivo e controlo retrospetivo. Incluídos doentes com neoplasia do esófago propostos para QRT definitiva ou neoadjuvante, com disfagia grau >2 e/ou perda de peso >10%. Colocada PEG (método *pull*) antes do início de QRT. Avaliada sementeira tumoral por zaragatoa e histologia. Como controlo, utilizada coorte histórica de doentes sem PEG. Registo ACTRN12616000697482. ***Resultados:*** 29 doentes (grupo intervenção, GI) foram comparados com 30 controlos (GC). Sem diferença significativa nos principais *outcomes*: perda de peso durante a QRT 8.1 ± 5.5 kg versus 9.1 ± 4.2 kg ($p = 0.503$); mortalidade aos 6 meses após QRT ou cirurgia 17.2% versus 26.7% ($p = 0.383$); taxa de complicações perioperatórias 54.5% versus 55.6% ($p = 1.000$); admissões hospitalares não planeadas 34.5% versus 40.0% ($p = 0.661$). No GC, durante a QRT, 14 (46.7%) apresentaram disfagia graus 3–4, dos quais 12 necessitaram de nutrição por sonda nasogástrica ($n = 10$), gastrostomia cirúrgica ($n = 1$) ou dilatação esofágica ($n = 1$). No GI, 89.7% utilizaram a PEG durante QRT, em algum momento de forma exclusiva em 51.7%. Os eventos adversos foram sobretudo *minor* ($n = 12$; 41.4%), sobretudo infeções tardias peri-estoma; 1 complicação *major* (laparotomia exploradora por suspeita de interposição de cólon, não confirmada). Sem evidência citológica ou histológica de sementeira tumoral no estoma. ***Conclusão:*** Embora não se tenham observado diferenças na perda de peso, complicações cirúrgicas e mortalidade entre grupos, metade dos utentes necessitou de nutrição entérica exclusiva, tornando a colocação de PEG uma alternativa a considerar.

Introduction

Oesophageal cancer is the seventh most incident globally and the sixth in terms of mortality, with a mortality/incidence ratio of 0.89 [1]. It belongs to the cancer types with the highest risk for weight loss and malnutrition [2] and nutritional status is expected to further worsen with multimodal treatment [3]. In fact, nutritional intervention may lead to an improved treatment tolerance for patients receiving chemoradiation [3], while those who experience severe preoperative weight loss face a higher 5-year mortality rate after oesophagectomy [4].

Nutritional risk in these patients can potentially be ameliorated by the placement of a percutaneous endoscopic gastrostomy (PEG) tube. Some studies, most of them retrospective, have evaluated the benefits of PEG-tube placement in oesophageal cancer patients before multimodal treatments. Although some demonstrated better nutritional management in these cases, most had equal results in terms of perioperative complications, tolerance to chemoradiotherapy (CRT), and overall survival [3, 5–8]. Additional concerns regarding PEG-tube placement are the risk of tumour cells seeding in the stoma and affecting gastric vascularization, thereby precluding surgeons from using a gastric conduit after oesophagectomy, which is the reason why international guidelines so far advise against percutaneous gastrostomy in surgical patients [9]. Nevertheless, evidence suggests that these are rare events [5, 7, 8, 10].

Comparing PEG with other nutritional methods, it is less invasive and is associated with lower complication rates than jejunostomy [11]. Nasogastric tubes usually have lower functional and aesthetical tolerability in mid to long term [12] and, regarding endoscopic stents, although effective in improving dysphagia, it has not been demonstrated that these are effective in improving nutritional status [13–16] and may even be associated with a high complication rate [17].

The primary goal of this study was to assess the impact of PEG-tube placement on the nutritional status of patients with oesophageal cancer requiring definitive or neoadjuvant CRT. Secondary outcomes were (i) to evaluate procedure safety; (ii) to assess feasibility of oesophagectomy with a gastric conduit in these patients; (iii) to assess the risk of stoma tumour seeding.

Materials and Methods

A comparative study with a prospective arm (2016–2020) and a retrospective historical control cohort (2008–2010) was conducted in a Portuguese oncological centre.

Population

Patients aged 18 or higher with oesophageal cancer (squamous cell carcinoma or adenocarcinoma) or oesophageal-gastric junction cancer Siewert I (adenocarcinoma) with dysphagia grade >2 and/or weight loss >10% of body weight requiring isolated or neoadjuvant CRT were proposed for PEG-tube placement on a weekly multidisciplinary meeting, prior to the onset of therapeutic protocol (1–3 weeks before CRT, based on the clinical discretion of the treating physicians). Exclusion criteria included contraindication to PEG-tube placement (such as incapacity of handling the PEG tube, decompensated chronic liver disease, or presence of ascites with a clinical significance).

The study protocol was approved by the hospital's Ethical Committee (*Unidade de Investigação Clínica*) with the approval number UI/1011 and registered in the Australian New Zealand Clinical Trials Registry platform with the trial number ACTRN12616000697482. All patients provided written and oral informed consent to participate in the study and for publication of the results at least 48 h before the procedure.

The control group (CG) was a historical cohort of patients with the same characteristics (grade of dysphagia, weight loss, treatment with CRT) from existing records of oesophageal/oesophageal-gastric junction cancer patients, with first evaluation from January 2008 until December 2010. They were selected orderly starting with the most recent, in order to prevent selection bias, regardless of nutritional interventions during follow-up. No records were excluded.

Sample Size Calculation

Since this was a pilot study, there were no data available on the likelihood of finding positive results, so, according to the central limit theory which states that the sample distribution will be normal or almost normal if the sample size is large enough, generally assuming that a sample size of 30 is considered appropriate, it was assumed that it would be necessary to include 30 patients in the study.

PEG-Tube Placement Procedure

The PEG tube was placed by two gastroenterologists using the pull method, with antibiotic prophylaxis with intravenous cefazoline (2 g) administered immediately before the procedure. Standard gastroscopes were used (Olympus series 165 or 190). If the oesophageal tumour caused an unsurpassable stenosis with the endoscope with the smallest diameter available (ultra-thin endoscopes were available only in the second half of the study period), an oesophageal dilation was also performed by an experienced gastroenterologist, using a Savary-Gilliard® dilator (9 mm) or a hydrostatic balloon (10 mm). After PEG insertion, a peri-stoma swab was collected, with subsequent cytopathological evaluation. After the procedure, the patient was hospitalized for surveillance for 24 h and started enteral bolus 3 h post-procedure, if no complications occurred. Throughout the course of treatment, the patient could maintain oral diet in addition to enteral nutrition. A nutritional plan was established by a dietitian. In patients undergoing oesophagectomy, the PEG tube was removed during surgery and the peristoma tissue was sent for histopathological evaluation by a pathologist with expertise in digestive pathology. In non-surgical patients, the PEG was removed at the end of the treatment if oral nutrition was possible.

Chemoradiotherapy

According to the institution's protocol, T2–4 or N+ patients unfit for surgery, T3–T4a or N+ patients with conditions for surgery, and any patient with cervical oesophageal cancer undergo CRT with two cycles of 5-FU combined with cisplatin and radiotherapy (50.4 Gy), which may be personalized by the attending oncologist. These patients are re-staged after 4–6 weeks and the final decision to undergo surgery or proceed to definitive CRT is made.

Follow-Up

Nutritional outcomes, surgical complications, urgent hospital admissions, and any complication related to the PEG were registered. Nutritional status was evaluated using body mass index (kg/m^2). According to the hospital's protocol for oesophageal cancer patients, they have a first nutritional evaluation by the dietitian at diagnosis, at least twice during CRT (more often in case of increased nutritional risk), and after treatments. These records were used for the CG and were complement by medical records whenever necessary, since weight and dysphagia were systematically documented in the Oncology appointments, which occur every 2 weeks during CRT. In the intervention group (IG), patients' weight was also registered by a Gastroenterology Nurse (see later) every 2 weeks before CRT, weekly thereafter, at weeks 2 and 4 after CRT, and 1 month after surgery.

PEG-related complications were assessed according to type of complication, approach and severity (medical – minor, endoscopic or surgical – major adverse events [AEs]), and time (immediate – until 24 h after procedure, early – less than 7 days, late – 7 days or later). All the records were made by a nurse with more than 5 years of experience in the management of patients with gastrostomies. Follow-up was completed 6 months after surgery or definitive CRT.

Statistical Analysis

For statistical analysis, SPSS Statistics 26 (IBM) was used. Demographic and clinical characteristics were presented as frequencies. Continuous variables were expressed as average and standard deviation or as median and interquartile range, according to data distribution, and were compared using *t*-Student or Wilcoxon tests, respectively. Qualitative variables were compared using χ^2 or Fisher exact tests. A p value lower than 0.05 was considered statistically significant.

Results

Forty-seven patients were considered for the trial, of which 29 were included (IG) (Fig. 1). The initial goal of 30 patients was not achieved because of the time allocated for the study. These were compared to 30 patients from the historic cohort (CG). Both groups were similar re-

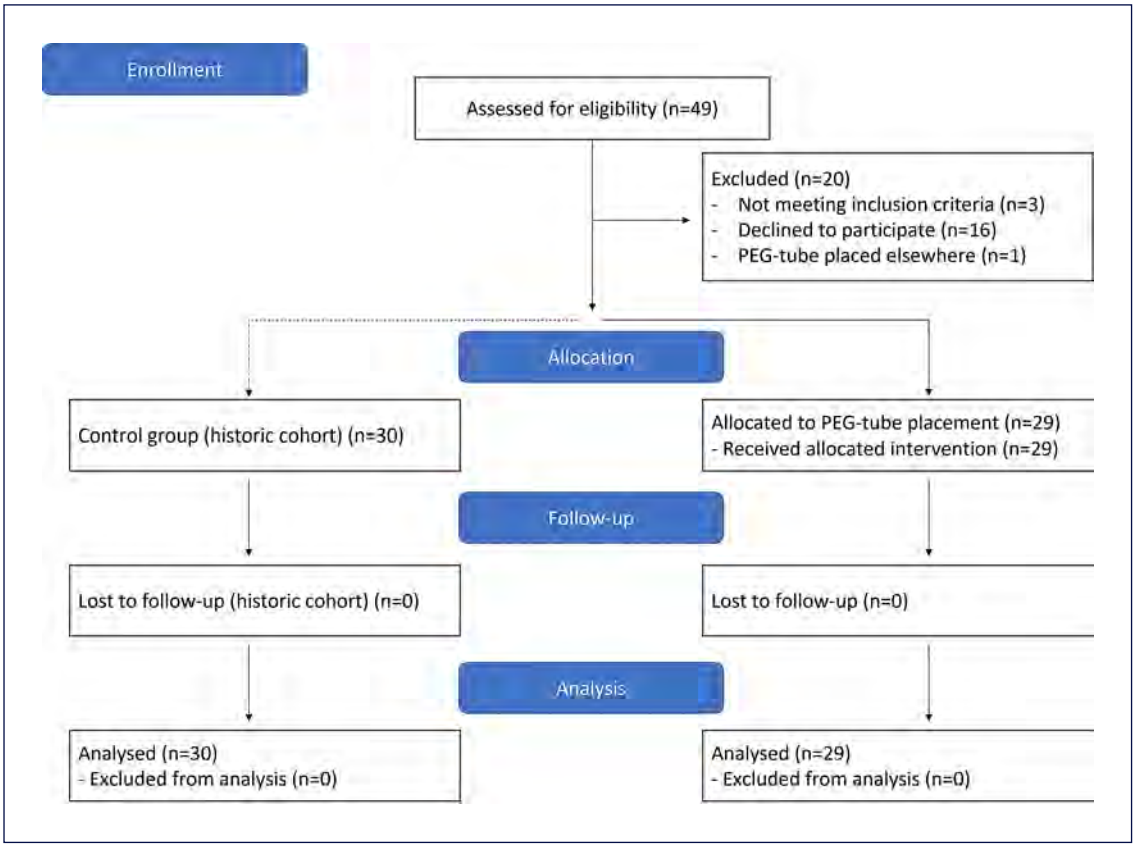

Fig. 1. Schematic representation of eligible patients.

garding demographic and clinical characteristics at baseline. In the IG and in the CG, there were mainly males, aged above 60 years old, with significant past or active alcoholic habits. The most common diagnosis was squamous cell carcinoma, frequently diagnosed in advanced stages. A weight loss higher than 10% was frequently found and dysphagia grade at diagnosis was higher than 2 in over a third of the cases. Table 1 describes patients' characteristics in detail.

In the CG, before CRT, 10 (33.3%) patients required oesophageal dilation and 2 (6.7%) enteral feeding by the nasogastric tube. During CRT, 14 (46.7%) patients presented with dysphagia grades 3 or 4, 12 of them with the need of additional nutritional therapy: nasogastric tube feeding (n = 10), surgical gastrostomy (n = 1), and oesophageal dilation (n = 1).

In the IG, PEG-tube placement success rate was 100%. Pre-procedural oesophageal dilation was necessary in 11 patients (37.9%). 89.3% patients used the PEG tube during CRT, exclusively at some point in 50%. The procedure was mainly associated with minor AEs (n = 12, 42.9%) and 1 major (exploratory laparotomy due to suspected colonic interposition, not confirmed). Minor AEs were managed conservatively and included bleeding (n = 2, 6.9%), which occurred in the first 24 h after procedure and peristomal infection (n = 10, 34.5%) which was diagnosed early (24 h to 7 days) after procedure in 3 patients and later in 7 cases. In those who underwent surgery (n = 12), technical success was not affected by PEG and it did not influence the type of surgery nor implied the use of colon as a conduit after oesophagectomy. There was no evidence of cytological or histological evidence of tumour seeding in the stoma.

After initial staging, neoadjuvant CRT was proposed to 55.2% (n = 16) of the IG and 60.0% (n = 18) of the CG (p = 0.708), but the strategy was changed to definitive CRT in 4 patients of the IG and 8 of the CG (Table 2). This was due to other comorbidities (IG, n = 2; CG, n = 1), disease progression (IG, n = 2; CG, n = 6), and patient's choice (CG, n = 1). Body mass index variation during CRT was similar between groups (median and IQR in the IG: −2.6 [−4.4, −1.7] and in the CG: −1.9 [−3.2, −0.9], p =

Table 1. Patients' characteristics at baseline

	IG (n = 29)	CG (n = 30)	p value
Male sex, n (%)	28 (96.6)	27 (90.0)	0.612
Age, mean ± SD (min–max), years	65.38±8.60 (50–79)	61.94±9.79 (40–78)	0.158
Alcohol, n (%)	28 (96.6)	25 (83.4)	
Past habits	19 (65.5)	5 (16.7)	0.195
Current habits	9 (31.0)	20 (66.7)	
Tobacco, n (%)	22 (75.8)	25 (83.4)	
Past habits	15 (51.7)	11 (36.7)	0.476
Current habits	7 (24.1)	14 (46.7)	
Squamous cell carcinoma, n (%)	26 (89.7)	24 (80.0)	0.216
Stage III–IV (AJCC 8th edition), n (%)	22 (75.9)	23 (76.7)	0.582
Location, n (%)			
Cervical oesophagus	10 (34.5)	3 (10.0)	
Upper thoracic oesophagus	1 (3.4)	5 (16.7)	
Mid thoracic oesophagus	10 (34.5)	13 (43.3)	0.115
Lower oesophagus	6 (20.7)	8 (26.7)	
Gastroesophageal junction	2 (6.9)	1 (3.3)	
Dysphagia at diagnosis, n (%)			
No dysphagia	1 (3.4)	0	
Grade 1/2	19 (65.5)	19 (63.3)	0.064
Grade 3/4	9 (31.0)	11 (36.6)	
BMI at diagnosis, mean ± SD (min–max), kg/m^2	22.1±3.9 (16.0–30.8)	22.2±4.2 (15.3–31.6)	0.918
Weight loss at diagnosis, mean ± SD, kg	−8.1±5.5 (11.54±7.72%)	−9.1±4.2 (12.69±5.09%)	0.503
BMI variation at diagnosis, mean ± SD, kg/m^2	−3.0±1.9	−3.2±0.4	0.332

Table 2. Treatment modalities

	IG (n = 29)	CG (n = 30)	p value
Treatment modality performed, n (%)			
Neoadjuvant CRT	12 (41.4)	10 (33.3)	0.523
Definitive CRT	17 (58.6)	20 (66.7)	
Type of surgery, n (%)			
Mckeown oesophagectomy	4 (33.3)	6 (60.0)	
Ivor Lewis oesophagectomy	8 (27.6)	2 (20.0)	0.099
Transhiatal oesophagectomy	0	2 (20.0)	

0.292) (Fig. 2), as were 6-month mortality after surgery or CRT (IG 17.2% and CG 26.7%, p = 0.383), perioperative complications (IG 54.5% and CG 55.6%, p = 1.000), and unplanned hospital admissions (IG 34.5% and CG 40.0%, p = 0.661) (Table 3).

In the univariate analysis, significant weight loss during CRT, defined as a weight loss of at least 10% during this period, was not associated with age (p = 0.302), alcohol (p = 0.851) or tobacco (p = 0.627) consumption, weight loss at diagnosis (p = 0.543), histological type (p = 0.803), tumour grade (p = 0.812), stage (p = 0.572), dysphagia grade at diagnosis (p = 0.255) or during CRT (p = 0.097). Similarly, unplanned hospital admission did not show a significant association with these variables (Table 4).

Discussion/Conclusion

In patients with oesophageal cancer treated with definitive or adjuvant CRT, prophylactic PEG-tube placement did not improve the most relevant clinical outcomes, namely, weight loss during CRT, unplanned hospital admissions, surgical complications, and mortality.

Table 3. Outcomes during and after treatment

	IG (n = 29)	CG (n = 30)	p value
Weight loss during CRT, median (IQR), kg	−5.0 (−6.0, −1.5) (6.85% [2.57–10.70%])	−5.2 (−8.9, −2.0) (8.30% [3.62–13.61%])	0.289
BMI loss during CRT, kg/m^2	−2.6 (−4.4, −1.7)	−1.9 (−3.2, −0.9)	0.292
Highest grade of dysphagia during CRT, n (%)			
Grade 1/2	14 (48.3)	16 (53.3)	0.100
Grade 3/4	15 (51.7)	14 (46.7)	
Highest grade of dysphagia after CRT, n (%)			
Grade 1/2	11 (37.9)	14 (46.7)	0.953
Grade 3/4	15 (51.7)	14 (46.7)	
6-Month mortality after CRT or surgery, %	17.2 (n = 5)	26.7 (n = 8)	0.383
Perioperative complications	6/12 patients	5/10 patients	
Fistula, n (%)	2	2 (6.7)	
Anastomotic dehiscence, n (%)	1 (10.3)	0	1.000
Pneumonia/aspiration, n (%)	3 (10.3)	2 (6.7)	
Arrhythmia, n (%)	0	1 (3.3)	
Days in intensive care after surgery, median (IQR)	6.0 (4.0–8.0)	4.0 (3.0–13.8)	0.654
Unplanned hospital admissions, n (%)	10 (34.5)	12 (40.0)	0.661
Infectious complications not PEG-related or febrile neutropenia	9 (31.0)	7 (58.3)	
Dysphagia	0	4 (33.3)	0.254
Disease progression	1 (3.4)	0	
Duration, median (IQR), days	10.0 (7.3–13.8)	5.5 (4.3–15.0)	

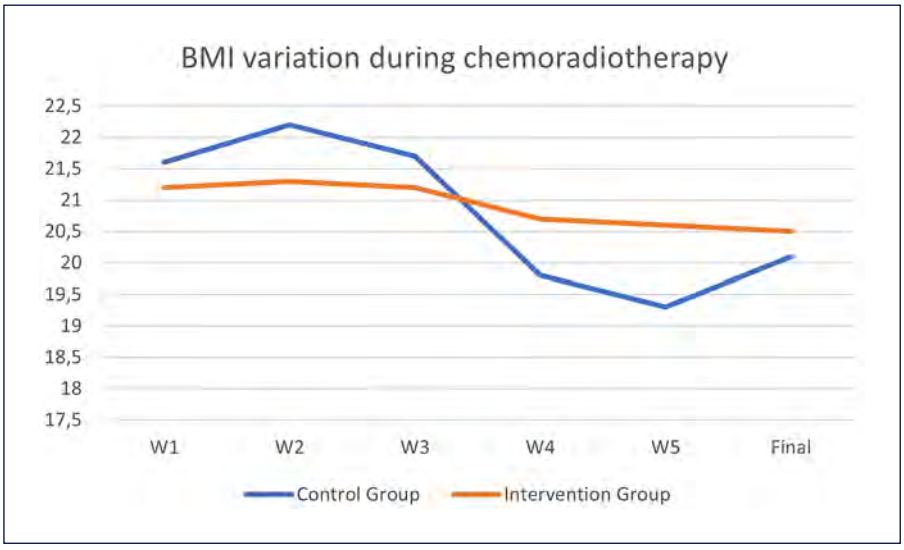

Fig. 2. Weight variation during chemoradiotherapy (CRT). *Y* axis, BMI (kg/m^2); *X* axis, week since the start of CRT.

This was in line with the findings of retrospective studies such as that of Bhatti et al. [7], as well as others with smaller samples [5, 6, 10]. Nevertheless, as depicted in Figure 2, weight variation was more pronounced in the CG, with possible metabolic implications, since weight fluctuation might be associated with an increased risk of all-cause mortality, as shown in the general population [18].

Comparing both groups, it was striking that almost half of the patients who were not submitted to PEG-tube placement before CRT required enteric nutritional support during treatment, which usually consisted of nasogastric tube feeding. On the other hand, most of the patients with prophylactic PEG used it complementarily and, in half of the cases, as an exclusive way of nutrition at some point during CRT.

