Portuguese Journal of Gastroenterology

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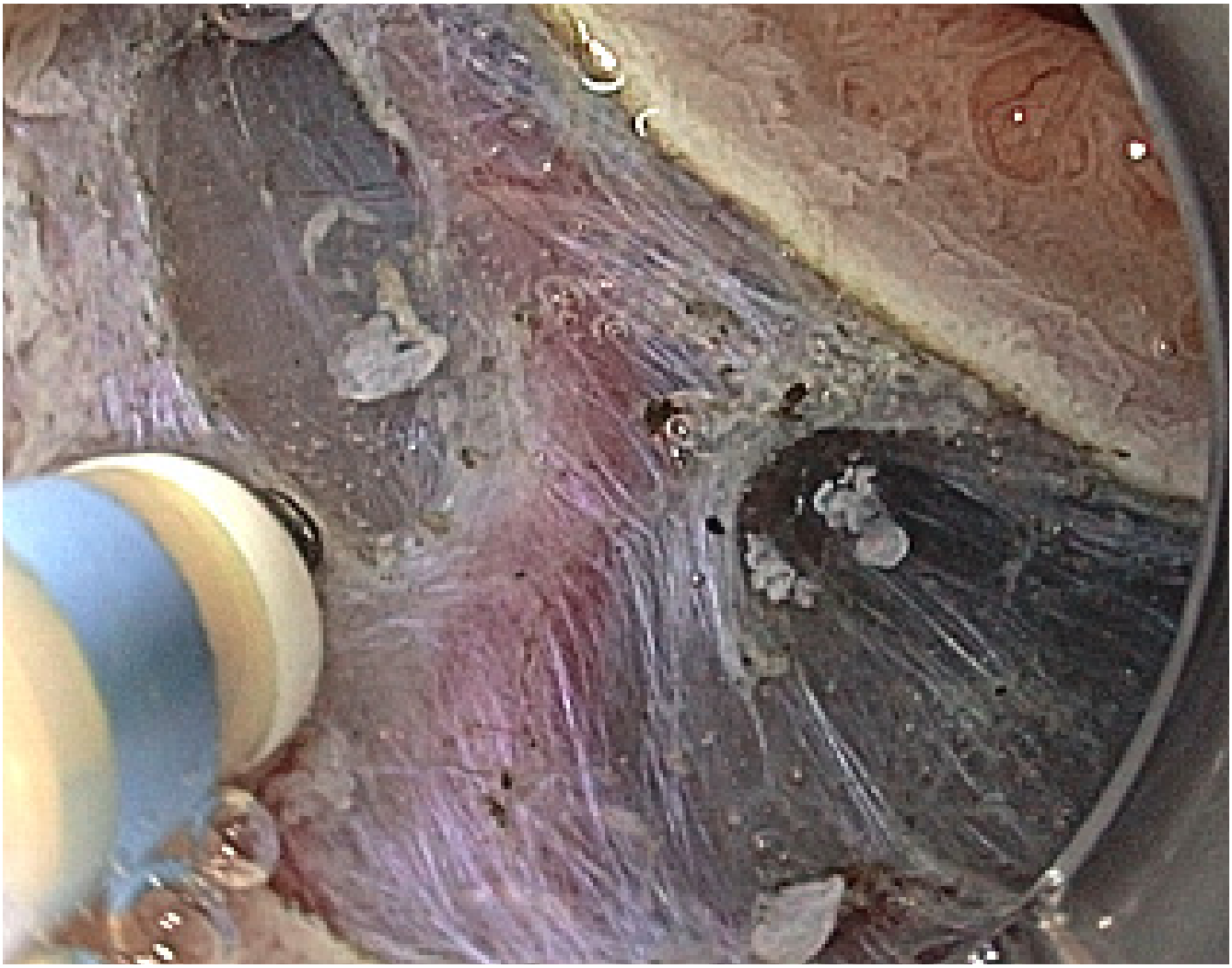

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Aims and Scope

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).
The journal publishes clinical and basic research articles on Gastroenterology, Digestive Endoscopy, Hepatology and related topics. Review articles, clinical case studies, images, letters to the editor and other articles such as recommendations or papers on gastroenterology clinical practice are also considered. Only articles written in English are accepted.

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Cover illustration
Cut in the anal squamous mucosa in a patient with a granular-mixed nodular laterally spreading tumor located at the anorectal junction. From Ferreira et al., pp. 41-47.

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Review Article

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Nutrition in Pancreatic Diseases: A Roadmap for the Gastroenterologist

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Keywords
Nutrition · Acute pancreatitis · Chronic pancreatitis · Pancreatic cancer

Abstract
While common pancreatic diseases, such as acute pancreatitis (AP), chronic pancreatitis (CP), and pancreatic cancer (PC), may greatly impact the normal pancreatic physiology and contribute to malnutrition, the adequate nutritional approach when those conditions are present significantly influences patients' prognosis. In patients with AP, the goals of nutritional care are to prevent malnutrition, correct a negative nitrogen balance, reduce inflammation, and improve outcomes such as local and systemic complications and mortality. Malnutrition in patients with CP is common but often a late manifestation of the disease, leading to decreased functional capacity and quality of life and increased risk of developing significant osteopathy, postoperative complications, hospitalization, and mortality. Cancer-related malnutrition is common in patients with PC, and it is now well recognized that early nutritional support can favorably impact survival, not only by increasing tolerance and response to disease treatments but also by improving quality of life and decreasing postoperative complications. The aim of this review was to emphasize the role of nutrition and to propose a systematic nutritional approach in patients with AP, CP, and PC.