Table 4. Risk factors for significant weight loss during CRT (≥10% of weight at diagnosis) and for unplanned hospital admissions (univariate/multivariate analysis)

Variable	Significant weight loss	Unplanned hospital admissions
Age	$p = 0.302$	$p = 0.848$
Weight loss at diagnosis	$p = 0.543$	$p = 0.224$
BMI at diagnosis	$p = 0.058$	$p = 0.339$
Alcohol	$p = 0.851$	$p = 0.190$
Tobacco	$p = 0.627$	$p = 0.069$
Histology	$p = 0.803$	$p = 0.409$
Tumour grade	$p = 0.812$	$p = 0.340$
Tumour stage	$p = 0.572$	$p = 0.488$
Dysphagia at diagnosis	$p = 0.255$	$p = 0.167$
Dysphagia during CRT	$p = 0.097$	$p = 0.596$
Treatment modality (isolated or neoadjuvant CRT)	$p = 0.408$	$p = 0.098$

PEG-tube placement was a feasible procedure, with minor AEs in around 40% of the cases, mostly late peristomal infections. However, 1 patient needed an exploratory laparotomy because colonic interposition was suspected but not confirmed. Infectious complications are already known to be the most common PEG-associated AEs [19, 20]. Zopf et al. [19] conducted a prospective multicentre study including 390 patients, where 33.6% had peristomal infection and the presence of malignant disease had a significant association with this risk, which may explain our findings. This complication rate is nonetheless higher than that reported in other studies such as that conducted by Margolis et al. [8], in which 103 patients with oesophageal cancer and PEG-tube placement were retrospectively evaluated. It is not clear whether this difference is due to technical differences, bias associated with the study type, or other reasons. Whether the high rate of peristomal infection is also attributable to the technique chosen (pull vs. "push"/gastropexy) is not clear since there are discordant reports comparing these groups [19, 21, 22].

Importantly, the PEG tube did not affect type of surgery or surgical technical success, as reported in other studies [5, 7, 10]. Matsumoto et al. [5] further consolidated these conclusions through intraoperative thermal imaging, which demonstrated that gastric blood flow was not affected by previous PEG.

Recently published guidelines from the European Society of Gastrointestinal Endoscopy recommend the percutaneous introducer ("push") technique for PEG placement in patients with head and neck cancer or oesophageal cancer [23, 24]. The main reason underlying this recommendation is the risk of metastasis to the PEG site. The meta-analysis from Siu et al. [25], including 121 cases, reported rates of 0.56% (95% CI: 0.40–0.79%) with the "pull" technique and 0.29% (95% CI: 0.15–0.55%) with the "push" technique. This difference is not neglectable and must be considered, despite the null rate of stoma tumour cells found in our study. It is also noteworthy that even in the "push" group, PEG site metastasis was found, supporting haematogenous or lymphatic spread of the tumour cells, an important mechanism, as already suggested in the literature [26, 27].

A notable advantage of this study was its prospective nature, which allowed a precise and unbiased data collection in the intervention arm. This was performed in a hospital with expertise in Oncology, where the best standard-of-care was applied, allowing an extrapolation of the results.

There are important limitations to mention, namely, the retrospective evaluation of the CG. However, since the patients in the historic cohort had both medical and nutritional follow-up, the records were very complete and possible errors in retrospective data collection were mitigated. It is also worth noticing that a small sample was used and it is possible that the study may have not been adequately powered. Other nutritional endpoints such as hand grip strength and albumin were not systematically assessed and were not included in our results, further limiting conclusion withdrawal. It would have been interesting to know the nutritional status of these patients 6 months post-CRT, but this variable was not foreseen, thereby not prospectively collected and not included due to the risk of collecting biased information.

In conclusion, this study strengthens current knowledge about prophylactic PEG-tube placement in oesophageal cancer patients undergoing multimodal treatment. This is a safe procedure, with predominantly minor AEs and no evidence of tumour cells seeding in the stoma in

the population studied. One of the main advantages of this intervention is avoiding invasive procedures aiming for enteral feeding during CRT.

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Statement of Ethics

The study protocol was approved by the hospital's Ethical Committee (Unidade de Investigação Clínica) with the approval number UI/1011 and registered in the Australian New Zealand Clinical Trials Registry 104 platform with the trial number ACTRN12616000697482.

Conflict of Interest Statement

All authors have no conflict of interest to declare.

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Author Contributions

Rita Vale Rodrigues elaborated the study protocol and was the main investigator together with Joana Lemos Garcia. Susana Mão-de-Ferro was the main person involved in reviewing scientific data. Sara Ferreira, Miguel Serrano, and Joana Castela were doctors involved in recruiting of the patients and data collection.

Raquel Sacarrão, Fátima Francisco and Liliana Sousa were the nurses involved in the regular follow-up of these patients. They were responsible for data collection during follow-up. António Dias Pereira was the Head of Department and supervised the process in all the steps.

Grupo Multidisciplinar de Cancro de Esófago e Estômago is the multidisciplinary team where these patients were recruited. It served as the link between Gastroenterologists, Surgeons, Oncologists, Radiotherapists, and Pathologists involved in these patients' process.

Data Availability Statement

Raw data are not publicly available since they were not foreseen during informed consent.

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Postcolonoscopy Colorectal Cancer in a Referral Center for Colorectal Cancer: Prevalence and Risk Factors

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Keywords
Colorectal cancer · Postcolonoscopy colorectal cancer · Colonoscopy

Abstract

Background and Aims: Colonoscopy is effective to detect and remove colorectal lesions. However, after a negative colonoscopy, cancers could be detected during the interval follow-up. This study was designed to identify characteristics and risk factors for postcolonoscopy colorectal cancer – interval type. ***Methods:*** Medical records of individuals who were newly diagnosed with colorectal cancer between January 2018 and December 2019 were reviewed. Clinical, demographic, and endoscopic variables were analyzed. Those with the diagnosis of colorectal cancer between two consecutive colonoscopies performed within the appropriated surveillance range were considered to have postcolonoscopy colorectal cancer – interval type. A comparison between the group of patients with non-postcolonoscopy colorectal cancer – interval type and the group of patients with postcolonoscopy colorectal cancer – interval type was then performed. ***Results:*** During the study period, 491 patients were newly diagnosed with colorectal cancer. Among them, 61 (12.4%) had postcolonoscopy colorectal cancer – interval subtype. Postcolonoscopy colorectal cancer – interval type was three times more prevalent on the proximal colon (p = 0.014) and was associated with the presence of two or more cardiovascular risk factors (aOR = 4.25; p = 0.016), cholecystectomy in the past (aOR = 10.09; p = 0.019), and family history of colorectal cancer on a first-degree relative (aOR = 4.25; p = 0.006). Moreover, isolated cardiovascular risk factors revealed a protective effect for the absence of all cardiovascular risk factors (aOR = 20; p = 0.034). The ROC curve associated with the multivariate model revealed a predictive power of 77.8% (p < 0.001). ***Conclusions:*** Postcolonoscopy colorectal cancer – interval type is more common in the proximal colon and in patients with a family history (first-degree relative) of colorectal cancer, two or more cardiovascular risk factors, and a history of cholecystectomy. All of these are easily detectable in clinical practice and may be of extreme importance in the control of postcolonoscopy colorectal cancer in the near future.

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Prevalência e fatores de risco para o cancro colorretal pós-colonoscopia: Experiência de um centro de referência

Palavras Chave
Cancro colorretal · Cancro colorretal pós-colonoscopia · Colonoscopia

Resumo
Introdução: A colonoscopia é eficaz a detetar e remover lesões do colon e reto. Contudo, após uma colonoscopia normal, podem ser detetadas neoplasias durante o intervalo de vigilância recomendado entre colonoscopias. O objetivo do estudo foi identificar características e fatores de risco para o desenvolvimento de cancro colorretal pós-colonoscopia – subtipo de intervalo. ***Material e Métodos:*** Estudo retrospetivo e unicêntrico realizado entre janeiro de 2018 e dezembro de 2019 que incluiu todos os doentes diagnosticados de novo com cancro colorretal. Variáveis clínicas, demográficas e endoscópicas foram obtidas após consulta do processo clínico. Doentes com diagnóstico de cancro colorretal entre duas colonoscopias consecutivas, realizadas no intervalo de vigilância recomendado, foram considerados como tendo cancro colorretal pós-colonoscopia – subtipo de intervalo. Foi, então, realizada a comparação entre o grupo de doentes com cancro colorretal não pós colonoscopia – subtipo de intervalo e o grupo de doentes com cancro colorretal pós colonoscopia – subtipo de intervalo. ***Resultados:*** Durante o período de estudo, 491 doentes foram diagnosticados de novo com cancro colorretal. Destes, 61 (12.4%) foram considerados como tendo cancro colorretal pós-colonoscopia – subtipo de intervalo. O cancro colorretal pós-colonoscopia – subtipo de intervalo foi três vezes mais prevalente no colon proximal ($p = 0.014$) e associou-se a presença de dois ou mais fatores de risco cardiovasculares (aOR = 0.45; $p = 0.016$), colecistectomia no passado (aOR = 10.09; $p = 0.0.19$) e história familiar de cancro colorretal num familiar de primeiro grau (aOR = 4.25; $p = 0.006$). Aquando da análise dos fatores de risco cardiovasculares isolados, observou-se um fator protetor aquando da ausência de todos os fatores de risco cardiovasculares (aOR = 20; $p = 0.034$). A curva ROC associada ao modelo multivariado revelou um poder preditivo de 77.8% ($p < 0.001$). ***Conclusão:*** O cancro colorretal pós-colonoscopia – subtipo de intervalo é mais comum no colon proximal e em doentes com história familiar (em familiares de primeiro grau) de cancro colorretal, dois ou mais fatores de risco cardiovasculares e história de colecistectomia. Todos estes fatores de risco são facilmente detetáveis na prática clínica e podem ser de extrema importância no controlo, a curto e longo prazo, do cancro colorretal pós-colonoscopia.

Introduction

Colorectal cancer (CRC) is one of the most common malignancies in the world, and its incidence and mortality has remained high in the past decades [1], resulting in a pressing problem in today's society. It has been shown that colonoscopy can be an effective tool to detect and remove the lesions, which exist in the colon and rectum [2]. Additionally, colonoscopy with polypectomy can reduce almost 30% incidence of the overall CRC mortality [3]. Despite all the effort related to screening, it is known that CRC could be diagnosed between the index colonoscopy (in which no cancer was found) and the subsequent colonoscopy [4]. This type of CRC, also called postcolonoscopy CRC (PCCRC), has been increasing globally, and with population growth, lifestyle change, and diet, PCCRC will be more frequent and common than ever.

According to the World Endoscopy Organization, PCCRC can be subcategorized into interval cancers and non-interval cancers [4]. Interval cancers are considered when the cancer is identified before the next recommended screening or surveillance examination. On the other hand, non-interval cancers are considered when cancer is identified at (type A) or after (type B) a recommended screening or surveillance interval or when no subsequent screening or surveillance interval for repeat colonoscopy was recommended (type C), up to 10 years after the index colonoscopy [4].

Previous studies have shown that the prevalence of postcolonoscopy CRC – interval subtype (PCCRCi) seems to be less than 10% [5]. Bressler et al. [6] found that the incidence of PCCRCi varies with the location, the incidence being 5.9, 5.5, 2.1, and 2.3% in the right colon, transverse colon, descending and sigmoid colon, and rectum, respectively.

PCCRCi could be correlated with features of colonoscopy (accounting for about 50–75%) and biological features of the lesion (accounting for about 30%) [7]. Factors associated with colonoscopy included: missed lesions that may be the result of inadequate bowel preparation, endoscopist adenoma detection rate, and morphology of the premalignant lesions (flat/sessile adenomas or serrat-

ed lesions, mainly when located in the right colon). Besides that, previous studies have shown that about 26% of PCCRCi occur in the same anatomic site where polyp was removed previously [8, 9]. Additionally, Tollivoro et al. [10] have shown that a polyp with more than 10 mm (proximal or distal), adenoma with or without advanced histology, and an incomplete colonoscopy were associated with PCCRCi. Overall, the progression time from adenoma to invasive cancer needs generally more than 36 months [8]. Thereby risk factors for early versus late cancer after a negative colonoscopy (12–36 months vs. >36 months after colonoscopy) included incomplete polyp excision in the colonic segment of the subsequent cancer, failure to examine the segment, and a polyp with 10 mm or more in the segment [10].

With regard to risk factors related to patients, it is known that patients with PCCRCi tend to be older, with a mean age of 74 years [11]. Also, many have family history of CRC [12], history of concomitant disease, history of diverticulosis, and so on.

Although robust and scientifically rigorous epidemiological studies have sifted out clinical and environmental elements linked to PCCRCi, our knowledge of the causes and mechanisms of this group of CRCs is far from complete. In this line of thought, we consider that more attention should be paid to the increasing incidence of PCCRCi, and more individualized decisions should be made with regard to surveillance range. So, the present study aimed to identify the characteristics and risk factors for the development of PCCRCi, thus being able to contribute to the better knowledge of this group of CRCs, and thus try to reverse the current global trend.

Material and Methods

Study Design and Patients

We performed a retrospective, observational, and single-center study at a Portuguese Reference Center for Colorectal Cancer, in which medical records of individuals who were newly diagnosed with CRC (identified from the national cancer registry) between January 2018 and December 2019 were reviewed. Inclusion criterion was confirmed diagnosis of CRC (based on imaging and/or histological criteria). Patients meeting any of the following criteria were excluded: age <18 years; inflammatory bowel disease; prior diagnosis of CRC; increased familial risk for CRC (two or more first-degree relatives with CRC or at least one first-degree relative with CRC before 50 years); or more than 10 polyps in the index colonoscopy; diagnosis of genetic syndromes that increase the likelihood of CRC, including Lynch Syndrome and Familial Polyposis.

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local Ethics Committee. Informed consent was not requested as this was an observational and retrospective study with no therapeutic intervention. The study protocol was authorized by the local ethics committee.

Data Collection

Medical records were reviewed. The following clinical and demographic parameters were considered for analysis: age of diagnosis, gender, residence (rural vs. urban), last colonoscopy and its endoscopic findings, neoplasia characteristics (location, histology, morphology, and staging at the time of diagnosis), family history of CRC, presence of cardiovascular risk factors (CVRFs) (obesity, hypertension, diabetes, dyslipidemia, and tobacco abuse), history of cholecystectomy, the need for surgery, chemotherapy or radiotherapy as treatment options and death directly related to the neoplasia were recorded. All the parameters were analyzed and described for purposes of population's characterization, not only in the patients with PCCRCi but also among the non-PCCRCi group.

Definitions

Patients with the diagnosis of CRC between two consecutive colonoscopies performed within the appropriated surveillance range were considered to have PCCRCi. The appropriated surveillance range between colonoscopies was defined according to guidelines adopted in the study center during the study period (there were no changes in the guidelines over the time of study period): patients with a normal colonoscopy or with a maximum of two adenomas/serrated adenomas ≤10 mm should repeat colonoscopy within 10 years; the ones with three to four adenomas/serrated adenomas ≤10 mm or with hyperplastic polyp ≥10 mm should repeat colonoscopy within 5 years; patients with advanced lesions (advance adenoma: ≥10 mm or high-grade dysplasia or villous component, including tubule-villous adenomas; advanced serrated adenoma: ≥10 mm; or with any grade of dysplasia); 5 or more adenomas/serrated adenomas or with a traditional serrated adenoma should repeat colonoscopy within 3 years.

PCCRCi is assumed if the diagnosis of CRC has been made within the recommended surveillance period with an extension of up to 6 months beyond the end of surveillance period. All other CRCs were considered non-PCCRCi. The PCCRCi rate was, then, calculated from the ratio between the number of patients with PCCRCi and the total number of CRC.

The staging of the neoplasia was made in the diagnosis, before neoadjuvant treatment. Location of the neoplasia was divided into two segments: proximal (cecum, ascending, and transverse) and distal (descending, sigmoid, and rectum).

Statistical Analysis

Statistical analysis was performed with Statistical Package for the Social Sciences® (SPSS), version 24.0. Variables were summarized according to their measurement type. Hence, for categorical variables, the authors present frequencies (*n*) and percentages (%). For continuous variables with symmetric distribution, means and standard deviations were calculated; for continuous variables without symmetric distribution, medians and percentiles P25 and P75 were calculated. The assumption of normality was verified by the Kolmogorov-Smirnov test, through the values of asymmetry and kurtosis, as well as by the analysis of histogram graphs. Chi-square (χ^2) tests were used to measure the association between categorical variables, complemented with size effect measures phi (φ) for 2 × 2 tables and Cramer's v for larger tables.

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Table 1. Population characteristics and comparisons with the 1:3 sample

Variable	Non-PCCRCi (total), *n* = 430	Non-PCCRCi (1:3), *n* = 183	PCCRCi, *n* = 61	Non-PCCRCi 1:3 versus	
				non-PCCRCi	PCCRCi
Location of neoplasia					
Proximal colon	129 (30%)	58 (31.8%)	27 (44.3%)	$\chi^2 = 2.84$ ($p = 0.985$)	$\chi^2 = 9.17$ ($p = 0.482$)
Distal colon	286 (66.5%)	119 (65.1%)	32 (52.4%)	$v = 0.07$	$v = 0.19$
Multiple subcategories of the colon	13 (3.0%)	6 (3.3%)	2 (3.3%)		
T staging					
1	51 (13.5%)	21 (13.1%)	7 (12.7%)	$\chi^2 = 0.14$ ($p = 0.987$)	$\chi^2 = 6.24$ ($p = 0.101$)
2	54 (14.3%)	22 (13.8%)	13 (23.6%)	$\varphi = 0.02$	$\varphi = 0.17$
3	167 (44.3%)	70 (43.8%)	27 (49.1%)		
4	105 (27.9%)	47 (29.4%)	8 (14.5%)		
Type of screening					
Without screening	167 (38.8%)	71 (38.8%)	0 (0.0%)	$\chi^2 = 0.37$ ($p = 0.959$)	$\chi^2 = 116.9$ (**$p < 0.001$**)*
Colonoscopy	8 (1.9%)	3 (1.6%)	30 (49.2%)	$v = 0.03$	$v = 0.69$
Fecal occult blood test	151 (35.1%)	61 (33.3%)	30 (49.2%)		
Radiotherapy					
No	369 (85.8%)	157 (85.8%)	55 (90.2%)	$\chi^2 = 0.01$ ($p = 0.994$)	$\chi^2 = 0.77$ ($p = 0.381$)
Yes	61 (14.2%)	26 (14.2%)	6 (9.8%)	$\varphi = 0.01$	$\varphi = 0.06$
Chemotherapy					
No	358 (83.3%)	158 (86.3%)	49 (80.3%)	$\chi^2 = 0.92$ ($p = 0.339$)	$\chi^2 = 1.29$ ($p = 0.257$)
Yes	72 (16.7%)	25 (13.7%)	12 (19.7%)	$\varphi = 0.01$	$\varphi = 0.07$
Surgery					
No	131 (30.5%)	56 (30.6%)	9 (14.8%)	$\chi^2 = 0.01$ ($p = 0.973$)	$\chi^2 = 5.88$ (**$p = 0.015$**)*
Yes	299 (69.5%)	127 (69.4%)	52 (85.2%)	$\varphi = 0.01$	$\varphi = 0.16$
Death					
No	339 (78.8%)	140 (76.5%)	60 (98.4%)	$\chi^2 = 0.41$ ($p = 0.522$)	$\chi^2 = 14.79$ (**$p < 0.001$**)*
Yes	91 (21.2%)	43 (23.5%)	1 (1.6%)	$\varphi = 0.03$	$\varphi = 0.25$
Findings on last colonoscopy					
Normal			38 (62.3%)		
Presence of polyps			22 (36.1%)		

n, number; PCCRCi, postcolonoscopy colorectal cancer – interval type. * Statistically significant *p* values ($p < 0.05$) are presented in bold.

Table 2. Univariate analysis of risk factors for PCCRCi

Variable	Non-PCCRCi 1:3 (*n* = 183)	PCCRCi (*n* = 61)	Crude OR	*p* value
Sex, *n* (%)				
Female	62 (33.9)	22 (36.1)	1	1
Male	121 (66.1)	39 (63.9)	0.91	0.756
Age at diagnostic, M (SD)	67.83 (13.78)	70.13 (8.88)	1.02	0.223
Right colon, *n* (%)				
No	133 (75.1)	36 (61.0)	1	1
Yes	44 (24.9)	23 (39.0)	1.93	**0.039***
CVRFs, *n* (%)				
0	33 (18.0)	4 (6.6)	1	1
1	45 (24.6)	11 (18.0)	2.02	0.263
2	41 (22.4)	18 (29.5)	3.62	**0.032***
3	38 (20.8)	19 (31.1)	4.13	**0.018***
4	26 (14.2)	9 (14.8)	2.87	0.109
Cholecystectomy, *n* (%)				
No	171 (95.0)	54 (88.5)	1	1
Yes	9 (5.0)	7 (11.5)	2.46	**0.088**†
Family history, *n* (%)				
No	102 (84.3)	29 (70.7)	1	1
First-degree relative	12 (9.9)	11 (26.8)	3.22	**0.012***
Not first-degree relative	7 (5.8)	1 (2.4)	0.50	0.528

n, number; M, mean; SD, standard deviation; PCCRCi, postcolonoscopy colorectal cancer – interval type. Statistically significant (* $p < 0.05$) and marginally significant († $p < 0.10$) *p* values are presented in bold.

Multivariate analysis using binary logistic regression was performed to identify predictors of PCCRC. For the purpose of logistic model building, a random sample of the non-PCCRC group, extracted from the data select cases menu in SPSS, was selected in order to accomplish the criterion on 1:3 relation with PCCRC group. Candidate variables for inclusion in a prediction model were any significant (or borderline significant) variables at univariate analysis or variables whose inclusion was supported by the existing literature [13]. Crude odds ratio and adjusted odds ratios (aOR) were determined to measure the effect size of risk factors for developing PCCRC. Bootstrap 1,000 samples were used to model validation and ROC curve to assess the precision of the multivariate risk score. Significance was considered for $p < 0.05$, except for the purpose of entering predictors in the multivariate model, where $p < 0.10$ was the threshold.

Results

In our study, 491 patients recently diagnosed with CRC were included. Among them, 61 (12.4%) patients had PCCRCi.

For the purpose of logistic model building, a random sample of 183 non-PCCRCi was selected in order to accomplish the criterion on 1:3 relation. Comparisons were made between the random sample of non-PCCRCi and the original sample of non-PCCRCi and PCCRCi (Table 1). Very similar results were found between the total sample of non-PCCRCi and the random sample, confirming the consistency of the sampling process.

Males were more prevalent for both PCCRCi patients (*n* = 39, 63.9%) and non-PCCRCi (*n* = 121, 66.1%), without significant differences between groups ($p = 0.756$). Mean age was slightly higher in the PCCRCi group (70.13 ± 8.88 years), also without significant differences ($p = 0.223$). Among patients with PCCRCi, the median time between diagnostic and the index colonoscopy was 5.0 years (P25 = 3.5, P75 = 6.8) with most patients having normal findings in previous colonoscopy (*n* = 38, 62.3%). Although we did not have access to all quality criteria of the index colonoscopy, all patients had colonoscopies with a bowel preparation allowing complete visualization of the entire colon and rectum.

Surgery was performed on 85.2% of the patients of the PCCRCi group and 69.4% of the non-PCCRCi ($\chi^2 = 5.88$ [$p = 0.015$], $\varphi = 0.16$). More deaths occurred in the non-PCCRCi group with 23.5% events, compared to a single event in the PCCRCi group ($\chi^2 = 14.79$ [$p < 0.001$], $\varphi = 0.25$), with a mean follow-up period of 2 years.

Table 3. Multivariate adjustment for PCCRCi risk factors and bootstrap 1,000 samples

Variable	Multivariate adjustment			Bootstrap 1,000 samples		
	aOR	95% CI	*p* value	bias	SE	*p* value
Sex, *n* (%)						
Female	1	1	1	1	1	1
Male	0.86	0.34–2.18	0.753	0.01	0.58	0.811
Age at diagnostic, M (SD)	1.02	0.98–1.05	0.379	0.01	0.02	0.322
Proximal colon, *n* (%)						
No	1	1	1	1	1	1
Yes	3.01	1.25–7.27	**0.014***	0.12	0.53	**0.011***
CVRFs, *n* (%)						
0	1	1	1	1	1	1
1	3.37	0.64–17.79	0.126	1.78	5.65	0.103
2	7.50	1.46–38.51	**0.016***	1.86	5.66	**0.010***
3	4.71	0.87–25.43	**0.072**†	1.78	5.64	**0.031***
≥4	5.89	0.84–41.31	**0.075**†	1.57	6.08	**0.021***
Cholecystectomy, *n* (%)						
No	1	1	1	1	1	1
Yes	10.09	1.45–70.06	**0.019***	1.73	7.85	**0.017***
Family history, *n* (%)						
No	1	1	1	1	1	1
First degree relative	4.25	1.53–11.82	**0.006***	0.11	0.68	**0.010***
Not first-degree relative	0.78	0.08–7.28	0.827	−7.02	9.80	0.488

Nagelkerke R^2 = 0.236; Hosmer-Lemeshow test with p = 0.273. *n,* number; M, mean; SD, standard deviation. Statistically significant (* $p < 0.05$) and marginally significant († $p < 0.10$) *p* values are presented in bold.

Univariate logistic regressions with crude OR showed an increased chance of PCCRCi for patients with CRC on the proximal colon (OR = 1.93, p = 0.039), two CVRFs (OR = 3.62, p = 0.032), and first degree of family history (OR = 3.22, p = 0.012). For the purpose of entering the multivariate logistic model, we considered marginally significant *p* values <0.10, thus interpreting as increased chance of PCCRCi for patients with cholecystectomy in the past (OR = 2.46, p = 0.088) as presented in Table 2.

Multivariate adjustment was made, and bootstrap results for all significant and marginally significant previously identified predictors were presented in Table 3. Gender and age were also included as confounders.

PCCRCi was more frequent in the proximal colon (aOR = 3.01, p = 0.014), and the risk of PCCRCi is associated with the presence of 2 CVRFs (aOR = 7.50, p = 0.016), cholecystectomy in the past (aOR = 10.09, p = 0.019), and family history of CRC in a first-degree relative (aOR = 4.25, p = 0.006). Marginally significant results for the association of PCCRCi with 3 CVRFs (aOR = 4.71, p = 0.072) and 4 CVRFs (aOR = 5.89, p = 0.075). These results suggest that the main threshold for increased chance of PCCRCi is two or more CVRFs. Moreover, isolated CVRF analysis revealed a protective effect for the absence of all CVRFs (aOR = 20; CI 95% 0.05–0.89; p = 0.034). Nagelkerke R^2 of 0.236 showed moderate quality. Hosmer-Lemeshow test was nonsignificant (p = 0.273), suggesting a good fit. Bootstrap 1,000 samples were used for model validation confirming significance for the previously identified variables. The ROC curve (Fig. 1) associated with the multivariate model was created, and an area under the curve was 77.8% ($p < 0.001$) suggesting a moderate precision for the adjusted model.

Discussion

There is no universally accepted definition of PCCRCi, with many studies [14–16] defining durations ranging from less than 1 year to over 10 years after a negative colonoscopy, and are likely to be a heterogeneous group depending on the study definition and population characteristics. This may contribute to the varying prevalence of PCCRCi across studies, ranging from 1.8% to 10% [5, 17]. Our study revealed a higher prevalence of PCCRCi (12.4%), which may support the increasing global trend. Nevertheless, this result should be carefully interpreted

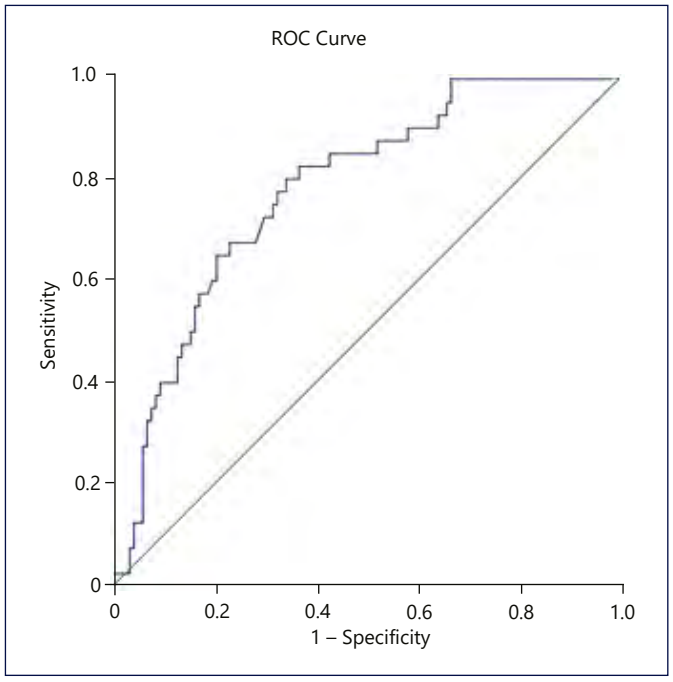

Fig. 1. ROC curve for multivariate logistic model.

considering the single-center, retrospective study design and the longer median time, 5 years, between colonoscopy and PCCRCi diagnosis (most studies calculate PCCRCi over a period of 0–36 months prior to diagnosis). A more restricted definition could lead to lower PCCRCi rate; however, our intention was to meet current guidelines and therefore bring us closer to real-world perception. A uniform, worldwide definition is essential to minimize the discrepancies among studies. Several studies [6, 11, 12, 18] showed that PCCRCi is more commonly found in female patients and that patients with PCCRCi were older [11, 19]; however, in the present study, neither gender nor age at diagnosis was statistically different in the group of patients with PCCRCi, although the age at diagnosis was slightly higher (70.1 vs. 67.8 years).

In our study, PCCRCi was three times more likely to affect the proximal colon; these results are consistent with a recent meta-analysis carried out by Singh et al. [17], which shows that PCCRCi was 2.4 times more likely to affect the proximal colon than the distal colon. The morphology of the polyps most often detected in the proximal colon (flat adenomas and serrated lesions) may potentially lead to missed lesions, explaining the higher frequency of PCCRCi in the proximal colon [20–22].

Most studies [8, 15, 20, 21] state that PCCRCi mainly develops due to missed lesions, incomplete polypectomy, or eventually new lesions, increasing the risk of CRC in the proximal colon. So, Ferreira et al. [23] emphasize that applying and evaluating colonoscopy quality criteria is essential to assess the effectiveness of screening colonoscopy and should become mandatory in all centers in the near future.

Samadder et al. [12] stated that a greater percentage (57.2%) of patients with PCCRCi presented adenomas at index colonoscopy. Our study showed conflicting results since among patients with PCCRCi, 62.3% had normal findings in previous colonoscopies and only 36.1% presented with polyps/adenomas. This result may be due to colonoscopy related-factors, such as poor-quality indicators that we did not have full access to.

In addition, we found that patients with PCCRCi had a family history of CRC in first-degree relatives, 4.25 times more commonly than the control group, which corroborates the evidence that family history of CRC is more common in PCCRCi and plays an important role in this kind of CRCs as stated in many previous studies [12, 22, 24, 25]. These results further support the idea that some of the PCCRCi may have biological basis (genetic and epigenetic) that further increases the risk of CRC in their relatives, especially those with a family history in a first relative. It also emphasizes the importance of researching the family history of CRC and encouraging adherence to surveillance guidelines in high-risk population.

In other studies, comparing PCCRCi and primary CRC, the presence of multiple comorbidities measured by Charlson Comorbidity Index was associated with PCCRC [11, 17, 19, 22, 26], being in a meta-analysis, the adjusted OR of 2.00 (95% CI 1.77–2.27; I^2 = 26%). That said, according to our results, the presence of two or more CVRFs makes the risk of developing PCCRCi 7.5 times more likely. Moreover, though isolated CVRF was not statistically significant for the development of PCCRCi, the absence of all 5 CVRFs seems to be protective. This was the first study to show a direct association between a cut-off of two or more CVRFs and the development of PCCRCi.

Additionally, it is well known that history of cholecystectomy plays an important role in the development of CRC [27–29]. This may be due to the drain of bile acids into the digestive system continuously because of a loss of bile storage and the relaxation of the Oddi sphincter following cholecystectomy and because of the changes in the composition and secretion of bile acids after cholecystectomy [30], thus contributing to the increased risk of developing CCR. Our study demonstrates that the history of cholecystectomy makes PCCRCi 10.09 times more probable, making our study the first to determine it as an

independent risk factor for the development of PCCRCi and to introduce it into a predictive model.

Finally, in most other studies [11, 31], staging of PCCRCi, by the time of diagnosis, was similar or tended to be lower compared with the other types of CRC [12, 17, 19] which is in agreement with our findings. Despite the short follow-up period (2 years), our data reveal a significantly lower mortality rate in the PCCRCi group, which is not consensual in previous studies [11, 17]. However, the earlier stage at diagnosis may correlate with a lower mortality rate in the PCCRCi group given the greater likelihood of curative treatments. More studies are needed to validate the association between earlier stages and lower mortality in this patient group.

Some limitations should be taken into consideration, since this is a retrospective study, in rare situations, some information may have been lost, namely, the presence of CVRFs and the family history of CRC. Also, endoscopic reports were only reviewed from clinical records as most colonoscopies were not performed in the hospital (reports were obtained from the attending physician's records) and also due to the death of some patients at the time of data collection, which made it difficult to assess some of the quality criteria of colonoscopies (clinical indication for colonoscopy, bowel preparation scale, adenoma detection rate, withdrawal time).

To our knowledge, this is the first study in a western population which found the cut-off of at least two CVRFs and the history of cholecystectomy as risk factors, in a multivariate analysis, for the development of PCCRCi. In conclusion, despite improved techniques for colonoscopy, the incidence of PCCRCi has increased during the past 10 years, showing that there is still much to know about the risk factors and behavior of PCCRCi.

Our data reveal that PCCRCi is more frequent in the proximal colon and identify three independent risk factors for its onset: presence of family history in a first-degree relative, two or more CVRFs, and the history of cholecystectomy. All of them are easily detectable in clinical practice and can be taken into account when defining surveillance intervals. Although the reduction of surveillance intervals, according to the identified risk factors, may lead to a decrease in the rate of PCCRCi, another important problem arises: adverse effects of anesthetic sedation. Therefore, it is essential to combine the patient's comorbidities, their life expectancy, and the individual need to reduce CRC surveillance intervals. Large prospective, multicenter, and randomized controlled trials are important to certify our findings, validate our prediction model, and attest the efficacy of a more individualized approach.

Statement of Ethics

Informed consent was not requested as this was an observational and retrospective study with no therapeutic intervention. The study protocol was authorized by the Braga Hospital ethics committee. The authors declare that the procedures followed were in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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None.

Author Contributions

M.G. was responsible for the design of the study, data analysis, and drafting of the manuscript. J.C., T.C., and A.R. were responsible for the analysis of the data and helped drafting the manuscript. M.G., R.C., and A.R. were responsible for the design of the study, data collection and interpretation, and critical revision of the work for important intellectual content. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author, Margarida Gonçalves. The data are not publicly available since they can contain information that could compromise the privacy of research participants.

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Narrow Band Imaging versus White Light for the Detection of Sessile Serrated Colorectal Lesions: A Randomized Clinical Trial

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Keywords

Colonoscopy · Quality · Sessile serrated lesion · Adenoma · Narrow band imaging · Chromoendoscopy

Abstract

Background: Colorectal cancer (CRC) is a leading cause of cancer. The detection of pre-malignant lesions by colonoscopy is associated with reduced CRC incidence and mortality. Narrow band imaging has shown promising but conflicting results for the detection of serrated lesions. ***Methods:*** We performed a randomized clinical trial to compare the mean detection of serrated lesions and hyperplastic polyps ≥10 mm with NBI or high-definition white light (HD-WL) withdrawal. We also compared all sessile serrated lesions (SSLs), adenoma, and polyp prevalence and rates. ***Results:*** Overall, 782 patients were randomized (WL group 392 patients; NBI group 390 patients). The average number of serrated lesions and hyperplastic polyps ≥10 mm detected per colonoscopy (primary endpoint) was similar between the HD-WL and NBI group (0.118 vs. 0.156, $p = 0.44$). Likewise, the adenoma detection rate (55.2% vs. 53.2%, $p = 0.58$) and SSL detection rate (6.8% vs. 7.5%, $p = 0.502$) were not different between the two study groups. Withdrawal time was higher in the NBI group (10.88 vs. 9.47 min, $p = 0.004$), with a statistically nonsignificant higher total procedure time (20.97 vs. 19.30 min, $p = 0.052$). ***Conclusions:*** The routine utilization of narrow band imaging does not improve the detection of serrated class lesions or any pre-malignant lesion and increases the withdrawal time.

Luz de banda estreita versus luz branca para a deteção de lesões serreadas sésseis do cólon e reto: um ensaio randomizado

Palavras Chave

Colonoscopia · Qualidade · Adenoma · Lesão serreada sessil · Cromoendoscopia · Luz de banda estreita

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Resumo

Introdução: O cancro do cólon e reto é a neoplasia mais frequente considerando os dois géneros. . A deteção de lesões pré-malignas por colonoscopia está associada a uma redução da incidência e da mortalidade. Estudos sobre a utilização da luz de banda estreita (NBI) na deteção de lesões serreadas tiveram resultados promissores, mas heterogéneos. ***Métodos:*** Realizámos um ensaio clínico randomizado para comparar o número médio de lesões serreadas e lesões hiperplásicas ≥10 mm com NBI ou luz branca de alta-definição (HD-WL). Como resultados secundários comparámos a prevalência e as taxas de deteção de lesões serreadas sésseis, adenomas e todas as lesões. ***Resultados:*** Foram randomizados 782 doentes (392 no grupo HD-WL e 390 no grupo NBI). O número médio de lesões serreadas e hiperplásicas ≥10 mm não apresentou diferença estatisticamente significativa entre dois grupos (0.118 vs. 0.156, $p = 0.44$). A taxa de deteção de adenomas (55.2% vs. 53.2%, $p = 0.58$) e a taxa de deteção de lesões serreadas sésseis (6.8% vs. 7.5%, $p = 0.502$) também não foram diferentes. O tempo de retirada foi maior no grupo NBI (10.88 vs. 9.47 min, $p = 0.004$) e o tempo total de procedimento teve um ligeiro aumento não atingindo significância estatística (20.97 vs. 19.30 min, $p = 0.052$). ***Conclusão:*** A utilização da luz NBI por rotina não aumenta a deteção de lesões serreadas nem de qualquer lesão pré-maligna e aumenta o tempo de retirada na colonoscopia.

Introduction

Colorectal cancer (CRC) is a leading cause of morbidity and mortality in the world, especially in Western countries [1, 2]. Worldwide, CRC accounts for 860,000 deaths [2]. Colonoscopy has been shown to decrease both the incidence of CRC and the related mortality by facilitating the detection and allowing the removal of adenomas [3–8] and is endorsed as the preferred option for CRC screening and adenoma surveillance [9–12]. The adenoma detection rate (ADR) is currently the main quality indicator for colonoscopy [13, 14] as a higher ADR results in lower risk of CRC and mortality [15]. However, conventional colonoscopy has been shown to miss lesions in tandem studies, especially sessile serrated lesions (SSLs) [16–18]. These lesions are different from adenomas; they are more frequent on the right colon and usually present with a flat morphology that makes them much harder to detect through optical colonoscopy. SSL also presents a different, faster carcinogenesis pathway and as result of these characteristics, they are associated with interval CRC, which is the occurrence of CRC after screening colonoscopy and before the next scheduled screening procedure [19, 20].

Narrow band imaging (NBI) has been shown to be effective for SSL detection in one trial performed in an academic center and in the setting of sessile serrated polyposis [21, 22]. In another RCT, Rex et al. [23] compared NBI (Olympus™ 190 series colonoscopes) and high-definition white light (HD-WL) colonoscopy for the detection of proximal serrated lesions in average-risk individuals. This trial showed a trend toward higher detection in the NBI but failed to achieve statistical significance for the primary endpoint (number of proximal serrated lesions) [23]. Few other trials have studied the effect of NBI on the detection of colorectal polyps and adenomas and some have also reported the incidence of serrated class lesions with nonsignificant results in most of them [24–27]. Recently, a meta-analysis pooled the results of these trials which showed a significant increase in the detection of serrated lesions with NBI [28].

Therefore, it is still unsettled whether NBI should be used systematically during colonoscopy withdrawal to increase detection of CRC precursor lesions. Our aim was to evaluate if the systematic usage of NBI during colonoscopy withdrawal contributes to a higher rate of SSL detection in an average CRC risk population.

Materials and Methods

Study Design

We performed a 2-arm superiority RCT to compare SSL detection between NBI and HD-WL optical colonoscopy. The study was approved by the Institutional Review Board at Hospital Beatriz Ângelo and NOVA Medical School and was registered at clinicaltrials.gov (NCT02876133). Patients were required to sign a written informed consent. The study was performed in one academic center between October 2016 and February 2021.

Study Population

Consenting individuals fulfilling the inclusion criteria were patients scheduled for elective colonoscopies, aged 40–74, cecal intubation and adequate bowel preparation according to the Boston Bowel Preparation Score (BBPS) >1 in each bowel segment, and without exclusion criteria: known polyposis syndromes, primary sclerosing cholangitis, inflammatory bowel disease, personal CRC history or colorectal surgery, contraindications to polypectomy, current pregnancy, and ASA > 3.

Outcomes

The primary endpoint was the average number of serrated lesions including hyperplastic lesions ≥10 mm detected per colonos-

copy. The secondary endpoints were SSL detection rate (number of patients with at least 1 SSL/total number of participants); serrated class lesions detected per colonoscopy (number of serrated lesions/total number of participants); ADR (number of patients with at least 1 adenoma/total number of participants); adenomas detected per colonoscopy (number of adenomas/total number of participants); malignant adenocarcinoma detection rate (number of malignant adenocarcinomas/total number of participants); incidence of procedure-related adverse events; withdrawal time.

Study Procedures and Data Collection

We used a block randomization table generated in STATA which was uploaded to the eCRF software and not accessible to the investigators. Randomization was concealed before the procedure and until patient assignment which occurred only after cecal intubation using the REDCap platform. Consenting patients were randomized to the NBI group or the white light colonoscopy group, after cecal intubation and before the withdrawal. Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at Sociedade Portuguesa de Gastrenterologia [29, 30]. REDCap is a secure, Web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails to track data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures to support data integration and interoperability with external sources.

The six participating endoscopists were all experienced in optical colonoscopy (defined by having performed a minimum of 300 colonoscopies) [31] and electronic chromoendoscopy with an ADR above 40% in all cases. The procedures were performed using a high-definition Olympus endoscope (CF-H190 or GIF-H190). Colonoscopies were performed either without sedation, under conscious sedation or under deep sedation, as requested by the assistant physician. Antispasmodics (butylscopolamine) could be administered during the procedure at the endoscopist discretion.

The histologic evaluation of each lesion was performed by pathologists in our center. The pathologists were blinded to the method used during the procedure. We recorded patient demographic and clinical data, including date of birth, sex, weight, height, body mass index, education level, smoking habits, personal history of polyps and polypectomy, date of previous colonoscopy, and family history of CRC; colonoscopy data, such as the endoscopist performing the procedure, colonoscope model, indication for the procedure, depth of sedation (no sedation, conscious, or deep sedation), the administration of antispasmodics (butylscopolamine), intubation and withdrawal times, Boston Bowel Preparation Score (BBPS) in each colon segment (ascending, transverse, and left colon), and adverse events; and for each lesion detected the location, size, morphology (Paris Classification [32]), and histology (hyperplastic, adenoma, SSL, or adenocarcinoma).

Sample Size

The prevalence of SSL at screening colonoscopy is close to 5% but ranges from 1 to 18%, with a mean of 1.62 lesions per case [33, 34]. For serrated lesions ≥10 mm, we based our estimate on Rex's trial [23] which had a proportion of 0.098 proximal lesions per colonoscopy with NBI. We believed that a 100% increase in yield could be a sufficient difference to consider routine use of NBI. Therefore, considering the number of lesions per patient as the primary endpoint and to have an 80% power at a 5% significance level to detect a difference from 0.049 to 0.098 lesions/colonoscopy, we would need a total sample size of 968 colonoscopies. We anticipated a 2% cross-over rate and therefore we adjusted the sample size to 987 colonoscopies. Cross-over was anticipated to occur in case of poor judgment of the bowel preparation quality where white light would be needed instead of NBI and in case of error by the endoscopist or equipment malfunction.