Nutrição nas Doenças Pancreáticas: Um Roteiro para o Gastrenterologista

Palavras Chave
Nutrição · Pancreatite aguda · Pancreatite crónica · Cancro pancreático

Resumo
Se por um lado, doenças pancreáticas comuns, tais como pancreatite aguda (PA), pancreatite crónica (PC) e cancro pancreático (CP), podem ter um grande impacto na normal fisiologia pancreática e contribuir para desnutrição, por outro lado, uma abordagem nutricional adequada nos doentes com essas patologias pode influenciar significativamente o seu prognóstico. Em doentes com PA, os objetivos do suporte nutricional são a prevenção da desnutrição, a correção de um balanço negativo de nitrogénio, a redução da inflamação, e a evicção de *outcomes* desfavoráveis, como desenvolvimento de complicações locais ou sistémicas ou morte. A desnutrição é comum em doentes com PC, sendo frequentemente uma manifestação tardia da doença, da qual resulta uma diminuição da capacidade funcional e da qualidade de vida, bem como um aumento significativo do risco de doença óssea, complicações pós-operatórias, hospitalizações e morte. A desnutrição associada ao CP é

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também habitual e é atualmente reconhecido que um suporte nutricional precoce pode influenciar favoravelmente a sobrevida, não só por aumentar a tolerância e resposta aos tratamentos, mas também por melhorar a qualidade de vida e diminuir as complicações pós-operatórias. O objetivo da presente revisão é salientar o papel da nutrição e propor uma abordagem nutricional sistematizada nos doentes com PA, PC e CP.

Introduction

Pancreas is a composite organ with both exocrine and endocrine functions, playing a major role in the digestive process and glucose control and ultimately influencing the nutritional status of an individual. Malnutrition can be defined as a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat-free mass) and body cell mass, leading to diminished physical and mental function and impaired clinical outcome from disease, and is more frequently diagnosed by a body mass index <18.5 kg/m^2 [1, 2]. While common pancreatic diseases, such as acute pancreatitis (AP), chronic pancreatitis (CP), and pancreatic cancer (PC), may greatly influence the normal pancreatic physiology and contribute to malnutrition, the adequate nutritional approach when those conditions are present significantly influences patients' outcomes. Despite its importance in gastrointestinal disorders and particularly in pancreatology, it has been recognized that nutritional knowledge among gastroenterologists is suboptimal [3]. For this reason, the aim of this review was to highlight the role of nutrition and to propose a systematic nutritional approach in patients with AP, CP, and PC.

Nutrition in Acute Pancreatitis

AP is an acute inflammatory process of the pancreatic parenchyma with variable involvement of other regional tissues and remote organ systems, being one of the most common gastrointestinal disorders requiring hospital admission [4]. The severity of AP is classified as mild, moderately severe, or severe based on organ failure and local or systemic complications [5]. While the majority of the patients develop mild AP with a self-limited course, up to 20% will develop moderately severe/severe AP with a mortality risk that can be as high as 35% [6]. Regardless of the etiology, initial management of AP consists of supportive treatment aimed at targeting the systemic inflammatory response syndrome (SIRS) with fluid resuscitation, pain control, and nutritional care [7].

Nutritional care plays a key role in mitigating the sequelae of SIRS. Oral nutrition (ON) and enteral nutrition (EN) are thought to promote the integrity of the gut mucosal barrier by preventing luminal mucosal atrophy, hence reducing gut permeability and the resulting bacterial translocation that potentiates AP-associated SIRS, multiorgan failure, and infection [8]. The SIRS also induces a highly catabolic state that increases metabolic demand, causing a negative nitrogen balance that promotes malnutrition. Therefore, the goals of nutritional care in AP are to prevent malnutrition, correct a negative nitrogen balance, reduce inflammation, and improve outcomes [9]. Based on the current evidence, an algorithm on the nutritional management of patients with AP is provided (Fig. 1).

Malnutrition Risk Screening and Assessment in Acute Pancreatitis

While patients with predicted mild to moderately severe AP should be screened for malnutrition within the first 48 h after admission using an appropriate validated tool, those with predicted severe AP should always be considered at nutritional risk. According to current guidelines, the Nutrition Risk Screening-2002 (NRS-2002) tool is the recommended screening strategy (Table 1) [1, 10]. However, as some risk groups with specific nutritional needs such as alcohol users and obese patients may be incorrectly evaluated when NRS-2002 is used alone, nutritional assessment should also comprise a complete evaluation of the patient, including comorbid conditions, function of the gastrointestinal tract, and risk of aspiration [1]. Subjects identified as at nutritional risk should be referred to the hospital nutrition department to undergo a thorough nutritional assessment, establish a nutritional diagnosis, and aid in defining a nutritional care plan and respective monitoring in conjunction with the multidisciplinary team responsible for the patient's management.