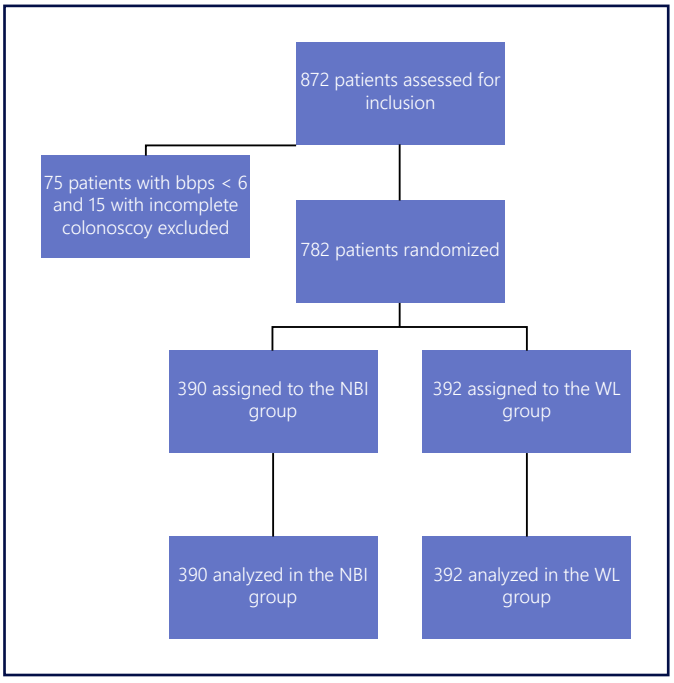

Fig. 1. Trial profile.

The statistical analysis was conducted with the SPSS software package, version 21 (Statistical Package for the Social Sciences; IBM Corporation, Armonk, NY, USA). Categorical variables are expressed as frequencies and percentages, while continuous variables are described as the means and standard deviations or medians and ranges. The χ^2 test and Fisher's exact test were used to explore associations between categorical variables. Differences in means for continuous variables and dichotomous variables were analyzed by *t* tests or Mann-Whitney U tests, as appropriate. The study was prematurely terminated due to the significant impact of COVID-19 pandemic on recruitment pace.

Results

Patient and Procedural Characteristics

A total of 872 patients were assessed for eligibility, with 90 patients excluded before randomization due to poor bowel preparation ($n = 75$) and failure to reach the cecum

Table 1. Baseline characteristics of the study population

	WL group (n = 392)	NBI group (n = 390)	p value
Age, years	61.44 (9.91)	60.89 (9.99)	0.444
Male sex, *n* (%)	204 (52.7)	212 (54.5)	0.618
Body mass index	27.67 (4.79)	27.76 (4.95)	0.813
Family history of CRC (1st degree)	93 (24.3)	68 (17.5)	0.19
Previous colonoscopy, *n* (%)	160 (41.5)	171 (44.0)	0.480
Median time since last colonoscopy (minimum-maximum), months	38 (1–228)	32 (1–249)	0.081
Personal history of polyps, *n* (%)	111 (28.8)	119 (30.7)	0.576
Indication			
Screening	72 (18.8)	89 (23.1)	0.122
FOBT	49 (12.8)	61 (15.8)	
Surveillance	101 (26.3)	103 (26.6)	
Diagnostic	162 (42.2)	133 (34.5)	

Table 2. Procedural characteristics

	WL group (n = 392)	NBI group (n = 390)	p value
Deep sedation, *n* (%)	130 (33.9)	135 (34.8)	0.272
Conscious sedation, *n* (%)	209 (54.4)	221 (57.0)	
No sedation, *n* (%)	45 (11.7)	32 (8.2)	
Mean BBPS			
Left colon	2.26 (0.438)	2.22 (0.415)	0.222
Transverse colon	2.40 (0.490)	2.37 (0.484)	0.470
Ascending colon	2.45 (0.503)	2.40 (0.495)	0.179
Butylscopolamine administration	114 (30.2)	125 (32.7)	0.447
Total time, min	19.30 (11.32)	20.97 (10.53)	0.052
Withdrawal time, min	9.47 (6.18)	10.88 (6.37)	0.004

(n = 15). From the included 782 patients, 390 were randomly assigned to NBI and 392 to HD-WL group. All patients received the allocated intervention. The trial profile is depicted in Figure 1.

Table 1 summarizes baseline characteristics. There were no differences between the two study groups regarding age, sex, family history of CRC, personal history of polyps, and colonoscopy indication.

Table 2 shows procedural characteristics. Mean withdrawal time was 1.41 min higher in the NBI group (10.88 vs. 9.47 min, p = 0.004), with a statistically non-significant higher total procedure time (20.97 vs. 19.30 min, p = 0.052). No significant differences were observed between the two study groups regarding depth of sedation, administration of antispasmodics (butylscopolamine), and bowel preparation quality in each colonic segment.

Outcomes

Table 3 summarizes the proportion of detected lesions by study group (HD-WL vs. NBI group). For the primary endpoint of the average number of serrated lesions and hyperplastic polyps ≥10 mm detected per colonoscopy, there was no significant difference between the two groups (0.118 vs. 0.156, p = 0.44).

Overall, no differences were observed in polyp detection rate (69.6% vs. 69.3%, p = 0.93), ADR (55.2% vs. 53.2%, p = 0.58), SSL detection rate (6.3% vs. 7.5%, p = 0.502), and serrated lesions including hyperplastic ≥10 mm detection rate (6.8% vs. 8.9%, p = 0.298) between HD-WL and NBI groups. Likewise, the number of adenomas (1.23 vs. 1.23, p = 0.996) and SSLs (0.11 vs. 0.13, p = 0.712) per colonoscopy was also not different. Finally, the adenocarcinoma detection rate was also similar (1.6% vs. 1.1%, p = 0.535).

Table 3. Lesions detected stratified by study group

	WL group (n = 392)	NBI group (n = 390)	ITT OR/MD; 95% CI; p value
PD(R), n (%)	268 (69.6)	269 (69.3)	0.987; 0.727–1.340; 0.933
ADR(R), n (%)	211 (55.2)	205 (53.2)	0.923; 0.695–1.226; 0.580
SSL detection (rate), n (%)	24 (6.3)	29 (7.5)	1.212; 0.692–2.122; 0.502
Serrated lesion and hyperplastic ≥10 mm detection rate	26 (6.8)	34 (8.9)	1.326; 0.780–2.257; 0.298
Adenocarcinoma detection rate	4 (1.1)	6 (1.6)	1.496; 0.419–5.344; 0.535
Number of lesions, mean (SE)	1.92 (0.114)	2.12 (0.130)	1.034; 0.975–1.097; 0.262
Number of adenomas per colonoscopy (SE)	1.236 (0.090)	1.236 (0.112)	1.000; 0.931–1.074; 0.996
Number of SSLs per colonoscopy (SE)	0.113 (0.029)	0.130 (0.036)	1.043; 0.833–1.307; 0.712
Number of serrated lesions (≥10 mm) per colonoscopy (SE)	0.118 (0.029)	0.156 (0.039)	1.089; 0.876–1.355; 0.442

ITT, intention to treat; OR, odds ratio; MD, mean difference; CI, confidence interval; PDR, polyp detection rate; ADR, adenoma detection rate; SSL, sessile serrated lesion.

Discussion

We performed a randomized controlled trial design to determine whether NBI improves the detection of serrated lesions and hyperplastic lesions ≥10 mm. Our results did not show a significant difference in the detection of these lesions or in any other lesions (adenomas, SSLs, all polyps, and invasive cancer). It is important to acknowledge the high detection rates (ADR of 54% and SSLR of 7%) in this study as the effect of optimization strategies decreases with high detection rates.

Nonetheless, our study is in line with the large RCT performed by Rex et al. [23] which recruited 800 patients and looked at the detection of serrated class lesions proximal to the sigmoid colon and only found a nonsignificant trend in favor of NBI (204 vs. 158, p = 0.085) [23]. However, in a recent meta-analysis, which included three studies and pooled the results of 1931 colonoscopies, there was a higher detection of serrated adenomas in the NBI group (RR 2.04, 95% confidence interval: 1.18–3.54, p = 0.001) [28]. Yet, none of the included trials was specifically designed for serrated lesions and only Visovan et al. [24] reported a positive result. This was the trial with the highest weight in the meta-analysis, but it did not actually report the SSLs detection in the original manuscript published in the Bosnian Journal of Basic Medical Sciences [24]. Another relevant limitation of the meta-analysis is the exclusion of the 800 patients' trial by Douglas Rex because it used proximal serrated lesions as the endpoint instead of histologically determined SSLs.

Another important point of our study was the increased inspection (withdrawal) time by an average of 85 s in the NBI group. We believe this effect was probably associated with the known need for better washing and suction of the colon as NBI image is severely impaired by the presence of colonic residue and even clear fluids. This effect has also been seen in other trials studying NBI [28].

Strengths of this study include the randomized design and large sample size, using an endpoint that included SSLs according to the pathologist, and large hyperplastic lesions which are also a significant finding. An option would be to have all endoscopically suspicious lesions for serrated morphology double checked by a second expert digestive pathologist.

The main limitations were the uncontrolled withdrawal time which was higher in the NBI group and the impossibility to blind the endoscopist, which is inevitable in these studies. However, we have previously studied and reported colonoscopy quality outcomes that may help as a benchmark. Previously, we published in GE an observational study from 2012 to 2014 with a routine ADR of 36% and an SSL detection rate of 1% [35]. These figures improved in our latest report with data from 2017 to 2019 with an ADR of 55% and SSL detection rate of 4% [36]. The data shown demonstrate the overall detection improvement during routine colonoscopies in our department in recent years and are in line with the outcomes reported in our control group. Nevertheless, one must acknowledge that the prevalence of pathology is increased by including cases not restricted to a pure screening population. Another important limitation is that our study was prematurely terminated due to COVID-19 pandemic and we were 205 hundred cases short. To better understand, we calculated that this sample with these results has a power of 71% to detect the prespecified effect in the sample size calculation. Therefore, it would be very un-

likely that with an extension of the trial the primary endpoint would be met.

In this study, we used SSLs and large hyperplastic polyps as a combined endpoint to overcome the limitation of the known pathological identification of SSL. Unlike in Rex's trial [23], we did not include all proximal hyperplastic lesions, and this may have contributed to a smaller effect of NBI.

In the future, studies should have a large sample size determined by the endoscopists (and pathologists) detection rates and include data on location, size, endoscopic assessment, and histology of all lesions in order to detect small differences and to allow effective meta-statistical assessment of the existing trials. Finally, we must acknowledge that although NBI did not improve the detection of serrated lesions, it has been shown to be useful in other situations such as the characterization of epithelial lesions [37, 38].

The present study is one of the largest randomized controlled trials studying the effect of NBI for the detection of colorectal lesions and more specifically SSLs and large serrated class lesions. It failed to show a significant effect other than an increase in the withdrawal time. We conclude that a beneficial detection effect of NBI is unlikely and overwhelmed by an increase in procedural time.

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The authors would like to acknowledge the support of the Portuguese Society of Gastroenterology by granting the use of the REDCap software. Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at Sociedade Portuguesa de Gastrenterologia. REDCap is a secure, Web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources.

Statement of Ethics

The study was approved by the Institutional Review Board at Hospital Beatriz Ângelo and NOVA Medical School. Patients were required to sign a written informed consent before the inclusion in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.O.F., M.D.-R., J.C., and M.C. were responsible for study design, analysis, and writing of the manuscript. A.O.F., J.R., C.N., C.F.-G., M.P.C.-S., L.R., C.P., and L.G. were responsible for the procedures and data collection.

Data Availability Statement

The data that support the findings of this study are not publicly available due to containing information that could compromise the privacy of research participants but are available from the corresponding author [A.O.F.] upon reasonable request.

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Multicenter Study on the Performance of Imaging Tests Compared to Endosonography-Guided Fine-Needle Aspiration in the Diagnosis of Solid Pseudopapillary Neoplasms of the Pancreas

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Keywords

Endoscopic ultrasound · Endoscopic ultrasound-guided fine-needle aspiration · Diagnosis · Pancreatic cancer · Pathology/surgery · Pancreatic neoplasm · Solid-pseudopapillary tumor · Solid-pseudopapillary neoplasm

Abstract

Introduction: Imaging diagnosis of pancreatic solid-pseudopapillary neoplasms (SPNs) is difficult. Preoperative diagnosis by endosonography-guided fine-needle aspiration (EUS-FNA) is possible and has been reported in the literature in pancreatic tumors. However, its usefulness is still controversial. The aim of this study was to determine the accuracy of the EUS-FNA in the diagnosis of patients with SPN and describe the findings in computerized tomography (CT), magnetic resonance cholangiopancreatography imaging (MRI/MRCP), and EUS therefore comparing the imaging methods alone to the findings of microhistology (McH) obtained by EUS-FNA. ***Materials and Methods:*** We retrospectively reviewed the medical records of patients undergoing EUS-FNA with suspected SPN in imaging studies in 5 Brazilian high-volume hospitals (two university hospitals and three private hospitals). The demographic data; findings in CT, MRI/MRCP, and EUS; and McH results obtained by EUS-FNA were noted prospectively. The final diagnosis was obtained after the anatomopathological examination of the surgical specimen in all patients (gold standard), and we compared the results of CT, MRI/MRCP, EUS, and the McH with the gold standard. ***Results:*** Fifty-four patients were included in the study, of which 49 (90.7%) were women with an average age of 33.4 (range 11–78) years. The most common symptom presented was abdominal pain, present in 35.2% patients. SPN was detected incidentally in 32 (59%) patients. The average size of the tumors was 3.8 cm (SD: 2.26). The most common finding at EUS

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was a solid, solid/cystic, and cystic lesion in 52.9%, 41.1%, and 7.8% patients, respectively. The final diagnosis was 51 patients with SPN and 3 with nonfunctioning pancreatic neuroendocrine tumors (NF-NET). The correct diagnosis was made by CT, MRI/MRCP, EUS isolated, and EUS-FNA in 21.9%, 28.88%, 64.71%, and 88.24%, respectively. EUS-FNA associated with CT and MRI increased diagnostic performance from 22.72% to 94.11% and from 29.16% to 94.11%, respectively. ***Conclusions:*** SPN are rare, incidentally identified in most cases, and affect young women. Differential diagnosis between SPN, NF-NET, and other types of tumors with imaging tests can be difficult. EUS-FNA increases preoperative diagnosis in case of diagnostic doubt and should be used whenever necessary to rule out NF-NET or other type of solid/cystic nodular lesion of the pancreas.

Estudo Multicêntrico Comparando o Desempenho dos Exames de Imagem com a Punção Aspirativa por Agulha Fina Guiada por EUS no Diagnóstico de Neoplasias Pseudopapilares Sólidas do Pâncreas

Palavras chaves
Ultrassom endoscópico · Aspiração por agulha fina guiada por ultrassom endoscópico · Diagnóstico · Câncer de pâncreas · Patologia/Cirurgia · Neoplasia pancreática · Tumor sólido pseudopapilar · Neoplasia sólida pseudopapilar

Resumo
Introdução: O diagnóstico por imagem da neoplasia pseudopapilar sólida do pâncreas (NPS) é difícil. O diagnóstico pré-operatório obtido pela endosonografia com punção aspirativa por agulha fina (USE-PAF) é possível e tem sido relatado na literatura em tumores do pâncreas. No entanto, sua indicação é controversa e merece discussão. O objetivo do estudo foi determinar a acurácia da USE-PAF no diagnóstico de pacientes com NPS, descrever os achados da tomografia computadorizada (TC), colangiopancreatografia por ressonância magnética (RM/CPRM) e USE, comparando os métodos de imagem isolados aos achados da microhistologia (McH) obtida pela USE-PAF. ***Material e Métodos:*** Revisamos retrospectivamente os prontuários de pacientes submetidos à USE-PAF com suspeita de NPS em exames de imagem de 5 hospitais brasileiros de alto volume (dois universitários e três privados). Foram anotados prospectivamente os dados demográficos, os achados da TC, RM/CPRM e USE e o resultado da McH obtida pela USE-PAF. O diagnóstico final foi obtido após o anatomopatológico da peça operatória em todos os pacientes (padrão-ouro). Comparamos os resultados da TC, RM/CPRM, EUS isoladas e da McH obtida pela USE-PAF com o padrão-ouro. ***Resultados:*** Cinquenta e quatro pacientes foram incluídos no estudo, 49 (90.7%) eram mulheres com média de idade de 33.4 (11–78) anos. O sintoma mais frequente foi dor abdominal, presente em 35.2%. A NPS foi detectada acidentalmente em 32 (59%) pacientes. O tamanho médio da lesão foi de 3.8 cm (SD: 2.26). O achado mais comum à USE foi lesão sólida, sólida/cística e cística em 52.9%, 41.1% e 7.8%, respectivamente. O diagnóstico final foi NPS (51) e tumor neuroendócrino pancreático não funcionante [NF-NET] (3). O diagnóstico correto feito pela TC, RM, USE e USE-PAF foi feito em 21.9%, 28.9%, 64.7% e 88.2%, respectivamente. A USE-PAF associada a TC e a RM aumentou o desempenho diagnóstico de 21.9% para 94.1% e de 28.8% para 94.1%, respectivamente. ***Conclusões:*** NPS são raras, identificadas de forma acidental na maioria dos casos e afetam principalmente mulheres jovens. O diagnóstico diferencial entre NPS, NF-NET e outros tipos de lesões com exames de imagem isolados pode ser difícil. A USE-PAF aumenta a chance do diagnóstico pré-operatório em caso de dúvida diagnóstica e deve ser usado sempre que necessário para descartar NF-NET ou outro tipo de lesão nodular sólida ou sólido/cística do pâncreas.

Introduction

Pancreatic solid-pseudopapillary neoplasms (SPN) are rare, and 90% occur in women in their 3rd and 4th decades of life [1]. The symptoms are nonspecific or absent and are mostly incidentally diagnosed during imaging exams such as abdominal ultrasound, computerized tomography (CT), or magnetic resonance cholangiopancreatography imaging (MRI/MRCP) [2]. SPN appears as a circumscribed, encapsulated, solid mass but eventually with cystic areas [3]. Most patients have localized disease, and up to 15% have metastasis or vascular invasion [4]. Conventional treatment is surgical resection, and unlike pancreatic ductal adenocarcinoma (PDAC), the result is favorable with a 5-year survival rate of 97% [1].

Based on isolated imaging exams, the accurate diagnosis of SPN is difficult, especially in solid or solid/cystic lesions, and can commonly mimic a nonfunctioning pancreatic neuroendocrine tumor (NF-NET), serous cystad-

enoma (SCA), and less commonly a PDAC [5]. Surgical indication is based on the presence of a pancreatic nodule, usually leading to the execution of a procedure with a high morbidity and mortality rates without a preoperative diagnosis and previous anatomopathological confirmation. Endosonography (EUS) is increasingly being used in the evaluation of pancreatic tumors. The classificatory diagnosis made by preoperative EUS-guided fine-needle aspiration (EUS-FNA) (NF-NET <2.0 cm or SCA) would prevent unnecessary surgery. Recently, some studies evaluated the role in EUS-FNA in SPN [6–11], as well as comparing it with CT [12] and MRI for diagnosis, but its accurate performance in SPN diagnosis remains unclear. The aim of this study was to describe the imaging findings (CT and MRI/MRCP) and compare them to the accuracy of the EUS-FNA in the preoperative differential diagnosis of pancreatic solid or solid/cystic lesions.

Materials and Methods

This was a retrospective and multicentric case series, carried out in three reference university hospitals and two private tertiary referral hospitals in Brazil. The study was approved by the Research Ethics Committee of each institution and complied with the regulations of the Health Insurance Portability and Accountability Act (HI-PAA). The study was approved by the Research Ethics Committee on 07/22/2019 under number: 3.518.999.

The medical records of all patients submitted to EUS-FNA in the digestive endoscopy sectors of each of the centers involved in the study, between January 1997 and January 2020, were retrospectively reviewed. The selected patients had EUS-FNA before surgery and had suspected diagnosis of SPN, NF-NET, SCA, or other type of pancreatic lesion at CT, MRI/MRCP, and EUS with postoperative pathological evaluation detected SPN. All selected patients signed an informed consent form before undergoing EUS-FNA. Age, sex, symptoms and CT, MRI, and EUS-FNA findings were noted, and the final diagnosis was obtained after the histological examination of the surgical specimen in all patients.

EUS was performed with conscious sedation or anesthesia monitored by an anesthesiologist. All procedures were performed by experienced doctors, always using a linear echoendoscope. All biopsies were made under the same procedure. Specifics of the fine-needle gauge (19 G, 22 G, 25 G, and 20 G), number of needle passes, and results of microhistology (McH), in addition to the surgical pathology results, were recorded. The occurrence of adverse events (AE) was also documented.

Sample Handling

Samples obtained by FNA were deposited in 10% formalin (6–24 h) and followed the routine of the pathological anatomy sector of each center participating in the study. The blocks and biopsies embedded in paraffin were subjected to semi-series histological sections of 3-μm thick, at three different depth levels, stained by the hematoxylin-eosin (H/E) method. CellSens Micro Imaging Software (Olympus America Inc., Center Valley, PA, USA) was used to dimension samples in millimeters.

The diagnosis of SPN was confirmed through histology with H/E and, when possible, immunohistochemistry (IHC). The sections stained with H/E from both FNA and surgical samples were reviewed by specialized pathologists to confirm the diagnosis. The IHC markers (primary antibodies) used in the analysis included β-catenin, CD10, progesterone receptor, CD99, and chromogranin A [13].

Statistical Analysis

The collected and recorded data were stored in a database. The statistical analysis of continuous variables was described as mean and standard deviation and dichotomous variables expressed as simple proportions. The definitive diagnosis of SPN was based on surgical histological analysis specimen, and the patients who did not have it were excluded from the study. True-positive cases were the ones that after undergoing CT, MRI/MRCP, EUS, and McH had the SPN diagnosis histologically confirmed. True-negative cases were the ones that after undergoing imaging test or McH had the NF-NET or SCA diagnosis like a final diagnosis. False-positive cases were the ones that after undergoing imaging test or McH had the SPN, but the final diagnosis was different. False-negative were the ones that after undergoing imaging tests or McH revealed a different diagnosis from the SPN. To assess the diagnostic gain acquired with the combination of imaging tests, the numbers of truly positive cases from each method were added. The comparison between the results obtained in the imaging exams was performed using the McNemmar test for each pair of groups (CT + EUS; CT + EUS-FNA; MRI + EUS; and MRI + EUS-FNA). The association between the size of the needle used and the diagnosis obtained in the McH was tested using Fisher's exact test. The level of statistical significance adopted was 95%. The analyses were performed using the Stata 14 software.

Results

Fifty four patients with suspected SPN were initially studied. Three patients had a NF-NET tumor type G1 as a final diagnosis after surgical resection. The others (n = 51) had the diagnosis of SPN confirmed by McH, anatomopathological report of the surgical specimen, and IHC analysis. Of the 51 patients with confirmed SPN, 90.2% (n = 46) were female and 9.8% (n = 5) were male, and the mean age was 33.6 years (SD 14.46) (Table 1).

It was noted that 21 (41.2%) patients were symptomatic, being the most common symptoms abdominal pain and weight loss associated with nausea or vomiting. Jaundice was present in 4 (7.8%) patients. SPN was detected incidentally in 32 (59.3%) of the patients. The average size of the lesion was 3.8 cm (SD 2.26), and the lesions were distributed between the body (20), head/uncinate (22), and tail (9) portions of the pancreas. One patient had two synchronous lesions identified on the body and tail of the

Table 1. Characteristics of patients submitted to EUS-FNA with suspected diagnosis of SPN on imaging exams in 5 different endoscopy centers in Brazil between January 1997 and January 2020

	N	%
Sex		
Female	46	90.2
Male	5	9.8
Age	Average: 33.66	SD: 14.46
Symptoms		
Asymptomatic	30	58.8
Abdominal pain	18	35.2
Weight loss	6	11.7
Nausea/vomiting	7	13.7
Jaundice	4	7.8
Acute pancreatitis	2	3.9
Blunt trauma	2	3.9
Tumor size	Average: 3.87	SD: 2.26
Tumor location		
Head	22	43.14
Body	20	39.22
Tail	9	17.65
Echogenicity		
Solid/cystic	21	41.1
Cystic	4	7.8
Solid	27	52.9
Margin		
Well defined	42	82.3
Infiltrative	9	17.7
Calcification	3	5.8
Extrapancreatic spread		
Vascular involvement	4	7.8
Lymph node involvement	0	0
Liver metastases	0	0
Dilated main pancreatic duct, *n* (%)	5	9.8

Table 2. Relationship between the gauge used to perform fine-needle aspiration and the final histopathological result in patients with suspected SPN from 5 different endoscopy centers in the city of São Paulo between January 1997 and January 2020

	EUS-FNA McH+	EUS-FNA McH–	*p* value
Needle, *n* (%)			
19	6 (13.33)	3 (50)	0.175
20	5 (11.11)	0 (0)	
22	31 (68.89)	3 (50)	
25	3 (6.67)	0 (0)	

Table 3. Performance of imaging exams, including CT, in relation to the total number of cases that were submitted to each group of imaging exams and that later proved to be truly positive through postsurgical histological diagnosis

	CT only	CT + EUS	CT + EUS/FNA	*p* value
Truly positive test	9	34	48	<0.005
Truly positive cases	41	51	51	
Total, %	21.95	66.66	94.11	

pancreas. The solid, solid-cystic (microcystic), and cystic appearance was present in 27 (52.9%), 21 (41.1%), and 4 (7.8%) cases, respectively (Fig. 1). The lesion margin was well defined in 42 (82.3%) of the cases. Calcification was present in 3 (5.8%) patients. In 4 (7.8%) patients, there was vascular involvement detected by the EUS and confirmed by surgery, as well as dilation of the main pancreatic duct in 5 (9.8%) patients (Table 1).

EUS-FNA was performed on all patients, without the pathologist's presence of a rapid on-site evaluation (Table 2). The needles of 22 G in 34 (66.6%), 19 G in 9 (17.6%), 20 G in 5 (9.8%), and 25 G in 3 (5.8%) were used. A median of 2.5 needle passes (range 1–5) was performed for each lesion. The diagnostic performance of the EUS-FNA was not affected by the size of the needle ($p = 0.175$). No AE were documented in this case series. Surgical resection was performed in all patients who had no evidence of lymph nodes or distant metastases.

Preoperative Diagnostic Yield of CT, MRI, and EUS-FNA

CT was performed in 44 patients. PDAC was suspected in 17 (38.67%), SPN in 10 (22.72%), pancreatic cystic lesion in 4 (9.09%), NF-NET in 4 (9.09%), chronic pancreatitis in 3 (6.81%), SCA in 2 (4.54%), pancreatic pseudocyst in 2 (4.54%), hematoma after blunt trauma in 1 (2.27%), and common bile duct dilation in 1 (2.27%) case (Fig. 2). The combination of CT + EUS and CT + EUS-FNA significantly increased ($p < 0.005$) the diagnosis compared to CT only, which went from 22.72% to 66.66% and 94.11%, respectively (Table 3). The sensitivity, specificity, positive and negative predictive value, and accuracy for the SPN diagnosis obtained by CT was 22%, 66.7%, 90%, 6%, and 25%, respectively.

MRI/MRCP was performed on 48 patients. PDAC was suspected in 14 (29.16%), SPN in 14 (29.16%), pancreatic cystic lesion in 7 (14.56%), pancreatic pseudocyst in 4 (8.34%), NF-NET in 4 (8.34%), SCA in 2 (4.16%), chronic pancreatitis in 1 (2.08%), choledochal dilation in 1 (2.08%), and normal in 1 (2.08%) case (Fig. 3). The com-

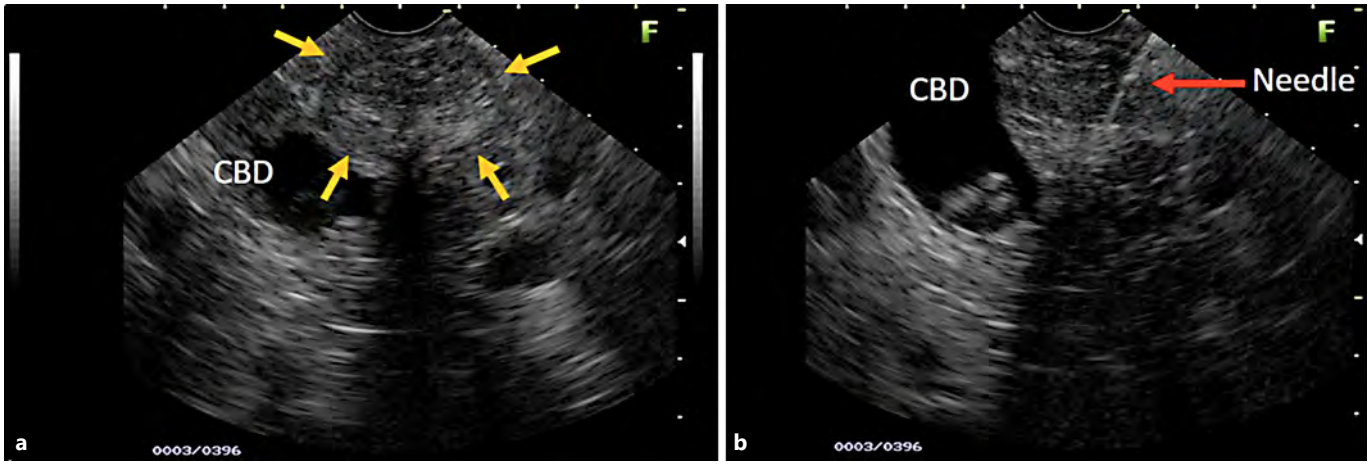

Fig. 1. a EUS image of a young patient with a hypoechoic area (yellow arrows), also heterogeneous with imprecise limits and a microcystic component, right next to the common bile duct (CBD) with stones inside (**a**, **b**). The EUS images suspected SPN. **b** Moment of the EUS-FNA (red arrow), with the 22-G needle positioned in the center of the lesion. The biopsy revealed chronic inflammatory process without evidence of SPN.

Table 4. Performance of imaging tests, including magnetic resonance imaging, in relation to the total number of cases that were submitted to each group of imaging exams and that later proved to be truly positive through postsurgical histological diagnosis

	MRI only	MRI + EUS	MRI + EUS/FNA	*p* value
Truly positive test	14	34	48	<0.005
Truly positive cases	45	51	51	
Total, %	28.89	66.66	94.11	

bination of MRI/MRCP + EUS and MRI/MRCP + EUS-FNA significantly increased ($p < 0.005$) the diagnosis compared to isolated MRI/MRCP, which went from 29.16% to 66.66% and 94.11%, respectively (Table 4). The sensitivity, specificity, positive and negative predictive value, and accuracy for the SPN diagnosis obtained by MRI was 31.2%, 66.7%, 93.3%, 6.1%, and 33.3%, respectively.

EUS alone suspected the diagnosis of SPN in 35 (64.85%). Two cases were not included in this analysis because they received a final diagnosis of NF-NET and had a previous result of SPN through EUS. EUS suspected PDAC in 9 (16.65%), NF-NET in 5 (9.25%), chronic pancreatitis in 1 (1.85%), pancreatic cystic lesion in 1 (1.85%), SCA in 2 (3.70%), and lymph node in 1 (1.85%). The McH obtained by the EUS-FNA diagnosed SPN in 45 (88.24%), NF-NET in 2 (3.92%), and was negative in 4 cases (7.84%), all confirmed as SPN after surgery. The sensitivity, specificity, positive and negative predictive value, and accuracy for the SPN diagnosis obtained by isolated EUS and EUS-FNA was 68.6%, 33.3%, 94.6%, 5.9%, and 66.7% and 90.2%, 66.7%, 97.9%, 28.6%, and 88.9%, respectively.

Discussion/Conclusion

SPN are rare [14], and the ultrasound and CT are the most used imaging methods for diagnosis and represent approximately 80% of imaging studies for the diagnosis of SPN. In the past few decades, the use of MRI has increased substantially, as has EUS, but it still accounts for only 5% of the imaging methods used for the diagnosis of SPN. In addition, there are few studies that determine the additional benefit offered by the EUS-FNA to imaging tests such as CT and MRI [15]. The benefit of the use of EUS in patients with solid and cystic pancreatic tumors with a yield approaching 78.8% and 71.4%, respectively, has been proven [16, 17]. Therefore, the inclusion of EUS-FNA increases the diagnostic accuracy of this type of tumor.

The results of this study highlight the difficulty of CT, MRI, and EUS in correctly classifying the SPN using only the image resources, with a diagnostic performance of

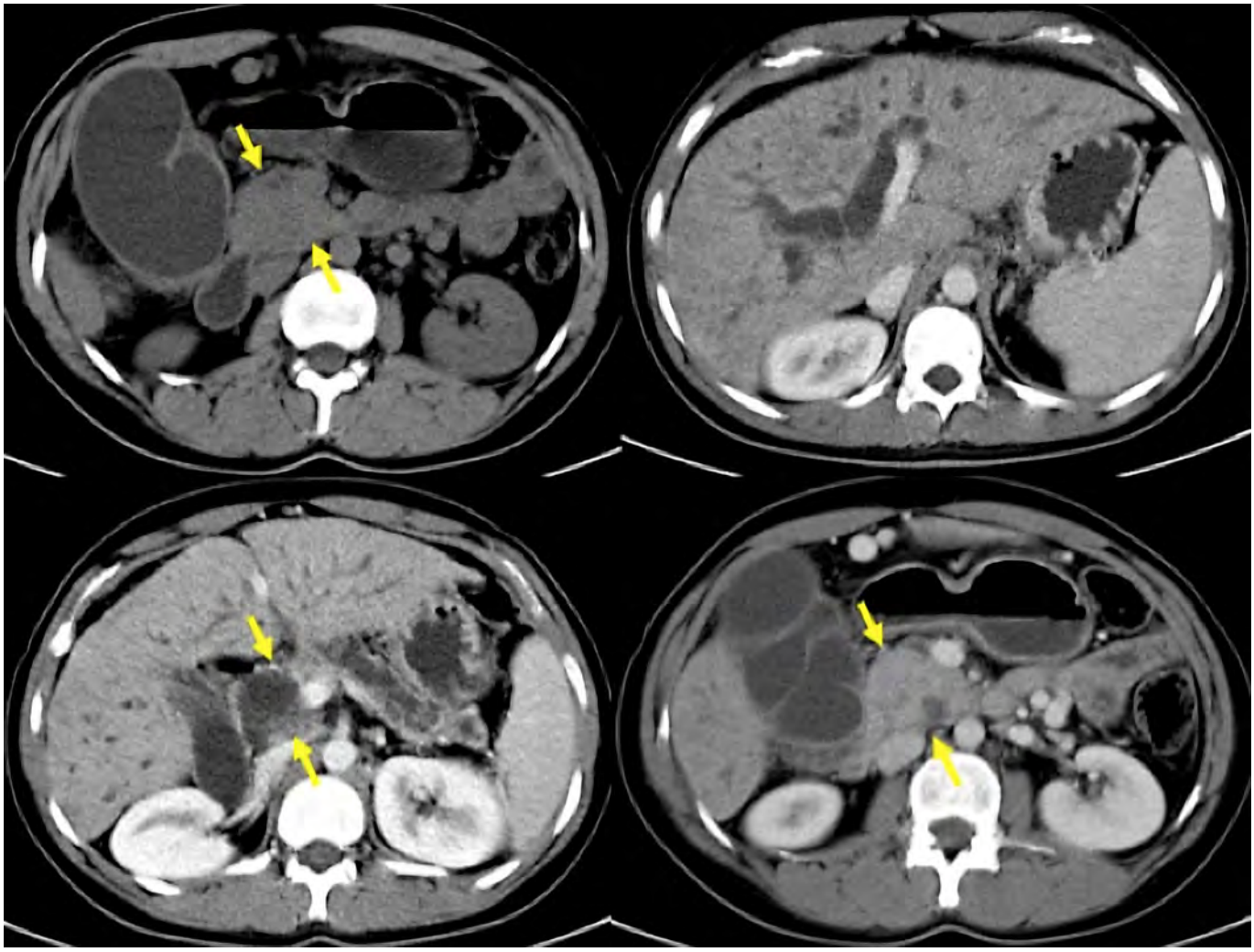

Fig. 2. CT images with enlarged pancreatic head, dilatation of the main pancreatic and choledochal duct, in addition to atrophy of the pancreatic gland in a 23-year-old woman with a history of chronic alcoholism (same case in Fig. 3).

21.95%, 28.88%, and 64.71%, respectively. These results are similar to another recent study, which was 23.5% and 41.2% for CT and EUS, respectively [12]. When we include the results of EUS-FNA, there is an increase in the diagnostic performance of CT (72.16%) and MRI (65.23%), rising up to 94.11% in both methods.

Classically, SPN are described as circumscribed, hypoechoic, solid, heterogeneous masses, and eventually with a cystic component. However, this appearance presents in just 60% of patients, with a predominantly solid lesion found in 32% of cases, suggesting a more classic appearance associated with an NF-NET [18]. In our series, the solid/cystic, solid, and cystic morphology was 52.9%, 41.1%, and 7.8%, respectively. SPN can mimic other pancreatic tumors, which can lead to diagnostic challenges [19]. This fact can be observed in our study, as CT and EUS suspected the presence of NF-NET in 9.75% and 7.8%, respectively, since the injuries identified by these exams had a predominantly solid component. When microcystic, SPN are similar to SCA and can cause diagnostic confusion, which occurred in 4% of the cases examined by CT, MRI, and EUS. The microcystic pattern must be recognized as part of the morphological spectrum of the SPN, which can lead to confusion regarding the presence of an SCA [5]. Previous CT and EUS studies, in which SPN was identified as other cystic lesions in the

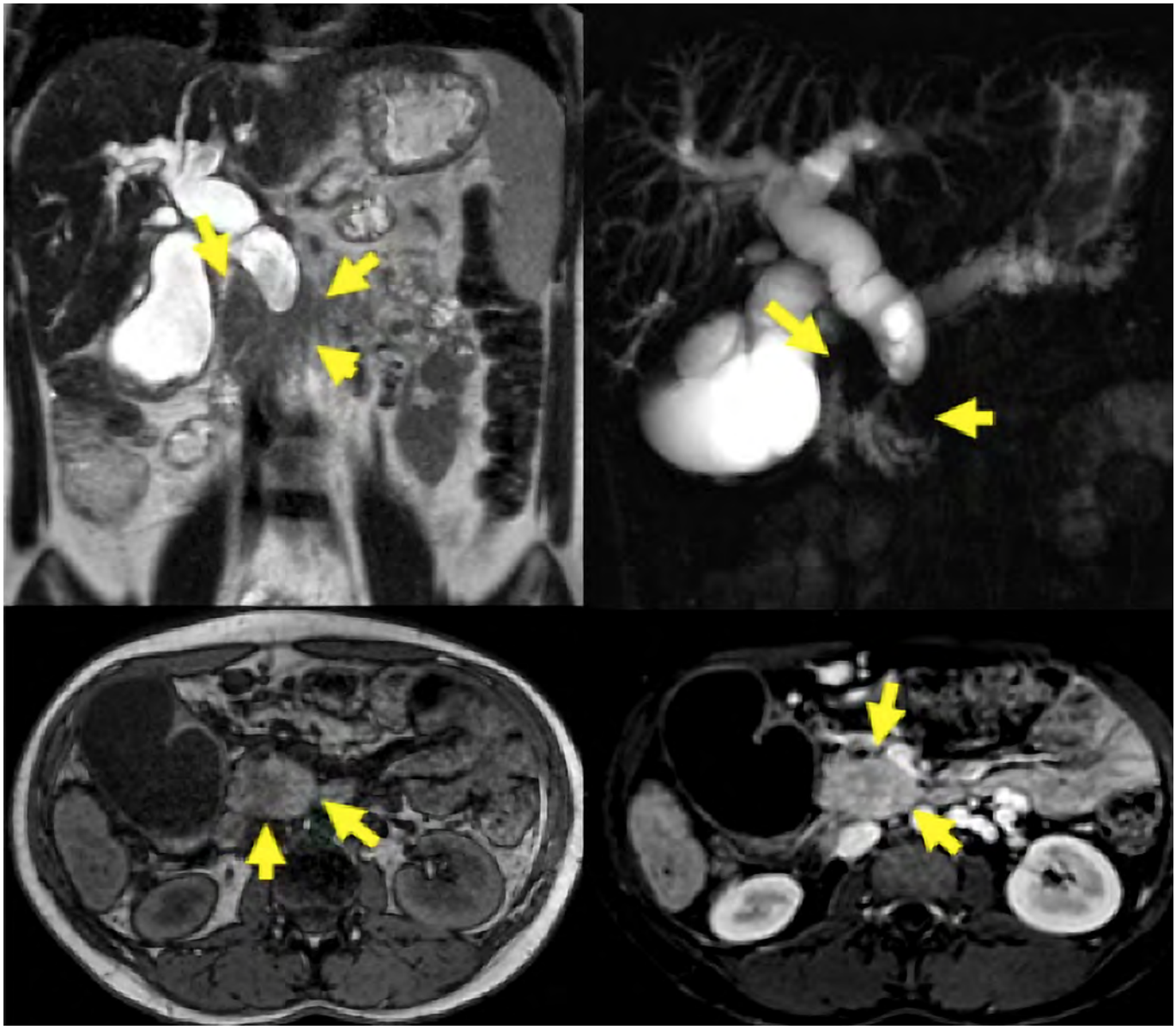

Fig. 3. A 23-year-old woman with signs of chronic pancreatitis on MRI/MRCP and an enlarged pancreatic head.

pancreas in up to 50% of cases, including benign lesions such as SCA, confirm the findings of our study [12, 20, 21].

Some cases were interpreted as pancreatic pseudocysts, highlighting the difficulty in determining the etiology of a cystic lesion based only on morphological characteristics of the image. This occurred in 7.31% and 15.55% of CTs and MRIs, respectively. Therefore, the importance of correctly classifying SPN is emphasized in this study, where 8 (33.3%) cysts were erroneously classified by CT, as pseudocysts (2), unspecific pancreatic cystic lesion (2), unspecific pancreatic cystic lesion with calcification (2), hematoma (1), and SCA (1), all which have prognosis and management completely different from those adopted in SPN. The same happened with MRI/MRCP which was normal in 3 patients and identified unspecific pancreatic cystic lesion in 4 and pseudocyst in 3 patients.

In the literature, rupture of the SPN is associated with abdominal trauma or may be spontaneous, which is rare.

To date, there have been only 3 cases of SPN with spontaneous rupture reported worldwide [22]. In our series, we had two young patients with blunt abdominal trauma who underwent imaging exams that suspected hematoma (1) and pancreatic pseudocyst (1). In these two cases, the EUS-FNA was crucial for the diagnosis of SPN, changing the management of these patients.

The ultimate aim of this study was to confirm the benefit of performing the EUS-FNA to increase the diagnostic performance of other conventional imaging tests such as CT and MRI. The EUS-FNA association increased diagnostic yield by almost 72.16% for CT and 65.23% for MRI. The results are similar to previous studies, which report a low sensitivity rate and absence of AE as in the current series [12]. Regarding the AE resulting from the EUS-FNA, the first case of neoplastic cell implantation in the stomach was recently described [23]. In our series, even after prolonged follow-up and interviews with patients and attending physicians, we did not observe this type of complication.

Two particular cases deserve to be discussed, since they had a strong suspicion of SPN on imaging exams. In the first, CT and MRI confirmed the diagnosis of pseudocyst, the EUS suspected SPN, and the EUS-FNA revealed NF-NET, which was confirmed by uncinate process resection. The second had CT, MRI, and EUS image exams with SPN morphology (solid-cystic), the McH obtained by EUS-FNA confirmed the presence of SPN, but the operative piece confirmed NF-NET. In this case, the diagnosis by McH confirming SPN was performed only by HE, as there was not enough material to perform the IHC. These findings corroborate those found in the literature where the EUS-FNA performed on suspected SPN has excellent positive and negative predictive value; however, the most common classification errors were with NF-NET which presents no clinical impact, just as it was observed in our series [7]. In addition, in 177 patients studied by the EUS-FNA with suspected NF-NET, discrepancies were reported in 14 patients. In 4 of them, the erroneous diagnosis was SPN. Accordingly, it is concluded that when an adequate sample is obtained, the most significant error is the incorrect classification, which is more often associated with SPN, but the damage associated with this diagnostic error is minimal [24].

The authors conclude that SPN are rare, incidentally identified in most cases and affect young women. Isolated CT, MRI/MRCP, and EUS have low rates of correct diagnosis, but the association with EUS-FNA increases preoperative diagnosis and should be used whenever necessary to rule out other pancreatic diseases such as NF-NET, SCA, or other type of solid/cystic nodular lesion of the pancreas. These results suggest that patients who do not have a clear diagnosis of SPN, as is usually the case, should undergo EUS-FNA.

Statement of Ethics

The study was approved by the Research Ethics Committee of each institution and complied with the regulations of the Health Insurance Portability and Accountability Act (HI-PAA). The study was approved by the Research Ethics Committee on 07/22/2019 under number: 3.518.999. All selected patients signed an informed consent form before undergoing EUS-FNA.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Vítor Doria Ricardo designed the study, drafted the article, and analyzed and interpreted the data; Giulia Marchetti, Arthur Ferraz de Almeida, César Vivian Lopes, Jerusa dos Santos Reis, Eduardo Aimoré Bonin, Wladimir Campos de Araújo, Marcel Autran Machado, and Samuel Galante Romanini analyzed the data. José Celso Ardengh approved the final version to be published. All the authors read and approved the final manuscript.

Data Availability Statement

The medical records of all patients submitted to EUS-FNA in the digestive endoscopy sectors of each of the centers involved in the study, between January 1997 and January 2020, were retrospectively reviewed. The selected patients had suspected diagnosis of SPN at CT, MRI, and EUS or with postoperative pathological evaluation. Age, sex, symptoms and CT, MRI, and EUS-FNA findings were noted, and the final diagnosis was obtained after the histological examination of the surgical specimen. All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Endoscopic Snapshot

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Gastric Bleeding: When the Image Says It All

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Keywords
Gastrointestinal stromal tumors · Hemorrhage · Endoscopic hemostasis

Hemorragia gástrica: quando a imagem fala por si

Palavras Chave
Tumores do estroma gastrointestinal · Hemorragia digestiva · Hemostase endoscópica

A 61-year-old man presented to the emergency department with hematemesis. The patient referred epigastric pain, anorexia, and vomits for the past 3 days. He had a medical history of dyslipidemia and chronic venous insufficiency under treatment with bioflavonoids and a statin. Physical examination was unremarkable. Laboratorial analysis revealed a serum hemoglobin of 9.6 g/dL (normal range 13–18 g/dL). Fluids and a bolus of esomeprazole were administered, and the patient was submitted to an esophagogastroscopy (Fig. 1). Esophagogastroscopy revealed a 5-cm spheric subepithelial lesion with central ulceration and pulsatile bleeding in the posterior wall of the gastric corpus (Fig. 1). Endoscopic treatment was performed with adrenalin injection in the ulcer margins and application of 4 clips on the vessel, which controlled the bleeding. Bite-on-bite biopsies of the ulcer borders were performed due to the suggestive features of a ruptured gastrointestinal stromal tumor (GIST) [1]. Due to the impossibility of complete closure of the ulcer and doubts if the bleeding completely stopped, *hemospray*® was applied over the lesion (Fig. 2). The biopsy samples were insufficient for histological characterization. A CT scan revealed a 5-cm nodular lesion with heterogeneous contrast enhancement in the posterior wall of the stomach without evidence of invasion of adjacent structures or metastatic disease. The differential diagnosis should be made with other potentially malignant subepithelial lesions of the stomach, namely, leiomyoma, glomus tumor, or neuroendocrine tumor. Nevertheless, the alternative diagnoses were less likely due to the ulceration, the location of the lesion, and the heterogeneous contrast enhancement in the CT scan [1–3].

The patient was submitted to an elective partial gastrectomy. The histological exam confirmed the diagnosis of a GIST with positive immunohistochemical staining for CD34, CD117, and DOG1 with preserved SDHB expression (stage pT2 G1 N0 R0) [4, 5]. One year after the diagnosis, the patient has no evidence of disease. This endoscopic snapshot illustrates a typical presentation of a large gastric GIST with massive luminal bleeding [5]. Endoscopic treatment was performed with success as a bridge to surgery [5].

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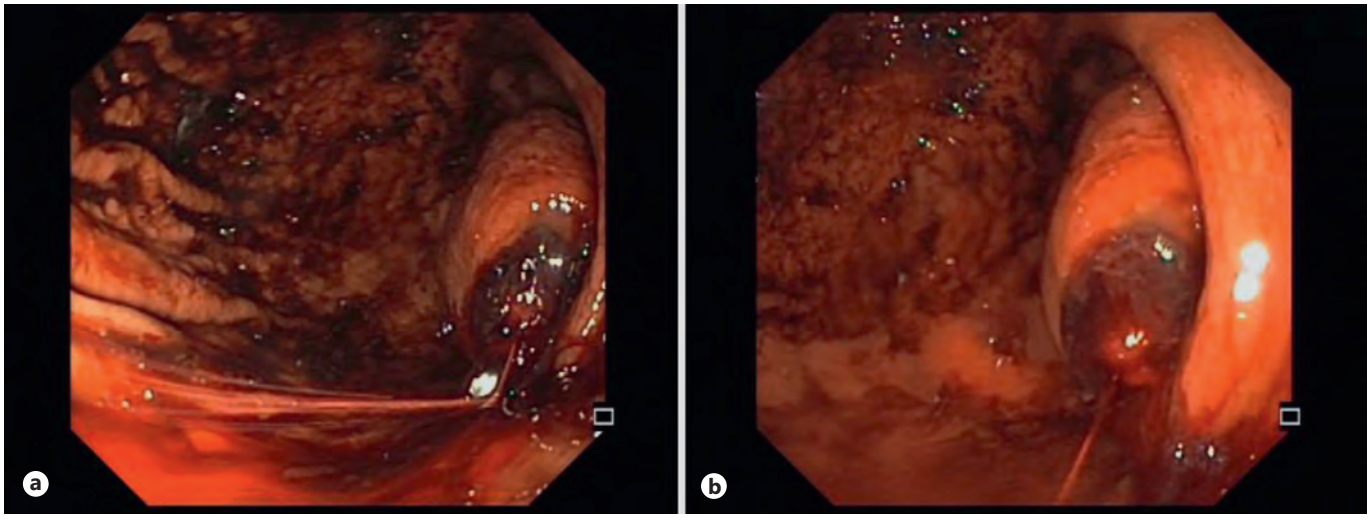

Fig. 1. a, **b** Endoscopic view of the gastric corpus before endoscopic treatment.

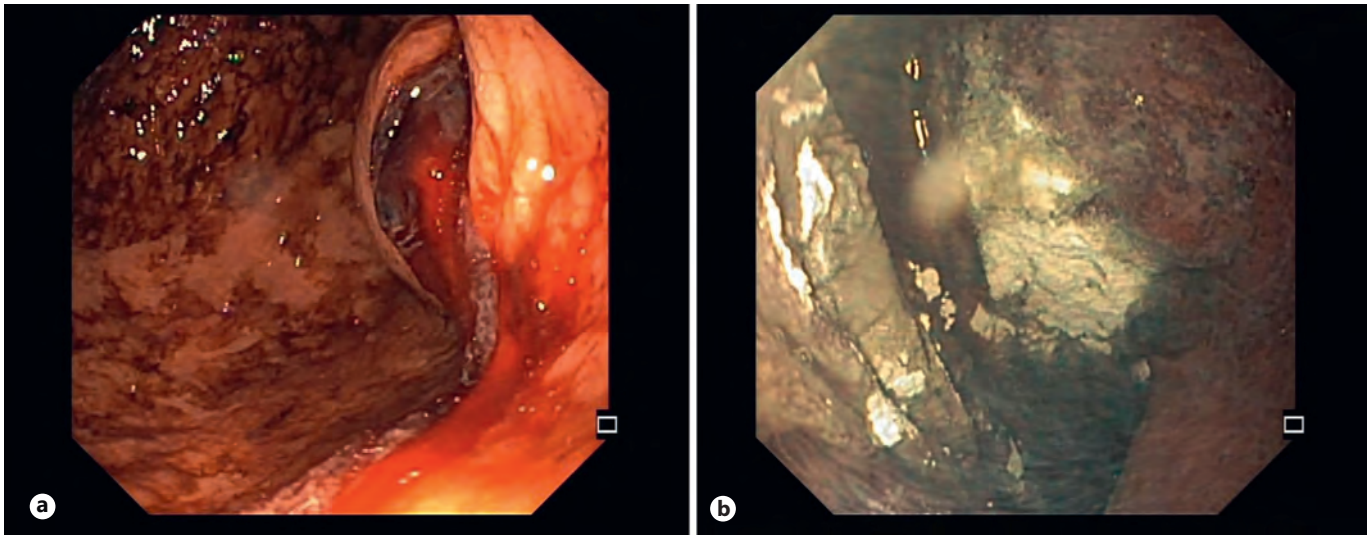

Fig. 2. Endoscopic view of the gastric corpus after adrenalin injection in the bleeding lesion (**a**) and at the end of the endoscopic treatment (**b**).

Statement of Ethics

Written informed consent was obtained from the patient 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

The authors have no funding to declare.

Author Contributions

S.S.M. performed the endoscopy and drafted the manuscript; R.G. and A.C.C. provided critical revision and completed the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author (S.S.M.) upon reasonable request.

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Gastric Peroral Endoscopic Myotomy as a Therapeutic Option in Refractory Gastroparesis: A Step-By-Step Description

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Keywords
Gastric peroral endoscopic miotomy · Endoscopic pyloromyotomy · Refractory gastroparesis · Pyloroplasty

G-POEM como opção terapêutica na gastroparesia refratária – uma descrição passo a passo

Palavras Chave
Miotomia endoscópica gástrica per-oral · Gastroparesia refratária · Piloromiotomia endoscópica · Piloroplastia

Gastroparesis is a chronic disorder characterized by delayed gastric emptying without evidence of stomach or proximal small intestine obstruction [1]. Its pathophysiology is unclear, although gastric arrhythmias, fundal and antral hypocontractility, pylorospasm, and antropyloroduodenal incoordination might be involved [1]. Dietary modifications and prokinetics are first-line treatments. When refractory gastroparesis is present, surgical or endoscopic treatment must be considered.

We present a case of a 68-year-old female patient, followed in gastroenterology consult due to nausea, persistent postprandial vomiting, early satiety, and belching. She has no relevant past medical or surgical history or medication. Esophagogastroduodenoscopy revealed food stasis but was otherwise normal. Gastric emptying scintigraphy (GES) showed emptying of 30% at 156 min, 46% at 217 min, and 54% at 260 min, with significant radiopharmaceutical retention (46% at 4 h 18 min), translating scintigraphic evidence of delayed gastric emptying (Fig. 1). The diagnosis of gastroparesis was made, and medical therapy was optimized. She had no improvement after 6 months, traducing a Gastroparesis Cardinal Symptom Index (GCSI) score of 3.33 points (0–5 points) [2]. Idiopathic refractory gastroparesis was admitted, and gastric peroral endoscopic myotomy (G-POEM) was proposed.

The procedure was performed with an endoscope (GIF-HQ190; Olympus Medical Systems, Tokyo, Japan), with a transparent distal cap (DH28GR; Fujifilm, Tokyo, Japan) and insufflation with CO_2. The patient was under general anesthesia and orotracheal intubation. The VIO®3 (Erbe Elektromedizin GmbH, Tuebingen, Germany) was used as the electrosurgical unit. Antibiotic (cefotaxime 1 g) was administered. The procedure began with submucosal injection, in the greater gastric curvature, 5 cm proximal to the pylorus with a solution of 100

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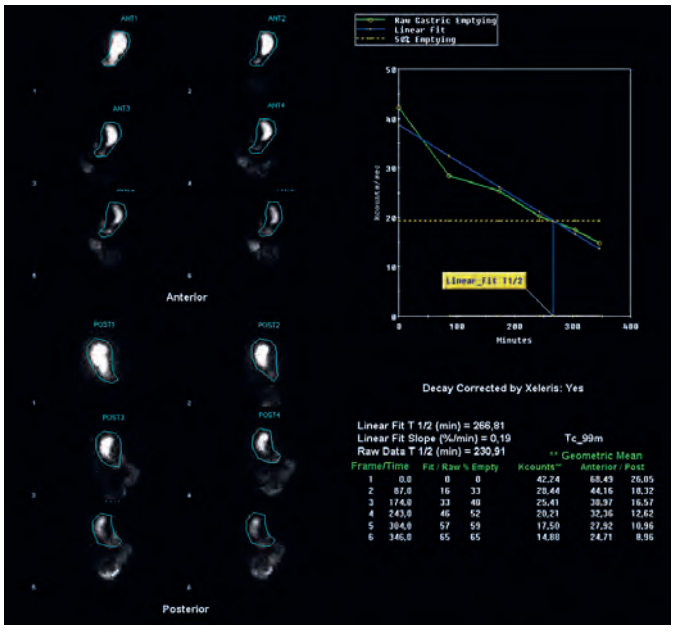

Fig. 1. Scintigraphic images before the G-POEM, with evidence of delayed gastric emptying.

mL normal saline, 1 mL indigo carmine, and 1 mL adrenaline, followed by a mucosal longitudinal incision with a triangle-tip knife, using dry-cut current effect 2. Then, a submucosal tunnel was created from the mucosal incision to the pylorus, with spray-coagulation current. Full-thickness pyloromyotomy involving circular and oblique muscle bundles was performed, from the pylorus extending 3 cm proximally toward the antrum (using triangle-tip and IT-nano™ knives [KD-640L, KD-612L/U; Olympus] with spray-coagulation and Endocut Q currents). The mucosal incision was closed with several clips (online suppl. video; see www.karger.com/doi/10.1159/000527016 for all online suppl. material,; Fig. 2a–f). The procedure was uneventful. On the day after, a gastro-duodenal transit excluded leakage. She started a liquid diet, with good tolerance, and was discharged on the second day, medicated with 40 mg pantoprazole bid and ciprofloxacin for 7 days. She was on a soft diet for 1 week and then proceeded to small meals low in fiber and fat.

Three months post-procedure, the GCSI score was of 2.11 points. Reassessment scintigraphy showed 29% gastric emptying at 50 min, 64% at 113 min, and 95% at 194

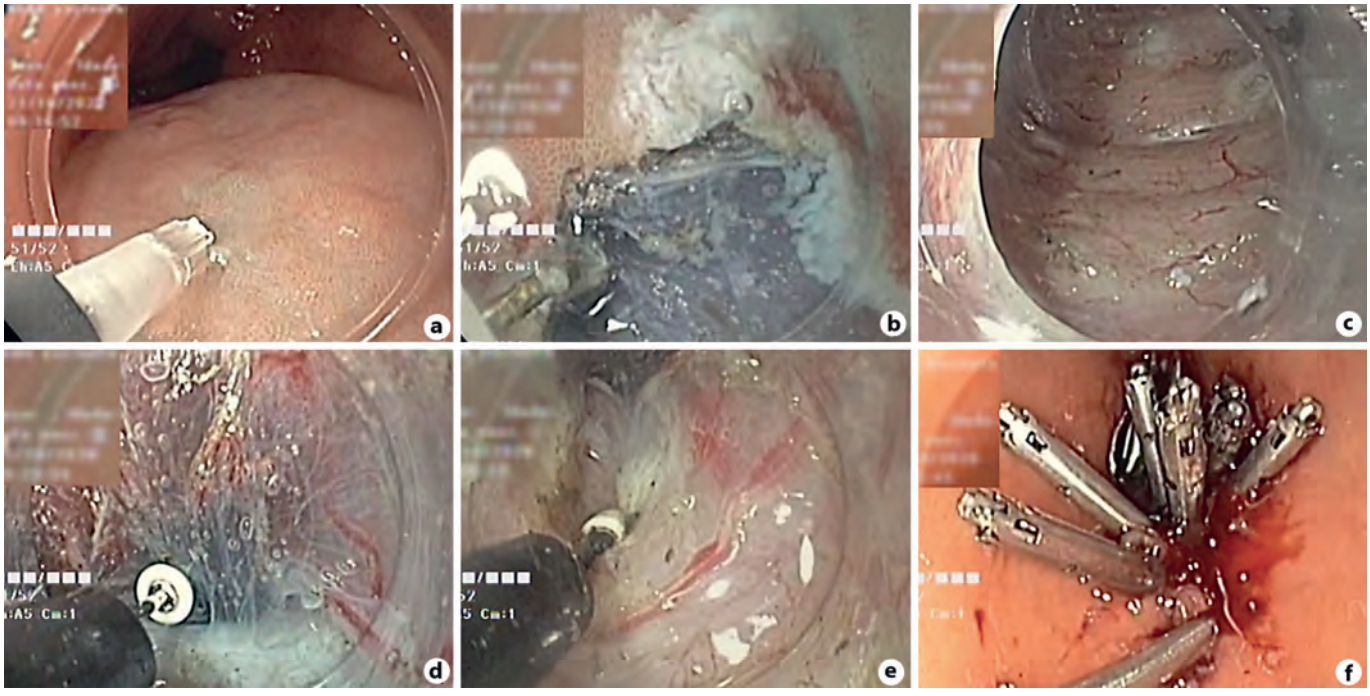

Fig. 2. a Submucosal injection 5 cm proximal to the pylorus. **b** Mucosal longitudinal incision. **c** Submucosal tunnel creation from the mucosal incision to the pylorus. **d**, **e** Full-thickness pyloromyotomy – from the pylorus extending 3 cm proximally toward the antrum. **f** Mucosal incision closed with clips.

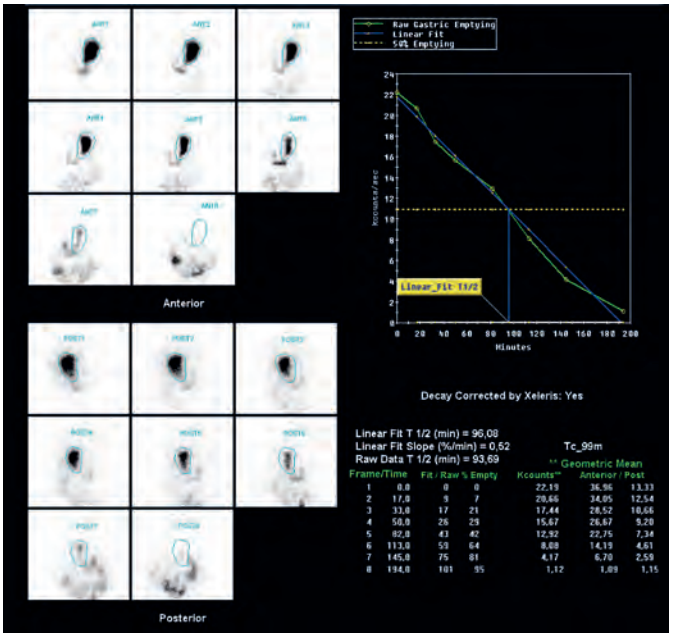

Fig. 3. Scintigraphic images after the G-POEM, with no evidence of delayed gastric emptying at any time.

min, with no evidence of delayed gastric emptying at any time (Fig. 3).

G-POEM has a reported clinical success rate of 56–90% [3, 4], with described clinical improvement sustained up to 12–18 months after the procedure [3, 5]. Most adverse events are mild, being capnoperitoneum the most common [1, 3]. When compared to surgical pyloroplasty, G-POEM has similar clinical success in terms of GCSI score and GES, with comparable adverse events [1]. According to a multicentric prospective study, G-POEM should be considered in patients with more severe symptoms along with significant retention on GES [3]. The G-POEM represents an advance in the endoscopic approach of refractory gastroparesis, with the advantage of being a minimally invasive technique.

Statement of Ethics

Ethical approval was not required for this study in accordance with local/national guidelines. The patient gave her written informed consent to publish this case and images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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None

Author Contributions

Carolina Chálim Rebelo is responsible for writing the clinical case and review of literature, and edited the video and script of the manuscript. Nuno Nunes performed the procedure, gave important scientific input, and reviewed the manuscript. Diogo Bernardo Moura and Francisca Corte-Real contributed with review of the literature. José Renato Pereira and Maria Antónia Duarte guaranteed the accuracy of the content and did the final review before submitting.

Data Availability Statement

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

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Clinical Case Study

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Infliximab Induction Strategies in Corticosteroid-Refractory Acute Severe Ulcerative Colitis: A Case Series and Literature Review

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Keywords
Acute severe ulcerative colitis · Accelerated infliximab induction · Intensified infliximab induction

Abstract
Acute severe ulcerative colitis (ASUC) is an emergent medical condition and particularly challenging to treat efficaciously. Infliximab is one of the medical salvage treatment options after corticosteroid refractoriness, but the best induction strategy is not yet defined. With this case series, the authors intend to describe three corticosteroid-refractory ASUC cases with different intensified/accelerated infliximab induction approaches and review the literature on this topic.The first case describes an 18-year-old girl with ASUC at disease onset with rapid progression to toxic megacolon, complicated also with anemia, hypoalbuminemia, and coagulopathy. After corticosteroid failure, both accelerated and intensified (10 mg/kg) infliximab regimen was completed within 11 days, with solid clinical response and colon imaging normalization. Second, we present a 26-year-old male with left-sided ulcerative colitis known for 2 years, under mesalazine, who developed a moderate flare and was started on infliximab after partial and inconsistent response to corticosteroids. During the induction period, he presented this time an ASUC episode, which motivated an early and intensified third dose with good clinical response. Finally, we describe the case of a 78-year-old man with ulcerative proctitis for 12 years presenting ASUC with proximal disease extension as well. After unsatisfactory response to corticosteroids, infliximab was initiated on an accelerated induction regimen, completed in 13 days, with the standard dose, achieving clinical remission. Accelerated or intensified infliximab induction plans are becoming current clinical practice in corticosteroid-refractory ASUC. Current guidelines refer to the possibility of this type of strategies, not determining the optimal regimen due to lack of solid evidence. Literature is mainly based on retrospective studies, not randomized, with heterogeneous groups according to disease severity, and the effect on colectomy rates, mainly on the long term, is not clear. Additional well-supported studies are needed on this subject in order to seek a more widely uniform approach.

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Estratégias de indução de infliximab na agudização de colite ulcerosa grave: uma série de casos e revisão da literatura

Palavras Chave
Agudização grave de colite ulcerosa · Indução acelerada infliximab · Indução intensificada infliximab

Resumo
A agudização grave de colite ulcerosa é uma emergência médica, particularmente difícil de tratar de forma eficaz. O infliximab é uma das opções de tratamento médico de resgate após refractariedade aos corticosteróides, porém a melhor estratégia de indução ainda não está definida. Com este relato de série de casos, os autores pretendem descrever três casos de agudização grave de colite ulcerosa refratária a corticosteróides com diferentes abordagens de indução intensificada/acelerada de infliximab e rever a literatura sobre este tópico. O primeiro caso descreve uma jovem de 18 anos com agudização grave de colite ulcerosa, à apresentação da doença, com rápida progressão para megacólon tóxico, complicada também com anemia, hipoalbuminemia e coagulopatia. Após ausência de resposta a corticosteróides, foi iniciado regime acelerado e intensificado (10 mg/kg) de infliximab, concluído em 11 dias, com resposta clínica e normalização das alterações imagiológicas do cólon. Em segundo lugar, apresentamos um homem de 26 anos com colite ulcerosa esquerda conhecida há 2 anos, sob messalazina, que apresentou uma agudização moderada da doença e iniciou infliximab após resposta parcial e inconsistente aos corticosteróides. Durante o período de indução, apresentou desta vez um episódio de agudização grave, o que motivou uma terceira dose precoce e intensificada com boa resposta clínica. Por fim, descrevemos o caso de um homem de 78 anos com proctite ulcerosa há 12 anos apresentando agudização grave de colite ulcerosa, também com extensão proximal da doença. Após resposta insatisfatória a corticosteróides, foi iniciado infliximab em regime de indução acelerada, completado em 13 dias, com a dose padrão, obtendo remissão clínica. Os esquemas de indução de infliximab acelerados ou intensificados têm vindo a tornar-se prática clínica habitual nos casos de agudização grave de colite ulcerosa refratária a corticosteróides. As diretrizes atuais referem a possibilidade deste tipo de estratégias, não indicando qual o regime ideal por falta de evidência sólida. A literatura baseia-se principalmente em estudos retrospetivos, não randomizados, com heterogeneidade de grupos de estudo de acordo com a gravidade da doença e o efeito nas taxas de colectomia, sobretudo a longo prazo, não é claro. Estudos mais fundamentados são necessários sobre esta matéria de modo a que seja possível uma abordagem amplamente mais uniforme.

Introduction

Ulcerative colitis (UC) is a lifelong disease characterized by chronic and continuous inflammation of the colon and rectum. Acute severe ulcerative colitis (ASUC) is a particular disease setting in inflammatory bowel disease [1] and is diagnosed according to the Truelove and Witts [2] criteria, combining signs of clinical disease severity and systemic toxicity. Despite the recent advances in inflammatory bowel disease management, it still constitutes a clinical and therapeutic challenge, with a 10–20% risk of early colectomy [3–5].

Corticosteroid therapy is the mainstay of ASUC treatment, which is successful in around two-thirds of patients. In steroid-refractory patients, infliximab (IFX) is well established as a second-line treatment in ASUC management [1, 6, 7].

Several pathophysiologic characteristics, namely, high inflammatory burden, low albumin levels, and increased IFX clearance, suggest that higher IFX dosages would be required in this context [8, 9]. Thus, intensification regimens with higher induction doses or shorter intervals have been proposed and attempted in order to increase therapeutic success [10]. Their role, however, is not clearly established due to controversial findings and lack of well-designed randomized control trials. Nevertheless, the most recent British Society of Gastroenterology guidelines recommend accelerated regimens in patients who fail to respond to IFX standard dose after 3–5 days [6]. We present 3 cases of ASUC treated with IFX intensified/accelerated regimens and discuss the evidence for and against this strategy.

Case Presentation

First, we present the case of an 18-year-old female with past medical history of asthma under inhaled corticosteroids. She presented in the emergency department with bloody diarrhea (>6 bowel movements/day), associated with 12% bodyweight loss, severe abdominal pain, and vomiting for 3 weeks. On physical examination, she was feverish (38.5°C), with increased heart rate

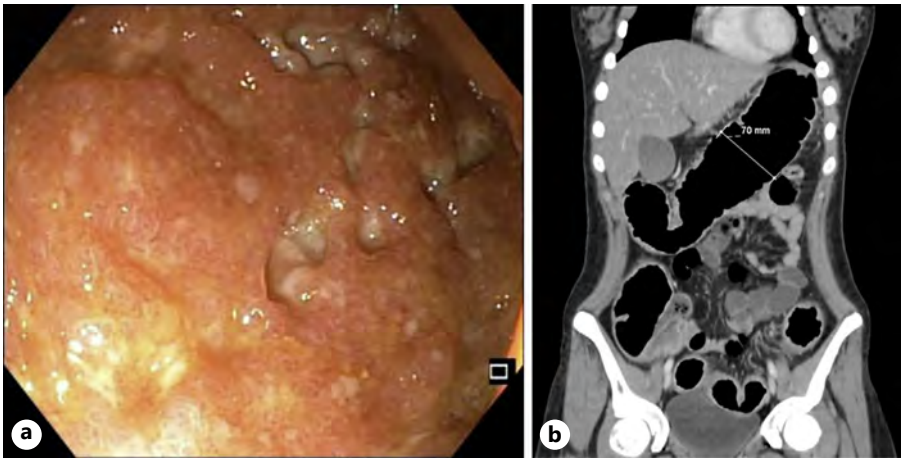

Fig. 1. a Proctosigmoidoscopy showing deep mucosal ulceration in the sigmoid (case 1). **b** Abdomen CT revealing transverse colon dilation, consistent with toxic megacolon (case 1).

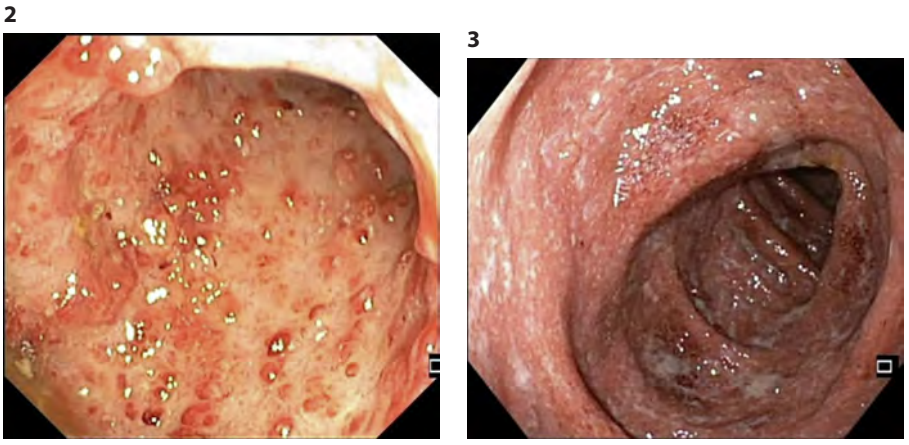

Fig. 2. Colonoscopy showing diffuse descendent colon ulceration and friable mucosa (case 2).
Fig. 3. Endoscopic appearance of the transverse colon, compatible with Mayo score of 3 (case 3).

(108 bpm) and diffuse abdominal tenderness with no signs of peritonitis. From blood analysis, severity signs were present, from which microcytic anemia (hemoglobin 11.9 g/dL), hypoalbuminemia (3.0 g/dL), and high C-reactive protein (CRP; 224 mg/dL) stood out. Hematological involvement with severe coagulopathy was also identified (INR 4.1). Proctosigmoidoscopy revealed the presence of deep ulcers throughout the visualized length (shown in Fig. 1a) compatible with severe UC, which biopsies confirmed. The patient underwent an abdominal computed tomography (shown in Fig. 1b) which revealed toxic megacolon and was then hospitalized under intravenous corticosteroids (1 mg/kg/day), after surgical team consultation.

At day 3 and 5, she showed only mild clinical response and our decision was to start IFX on a 10 mg/kg dosage. After first infusion, she had a good clinical response; however, this improvement only lasted for 3 days. Decision was agreed toward an accelerated induction regimen with this high-dose strategy and a new infusion was administered 5 days after the first. The temporary clinical improvement scenario repeated itself and the third infusion was taken after 6 days, completing the induction phase in just 11 days. IFX blood levels measured 3 days after drug induction conclusion were high (>20 μg/mL). This time and still under i.v. corticosteroids as adjuvant therapy, the clinical response got lasting and progressive, also with radiological normalization of colon diameter and metabolic correction of biomarker alterations and deficits, such as in iron and vitamin K. She was discharged with a 6/6 weeks IFX plan under proactive therapeutic drug monitoring (TDM), corticosteroid tapering, and plan to start combined therapy with immunosuppression on the short term. No drug-related events were recorded and 1 year after the hospitalization patient remains in remission with this strategy.

In second place, we present the case of a 26-year-old male diagnosed with left-sided UC for 2 years, under oral and topical mesalazine. He presented clinical deterioration for 3 months before being hospitalized. Workup revealed elevated CRP (83 mg/dL), hypoalbuminemia (1.9 g/dL), severe anemia (hemoglobin 8.3 g/dL), and an endoscopic Mayo score of 3 in the left colon (shown in Fig. 2). After partial clinical response to i.v. corticosteroids, symptomatic worsening was observed on day 4, when tapering was started, and IFX was initiated on the standard dose (5 mg/kg). He then maintained good clinical improvement and was discharged with corticosteroid tapering plan and a new scheduled IFX infusion in 2 weeks.

Two weeks after the second dose, he presented with an ASUC episode back in our institution and was hospitalized with i.v. corticosteroid resume and a new IFX infusion, this time at 10 mg/kg,

when TDM revealed unmeasurable trough levels and no antibodies. During hospitalization, by reason of severe weight loss and poor nutritional status, partial parenteral nutrition was initially used and progressively withdrawn until the time patient was discharged, when clinically stable, with IFX 10 mg/kg regimen every 4 weeks. Treatment with azathioprine was included on the last days of hospitalization and the patient remains now, 2 years after this episode, on remission under combined therapy, with IFX standard dosage, after tapering driven by TDM.

Finally, the third case is a 78-year-old male, previously followed for an ulcerative proctitis for 12 years, under oral mesalazine, as he refused long-term topical therapy. He came to the emergency department due to new onset of bloody diarrhea (>20 episodes/day) and tenesmus for 1 month. At clinical examination, he presented with severe dehydration (blood pressure of 94/52 mm Hg and heart rate of 150 bpm). Blood analysis revealed high CRP (18 mg/dL), hypoalbuminemia (2.6 g/dL), and hyperlactacidemia (4.7 mmol/L). He underwent a colonoscopy that revealed an extensive UC with diffuse deep ulcerations (Mayo score 3, shown in Fig. 3), mainly in the sigmoid and rectum. He started high-dose i.v. corticosteroids with no satisfactory response at day 3 and day 5. It was then decided to start IFX at the standard dose (5 mg/kg) that was reinfused at the same dose after 6 days due to clinical worsening. During the remaining 7 days of hospitalization, he achieved clinical response, in association with partial parenteral nutrition support, completing the induction phase in 13 days. Three years after this episode, he remains in disease remission under IFX standard maintenance plan.

Discussion/Conclusion

In this case series, we aim to illustrate 3 different types of patients and settings according to presentation and disease duration where ASUC is possible. Also, due to the absence of formal guidelines for IFX accelerated or intensified dose regimens, different strategies were considered depending on the episode's and individual's characteristics. Both accelerated and dose-intensified approach was used for the most severe case where it was observed rapid progression to toxic megacolon in a young female. On the other hand, a more cautious plan with standard dose acceleration was chosen for the older patient. It should be underlined that, although cyclosporine provides similar short-term outcomes compared to IFX, it is our institution current practice to prefer the anti-tumor necrosis factor (TNF) drug over the calcineurin inhibitor because of its easiness of use, the transition to the maintenance phase, and the less complex adverse event's profile.

ASUC is a medical emergency and a potential life-threatening condition. Approximately 1 in 5 patients with UC will face an acute exacerbation that requires hospitalization, often at the time of disease onset [11]. As the Truelove and Witts criteria remain the current severity stratification tool over time, also corticosteroids keep their role for decades as the cornerstone treatment for ASUC with response rates around 67% [12]. For the remnant portion of patients, in the absence of clinical improvement, although surgery must be taken into consideration, medical rescue treatments, including cyclosporine and IFX, can be used with proved efficacy [5].

In this setting of patients, IFX is reported to achieve response rates of 44–75%, although early colectomy rates remain relatively high, between 24% and 48% [13–15]. As previously mentioned, the best IFX induction regimen for salvage therapy is not yet well determined due to lack of supporting literature comparing different strategies, although accelerated regimens seem superior taking into account early colectomy-free survival [5]. Therefore, the approach chosen by each healthcare provider team still depends on the institution experience and some of the patient's characteristics and perceived risks.

There are some pathophysiological and pharmacokinetic factors that provide a rationale for the use of intensified or accelerated strategies in these severe cases. High inflammatory burden, or by other words disease severity, in ASUC translates into high TNF circulating levels. The clearance of IFX is directly associated with TNF in the systemic circulation, mainly due to the formation of immune complexes and consequent faster proteolytic degradation by the reticuloendothelial system [10]. Additionally, a study by Brandse et al. [16] clearly showed that high levels of IFX in stools of patients with UC were associated with nonresponse to treatment, especially in the severe cases, suggesting a role for repeated infusions to counterbalance monoclonal antibodies fecal loss. The damage of the intestinal epithelial barrier due to extensively ulcerated mucosa is also known for being responsible for protein loss and high incidence of hypoalbuminemia; therefore, it is reasonable to use albumin as a biomarker of drug clearance. The serum level of albumin and C-reactive protein (CRP) reflect the inflammatory status in daily practice, being associated with poorer outcomes, such as early and late colectomy [17], and recently a unicenter-based group proposed a protocol based on CRP/albumin ratio at presentation for the decision of intensified dose use and CRP at day 3 for accelerating dosing [18].

The results of this last single-center retrospective study did not detect a significant difference on early colectomy rates in those exposed to accelerated and standard strategies; however, the cohort for the first group had higher CRP levels at IFX start. This tendency is corroborated by a meta-analysis by Nalagatla et al. [19], where no associa-

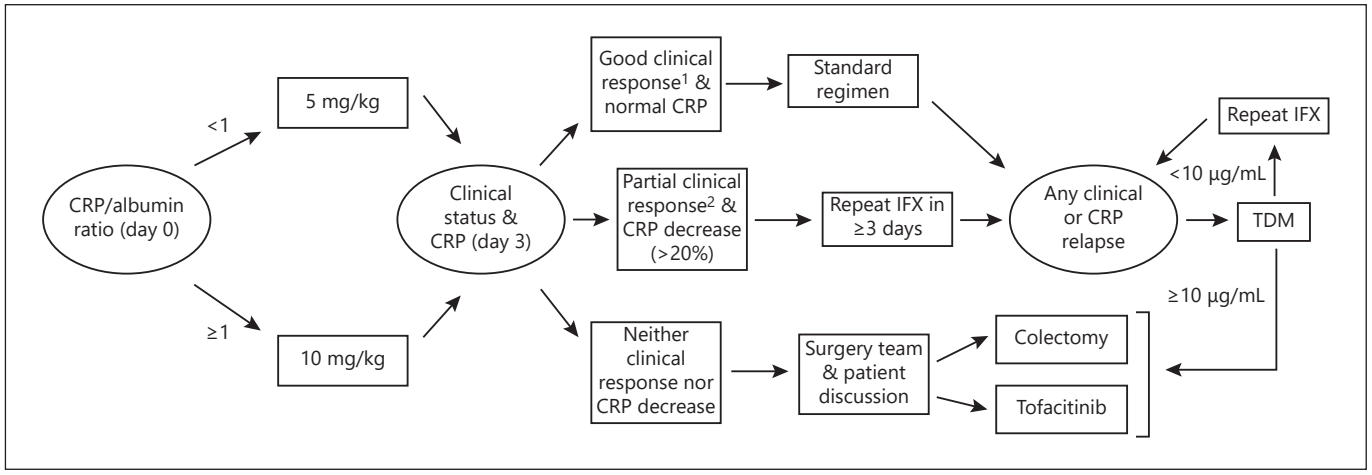

Fig. 4. Proposed decision algorithm for steroid-refractory acute severe colitis. [1]<4 bowel movements/day and no rectal bleeding. [2]Significant improvement on number of bowel movements/day and resolution of rectal bleeding. CRP, C-reactive protein; IFX, infliximab; TDM, therapeutic drug (IFX) monitoring.

tion is found between accelerated IFX induction therapy and lower rates of colectomy; however, as a retrospective study, the possible bias of different disease severity in both groups might play a role in the final results. Additionally, another systematic review and meta-analysis examining the impact on colectomy-free survival of different IFX induction dosages in ASUC conclude that the results were not statistically different between the standard induction group versus the accelerated or intensified induction dose groups, but again the meta-regression performed revealed higher CRP and lower albumin levels in the intensified group, both of these two prognostic factors being associated with higher risk of colectomy [20]. Partially pointing in an opposite direction, Gibson et al. [9] performed a retrospective analysis of a small group of patients with ASUC, showing that an accelerated induction may bring benefits in the shorter term with lower colectomy rates during induction, although no differences in colectomy during follow-up were seen.

As it becomes clear, there is much need for a robust randomized clinical trial that could unveil the beneficial outcomes of an accelerated or intensified induction strategy, currently used in a heterogeneous and irregular manner, comparing to standard regimens originated from pivotal studies (Table 1). Thus, we are eagerly looking forward to the results of the PREDICT-UC (Clinicaltrials.gov: NCT02770040), the only controlled trial of IFX dosing in ASUC, knowing that some questions will remain unanswered. Other aspects like identification of IFX induction levels threshold or additional clinical predictors which could indicate the need for either accelerated or intensified strategies should also be pursued. To date, there are still insufficient data to indicate what is the target trough level during ASUC treatment and consequently the role for TDM becomes unclear. A single study identified IFX serum concentrations of <16.5 and <5.3 µg/mL at week 2 and 6, respectively, as independent predictors for colectomy [21]. Curiously, it was also shown by Ungar et al. [22] that primary nonresponders did not have lower IFX levels compared to responders at week 2; however, a significant difference was seen at week 6. This points to the fact that pharmacokinetics is not the only driver for induction and that TDM role is limited to auxiliate on the assumption of treatment failure, when no clinical improvement is registered despite high IFX serum concentrations, rather than being a tool to pursuit a optimal value.

Taking in consideration what we found wiser from each protocol of accelerated regimens used in the studies available to date, we propose a possible algorithm of action in the steroid-refractory ASUC setting (shown in Fig. 4). Additionally, we considered as a possible salvage medical treatment option the rapidly acting janus kinase inhibitor, tofacitinib, although it is still controversial and lacking supporting evidence. The biggest retrospective study to date by Berinstein et al. [23] evaluating the effect of high-dose tofacitinib (together with corticosteroids) in biologic-experienced ASUC patients confirmed its beneficial effect on reducing the 90-day colectomy rate. Similarly, a case series published in 2022 revealed that 4 out

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Table 1. Summary of existing studies on intensified or accelerated IFX induction regimens

Author	Year	Type of study	Eligibility for rescue therapy	Sample size	IFX induction dose	IFX accelerated induction strategy	Endpoints	Relevant findings
Gibson et al. [9]	2015	Retrospective, unicentric	IV steroid-refractory ASUC	50	5 mg/kg	3 doses within 24 days	Colectomy rate during induction and follow-up (2 years) period	Standard regimen associated with shorter time to colectomy; rate of colectomy significantly lower during accelerated induction period; colectomy rates similar in both groups during follow-up
Gibson et al. [25]	2018	Retrospective, multicentric	IV steroid-refractory ASUC	145	5 mg/kg	3 doses within 42 days	Time to colectomy; time to IFX discontinuation	Time to colectomy significantly prolonged with use of accelerated dose in those with more severe disease; time to IFX discontinuation was shorter in the standard dose group
Nalagatla et al. [19]	2019	Retrospective, multicentric	IV steroid-refractory ASUC	213	5–10 mg/kg	If partial or nonresponders to first dose, second dose in 3–5 days	Inhospital, 3-, 6-, 12-, and 24-month colectomy rate	No difference between accelerated and standard IFX in need for short- or long-term colectomy; among those in the accelerated induction group, lower inhospital and long-term colectomy rates in the 10 mg/kg group
Chao et al. [17]	2019	Retrospective, multicentric	Mayo score ≥6; Mayo endoscopic score ≥2; IV steroid-refractory ASUC	72	5–10 mg/kg	(No accelerated strategy used for comparison)	3-month colectomy rate	Rate of colectomy at 3 months not significantly different between standard and high-dose IFX; higher need for shortened induction regimen in the 5 mg/kg group, which itself was an independent predictor for early colectomy
Govani et al. [18]	2020	Retrospective, unicentric	IV steroid-refractory ASUC	66	5–10 mg/kg	IFX repeated dose in 3 days if partial CRP response	90-day colectomy rate	No significant colectomy rate difference between the standard and accelerated induction group; 69.7% of those with incomplete response to IFX first dose were able to avoid colectomy with an accelerated strategy

IFX, infliximab; IV, intravenous.

of 5 IFX-refractory ASUC patients responded to high-dose tofacitinib, all remaining colectomy free at day 90 [24]. In the near future, we hope that recognition of inflammatory pathways specific for each patient can modulate therapeutic approaches bringing to clinical practice the goal of personalized medicine.

Statement of Ethics

This case report did not require ethics approval. Informed consent was obtained from the participants for publication of this case series report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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None.

Author Contributions

Pedro Bernardes Antunes was responsible for the design of the study, collecting the data, and drafting of the manuscript. Bruno Gonçalves and Bruno Arroja were responsible for the interpretation of the data. Raquel Gonçalves was responsible for critical revision of the work for important intellectual content. Tiago Leal was responsible for design of the study and critical revision of the work for important intellectual content. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

Data Availability Statement

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

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Clinical Case Study

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Severe Hypercholesterolemia Mediated by Lipoprotein X in an Immunosuppressed Patient: A Case Report

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Keywords
Lipoprotein X · Hypercholesterolemia · Hepatitis E

Abstract
Cholestatic liver diseases may be associated with increased plasmatic cholesterol due to an abnormal lipoprotein – lipoprotein X (LpX). Correcting the underlying cause of cholestasis is the critical treatment of LpX-associated hypercholesterolemia without any proven benefit from conventional lipid-lowering agents. In some situations, plasma exchange may apply to prevent associated complications, such as hyperviscosity syndrome. The authors present the case of a 44-year-old man with orbital inflammatory pseudotumor on prednisolone, admitted due to hepatocellular and cholestatic lesion and severe hypercholesterolemia. Laboratory investigation established that hepatitis E virus was responsible for liver injury and showed that LpX mediated the severe hypercholesterolemia. Reduction of the immunosuppressive load contributed to virus clearance. The consequent resolution of cholestasis and cholesterol removal by plasmapheresis allowed lipid profile normalization. The authors report the first case of LpX-associated hypercholesterolemia in a patient with hepatitis E-induced cholestasis and revisit the role of the liver in lipid metabolism.

Hipercolesterolemia grave mediada por lipoproteína X em doente imunossuprimido: caso clínico

Palavras Chave
Lipoproteína-X · Hipercolesterolemia · Hepatite E

Resumo
As doenças hepáticas colestáticas podem associar-se a um aumento do colesterol à custa de uma lipoproteína anómala, a lipoproteína X (LpX). Os agentes hipolipemiantes convencionais não apresentam benefício nesta entidade, pelo que o tratamento da hipercolesterolemia associada de LpX baseia-se na correção da causa subjacente da colestase. A plasmaferese pode ser necessária para evitar complicações, como a síndrome de hiperviscosidade. Os autores apresentam o caso de um homem de 44 anos com antecedentes de pseudotumor inflamatório da órbita sob prednisolona, admitido por lesão hepatocelular e colestática e hipercolesterolemia grave. A investigação laboratorial permitiu estabelecer a hepatite E aguda como responsável da lesão hepática e mostrou que a hipercolesterolemia grave foi mediada pela LpX. A redução da carga imunossupressora facilitou a eliminação do vírus da hepatite E. A consequente resolução da colestase coadju-

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vada pela remoção de colesterol por plasmaferese, permitiu a normalização mantida do perfil lipídico. Os autores relatam o primeiro caso de hipercolesterolemia associada a LpX em contexto de colestase induzida pelo vírus da hepatite E, e revisitam a importância do fígado no metabolismo dos lípidos.

Introduction

Hypercholesterolemia is a common finding in clinical practice. However, few conditions are associated with total cholesterol (TC) values greater than 1,000 mg/dL, primarily in patients with homozygous familial hypercholesterolemia and family lecithin acyltransferase deficiency [1, 2]. As the liver plays a pivotal role in lipid and lipoprotein metabolism, cholestatic liver diseases are associated with high levels of an abnormal lipoprotein with a density similar to very-low-density lipoprotein and low-density lipoprotein but different composition, the lipoprotein X (LpX) [3]. Recognition of this entity is of utmost importance as lipid-lowering agents are ineffective, and definitive treatment requires correcting the underlying cause of cholestasis [4].

Case Presentation

A 44-year-old Caucasian male was admitted to our gastroenterology department due to a 1-week clinical picture of jaundice, choluria, asthenia, and anorexia. He denied fever, abdominal pain, pruritus, weight loss, nausea, and vomiting. His medical history was remarkable for orbital inflammatory pseudotumor treated with prednisolone (60 mg/day) in the last 3 years. He has no family history of early-onset coronary artery disease or hyperlipidemia. Three months prior, his routine workup showed regular lipid panel and liver enzymology (shown in Table 1). There was no relevant epidemiological background, such as recent travel and eating uncooked meat. The patient denied alcohol or drug consumption. The physical exam only revealed jaundice; the remaining examination excluded encephalopathy, ascites, xanthelasma, or xanthomas.

Initial blood investigations revealed elevated hepatic enzymes displaying a mixed pattern (ALT >15 times and ALP > four times the upper limit of the reference range; with R factor 4.5) and severe hypercholesterolemia (TC >1,000 mg/day) (shown in Table 1). Blood counts, albumin, glycemia, and coagulation tests were unremarkable. Abdominal computed tomography excluded biliary

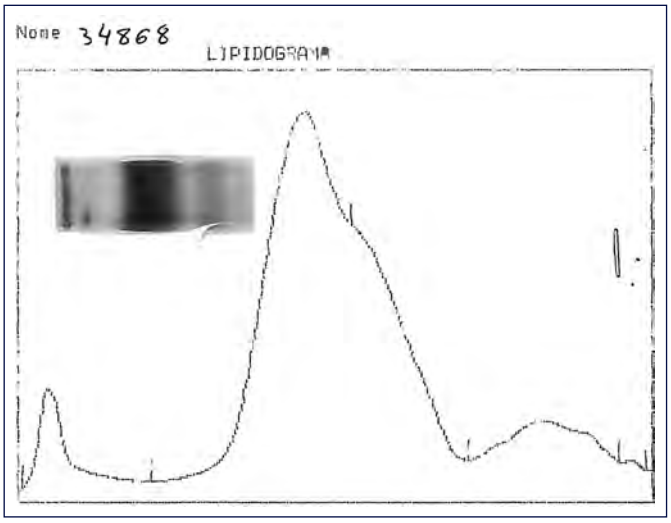

Fig. 1. Lipid electrophoresis: application point corresponds to the fraction with low protein content.

Table 1. Evolution of laboratory results over the time

Test (units) [normal range]	3 M before	Admission	Day 6	Day 7	Day 9	Discharge day 16	Day 28	6 M
Prednisolone, mg/day	60	60	50	PLASMA EXCHANGE	45	40	25	10
AST (U/L) [5–34]	22	131	164		152	61	32	33
ALT (U/L) [<55]	32	619	616		422	53	46	50
GGT (U/L) [12–64]	–	329	249		250	148	100	65
ALP (U/L) [40–150]	72	480	319		239	133	121	120
TBil (mg/dL) [<1.2]	0.86	18.03	16.76		13.47	2.90	0.9	0.81
CBil (mg/dL) [<0.5]	–	11.65	12.03		11.09	0.98	0.4	0.5
TC (mg/dL) [<200]	176	1,159	1,259		322	170	174	150
HEV IgM/IgG	–	+/–	–		–	–	–	–/+
Viral load HEV	–	Detectable	–		–	–	–	Undetectable

M, months; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gama glutamiltransferase; ALP, alkaline phosphatase; TBil, total bilirubin; CBil, conjugated bilirubin; TC, total cholesterol; HEV, hepatitis E virus.

Table 2. Additional laboratory workup

Laboratory workup (units) [normal range]		
Hepatitis etiology	HAV IgM/IgG	(–, +)
	HBV AgHBs/anti-HBc/anti-HBs	(–, –, +)
	Anti-HCV	(–)
	HEV IgM/IgG/RNA HEV	(+, –, detectable)
	CMV IgM/IgG	(–, –)
	EBV IgM/IgG	(–, –)
	HSV 1/2 IgM/IgG	(–, –)
	IgG (mg/dL) [700–1,600]	710
	IgM (mg/dL) [40–230]	70
	ANA	Negative
	Anti-LKM1	Negative
	ASMA	Negative
	AMA	Negative
Lipid panel	TC (mg/dL) [<200]	1,159
	LDL measured/calculated (mg/dL) [<100]	579/992
	HDL cholesterol (mg/dL) [>60]	18
	Triglycerides (mg/dL) [<150]	312
	ApoB (mg/dL) [Normal <130]	122
Additional investigation	TSH (mU/L) [0.5–5]	2.2
	Urinalysis	Hematuria or proteinuria

HAV, hepatitis A virus; HBV, hepatitis B virus; AgHbs, antigen hepatitis b surface; Anti-HBc, hepatitis B core antibody; Anti-HBs, hepatitis B surface antibody; HCV, hepatitis C virus; HEV, hepatitis E virus; RNA, ribonucleic acid; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV 1/2, herpes simplex virus 1/2; Ig, immunoglobulin; ANA, antinuclear antibodies; LKM1, liver kidney microsome type-1; ASMA, smooth-muscle antibody; AMA, antimitochondrial antibodies; LDL, low-density-lipoprotein cholesterol; HDL, high-density-lipoprotein cholesterol; TSH, thyroid-stimulating hormone.

obstruction. Moreover, the diagnostic workup showed acute hepatitis E virus (HEV) features, excluding the remaining viral and autoimmune etiologies (shown in Table 2). A percutaneous liver biopsy denoted cholestasis, mixed lobular inflammatory infiltrate, and focal hepatocellular necrosis. We decided to taper prednisolone with close ophthalmologic surveillance; we did not start antilipemic medications.

Further investigation of the hyperlipidemia ruled out hypothyroidism and nephrotic syndrome (shown in Table 2), and we excluded primary causes due to the new onset and the absence of family history. We hypothesized hypercholesterolemia secondary to LpX due to cholestatic viral hepatitis. This diagnosis was supported by TC elevation without proportional elevation of apolipoprotein B (ApoB) and a calculated LDL cholesterol higher than measured (shown in Table 2). A nonquantitative fasting lipoprotein electrophoresis showed a band at the application site with slow migration, suggesting the presence of low density and protein fraction, such as Lp-X (Fig. 1).

Given the persistently high lipid levels, which could trigger complications related to hyperviscosity syndrome, the patient underwent plasma exchange, with a marked decrease in plasmatic cholesterol (shown in Table 1), after one single session. Along with the tapering of corticosteroids, we observed a favorable clinical course, with a complete resolution of liver tests (shown in Table 1). No new ophthalmological alterations were detected, the lipid profile remained normal (without anti-lipemic drugs), and we excluded chronic HEV infection.

Discussion

The liver is a critical organ in lipid and lipoprotein metabolism. In 1969, Seidel et al. [5] described for the first time a lipoprotein rich in phospholipid and free cholesterol in patients with cholestasis; due to its unknown origin, it was denominated as Lp-X. LpX is an abnormal lipoprotein with a density similar to very-low-density lipoprotein and LDL but different lipid and apolipoprotein compositions [3, 5, 6]. It is rich in phospholipids and free cholesterol (80–90%) and poor in cholesterol esters (<5%), triglycerides, and proteins. Unlike LDL, it contains albumin dissolved in its aqueous core. The apolipoproteins encountered on its surface comprise Apo AI, E, and C, although never ApoB [3, 5, 6].

The pathogenesis is poorly understood. Biologically, cholesterol is eliminated by conversion to bile acids [3]; however, when biliary stasis develops, there is progressive retention of bile salts in hepatocytes, which stops the production of new bile acids accumulating cholesterol within the liver cells [3, 7, 8]. Subsequently, there is a reflux of cholesterol into the circulation [4]. LpX is associated with cholestatic liver diseases, including primary biliary cholangitis [4], bile duct obstruction, graft versus host disease in liver transplant recipients [9], deficiency of lecithin acyltransferase enzyme [1], granulomatous hepatitis [10], and other causes of hepatitis [11].

HEV infection is considered one of the common causes of acute fecal-oral-transmitted hepatitis in developing countries [12]. Still, in developed countries, HEV is estimated to account for less than 1% of cases of acute viral hepatitis despite being an often-overlooked cause. Evidence suggests that autochthonous transmission is zoonotic due to undercooked pigs and deer [13, 14]. HEV has an incubation period of 3–8 weeks, followed by a prodromal phase and acute icteric hepatitis lasting for days to several weeks. Acute HEV is usually clinically silent [13]. Marked cholestatic hepatitis with persistent jaundice and elevation of serum alkaline phosphatase is uncommon. In immunocompromized patients, anti-HEV IgM may be falsely negative; therefore, the gold standard for diagnosing acute HEV is the detection of HEV RNA in biological samples [13]. Acute HEV infection is usually self-limiting in immunocompetent patients and requires only supportive treatment. However, in immunocompromized patients, primarily reported in solid organ transplant recipients [15], HEV may not be cleared spontaneously and causes chronic hepatitis. Reducing the dosage of immunosuppressive therapy helps eliminate HEV [16, 17], so we reduced the immunosuppressive load with clinical improvement and no evolution to chronic HEV. Ribavirin is the treatment of choice in chronic HEV (14).

Cholesterol values greater than 1,000 mg/dL may be encountered with the presence of the LpX fraction [7, 18]. Methods for its direct determination are poorly available in conventional laboratories [18], so knowledge about the composition of this lipoprotein may be helpful in diagnosis. LpX does not contain ApoB, so it is frequent to find an excessive elevation of TC that is not accompanied by a proportional elevation of ApoB (increased TC/ApoB ratio) [4], as in our patient. A discrepancy between LDL-C calculated by the Friedewald formula and measured supports the presence of LpX [3, 4, 18]. In our patient, the calculated LDL cholesterol was 992.8 mg/dL, whereas the measured one was 579 mg/dL; this is because LpX interferes with the precipitation of chylomicrons, preventing their correct measurement. Demonstrating the presence of LpX can be done by lipoprotein electrophoresis using a commercially available kit [4, 18]; a low protein fraction may exist near the application point [18], as we observed in our case patient. Other alternative techniques for LpX determination have also been described, for example, agarose electrophoresis, non-denaturing polyacrylamide gradient gel electrophoresis, and nuclear magnetic resonance spectroscopy [18].

Apo-B's absence results in LpX uptake by hepatocytes instead of macrophages, so liver dysfunction drives lower clear-up LpX from the plasma. Therefore, correction of the underlying cause is pivotal. Lipid-lowering agents such as statin and ezetimibe will not affect cholesterol levels in this setting and carry potential toxicity [4]. Lipoprotein apheresis is a temporary measure usually reserved for complications such as hyperviscosity syndrome, xanthomata, and cholesteroloma [4, 18, 19] when underlying cause resolution is not feasible or inadequate. The benefit appears to be greater with plasmapheresis than with lipoprotein apheresis [20]. Given that our patient had persistently high cholesterol levels and the high immunosuppressive burden delayed the resolution of the cause of cholestasis (lower viral clearance of HEV), he successfully and safely underwent plasmapheresis.

Thus, considering our case report, in routine practice, abnormalities in the lipid panel should raise suspicion about the presence of LpX, especially in patients with hypercholesterolemia and cholestasis. Recognizing this condition allows the correct therapeutic management and the prevention of complications. We describe the first case reported in the literature of LpX-associated hypercholesterolemia due to acute hepatitis E, responding to spontaneously eliminating HEV after weaning immunosuppressive therapy, aided by concomitant plasmapheresis (one session).

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Statement of Ethics

The patient gave written informed consent for the publication of this manuscript. Aside from age and sex, identifying information was removed, and the images provided were anonymized to protect patient confidentiality.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

Cristiana Sequeira performed the material preparation, data collection, and first draft of the manuscript. All the authors read and approved the final manuscript.

Data Availability Statement

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

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INFORMAÇÕES ESSENCIAIS COMPATIVEIS COM O RESUMO DAS CARACTERISTICAS DO MEDICAMENTO. DENOMINAÇÃO DO MEDICAMENTO: Dioralyte, pó para solução oral. **COMPOSIÇÃO QUALITATIVA E QUANTITATIVA: Substâncias activas** g/saqueta: Glicose 3,56; Cloreto de sódio 0,47; Cloreto de potássio 0,30; Citrato dissódico 0,53. **INDICAÇÕES TERAPÊUTICAS:** Correcção da perda de líquidos e electrólitos nos lactentes, crianças e adultos. Tratamento da diarreia aquosa de várias etiologias, incluindo as gastrenterites, em todos os grupos etários. **POSOLOGIA E MODO DE ADMINISTRAÇÃO:** Cada saqueta deve ser sempre dissolvida em 200 ml de água. O volume de Dioralyte reconstituído a tomar deve ser decidido pelo médico assistente, tendo em consideração o peso do doente e o estado e gravidade da situação. Um princípio básico no tratamento da diarreia é a substituição da perda de líquidos e a manutenção de uma ingestão de líquidos suficiente para repor a sua perda nas fezes. A ingestão diária deve ser baseada num volume de 150 ml/Kg de peso nos lactentes e 20–40 ml/Kg de peso nos adultos e crianças. Uma aproximação razoável é a seguinte: -lactentes – 1 a 1,5 vezes o volume alimentar habitual, - crianças – 1 ou 2 saquetas após cada dejecção diarreica, - adultos – 1 ou 2 saquetas após cada dejecção diarreica. Inicialmente, podem ser necessárias maiores quantidades de Dioralyte para assegurar uma reposição precoce do equilíbrio hidro-electrolítico. Nos estadios iniciais do tratamento da diarreia, todos os alimentos, incluindo o leite de vaca e o leite artificial, devem ser interrompidos. Não se deve no entanto interromper o aleitamento materno. Nas crianças amamentadas sugere-se que se dê à criança o mesmo volume de Dioralyte do que o da alimentação normal, seguindo-se o aleitamento. Pode ser necessário, durante este período, a expressão do leite residual da mama. Após 24-48 horas, quando os sintomas desaparecerem, a dieta normal deve ser retomada gradualmente para evitar o agravamento da situação. O regime sugerido para o tratamento da diarreia infantil grave baseado no peso corporal em Kg é apresentado no quadro anterior. Quando a diarreia é acompanhada de vómitos, sugere-se ingestão frequente de pequenas quantidades de Dioralyte. No entanto, é importante que seja tomado o volume total necessário de Dioralyte. Quando o funcionamento dos rins é normal torna-se difícil superhidratar por via oral e quando existem dúvidas acerca da dosagem correcta, mais vale tomar a mais do que a menos. **CONTRA-INDICAÇÕES:** Não se conhecem contra-indicações ao Dioralyte. No entanto, existem algumas situações em que o tratamento com Dioralyte é inapropriado, tais como por exemplo, situações de oclusão intestinal requerendo intervenção cirúrgica, ou em caso de vomitos persistentes e desidratação grave ou diarreia infantil grave em que será necessária uma terapêutica por via intravenosa. **ADVERTÊNCIAS E PRECAUÇÕES ESPECIAIS DE UTILIZAÇÃO:** O Dioralyte só deve ser reconstituído com água. Cada saqueta deve ser sempre reconstituída em 200 ml de água. Uma solução mais fraca do que a recomendada não contem a concentração óptima de glicose e electrólitos e uma solução mais forte do que a recomendada pode provocar desequilíbrio electrolítico. Se a diarreia não melhorar rapidamente, os doentes deverão ser reavaliados. Nos idosos, a administração de soluções contendo glucose e electrólitos deve ser cuidadosa em caso de alterações renais ou hepáticas graves ou em outras situações em que o balanço electrolítico normal se encontre alterado. Nos lactentes, deve interromper-se durante 24 horas a alimentação com leite de vaca ou leite artificial, que deverão ser reintroduzidos gradualmente quando a diarreia tiver diminuído. Não se deve interromper o aleitamento materno. **EFEITOS INDESEJÁVEIS:** Podem ocorrer náuseas ou vómitos após a administração da solução, em particular quando esta é ingerida com demasiada rapidez. Estão também descritos casos isolados de desconforto abdominal e de obstipação.Data da revisão do texto: Janeiro de 2004. **TITULAR DA AUTORIZAÇÃO DE INTRODUÇÃO NO MERCADO:** KORANGI - Produtos Farmacêuticos, Lda. Medicamento não sujeito a receita médica. **Para mais informações contactar o Titular da Autorização de Introdução no Mercado**

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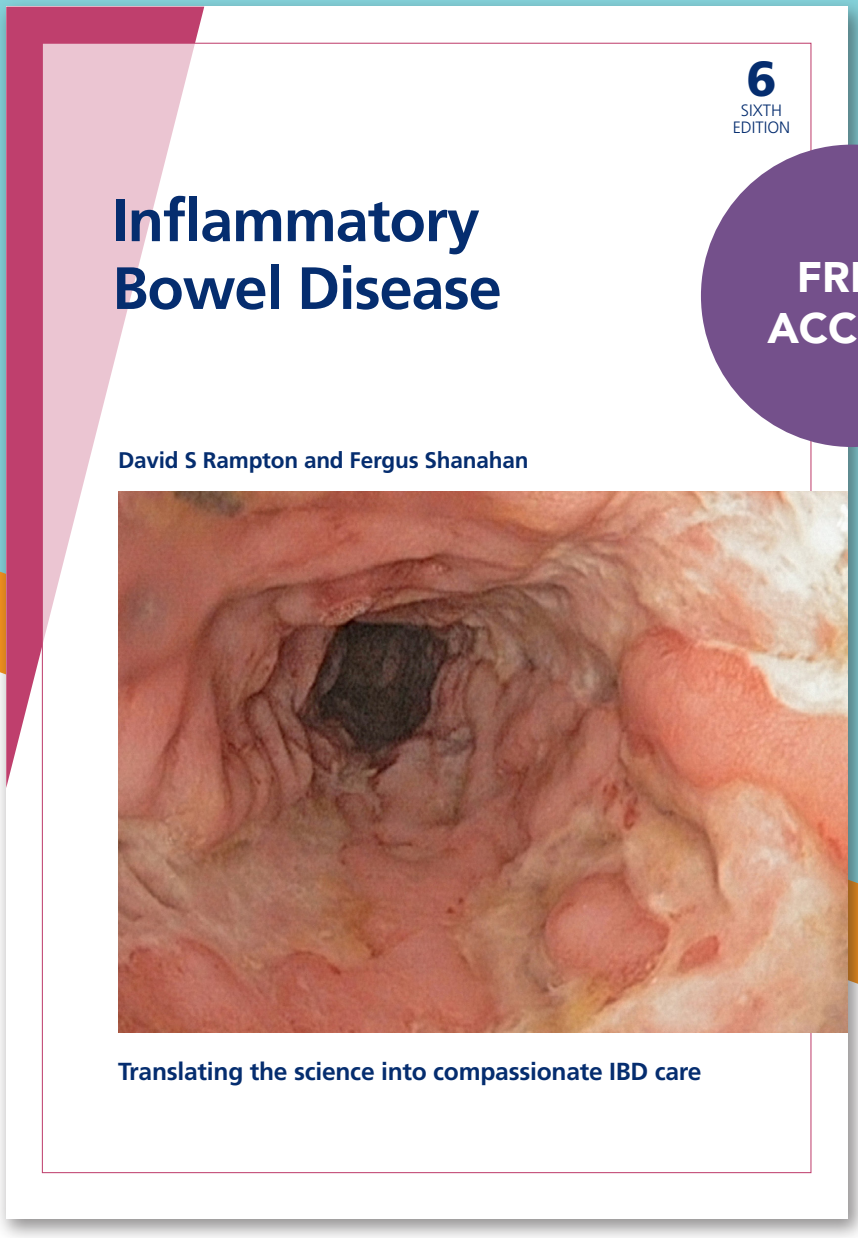

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