Nutritional Therapy in Acute Pancreatitis

Historically, the initial management of AP prioritized "pancreatic rest" with nil per os and total parenteral nutrition (PN) with the rationale that patients would be at risk for worsening clinical course if the pancreas was stimulated by ON or EN. However, many studies showed that timely administration of ON or EN can help protect the gut mucosal barrier and reduce bacterial translocation, thereby

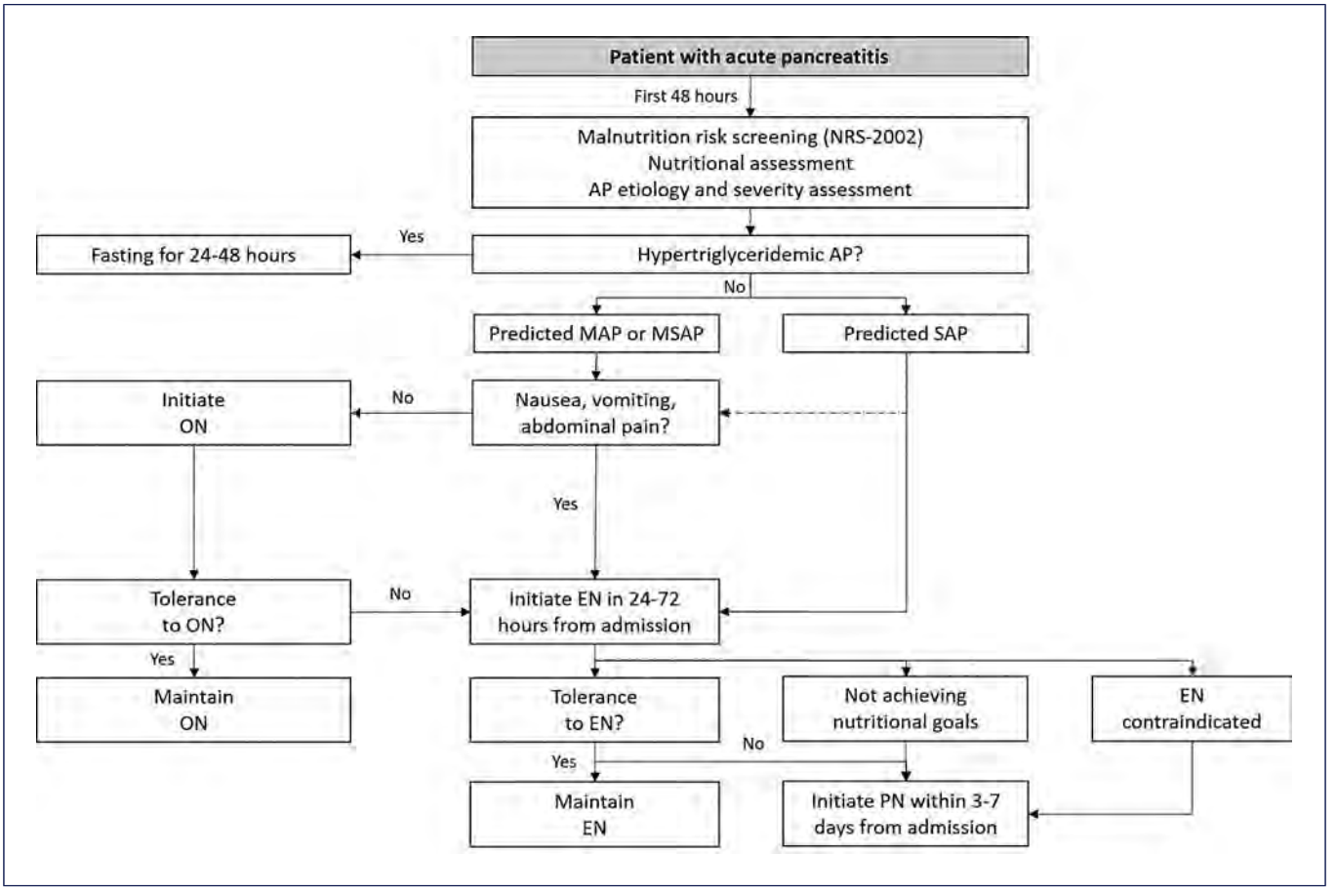

Fig. 1. Algorithm suggesting nutritional management in AP. AP, acute pancreatitis; EN, enteral nutrition; MAP, mild acute pancreatitis; MSAP, moderately severe acute pancreatitis; NRS-2002, Nutrition Risk Screening-2002; ON, oral nutrition; PN, parenteral nutrition; SAP, severe acute pancreatitis.

reducing the local and systemic complications and death [9, 11–14]. Therefore, in patients with predicted mild or moderately severe AP, ON is recommended as soon as clinically tolerated, independently of serum lipase concentration [7, 15]. Upfront ON with a soft diet seems to be more beneficial regarding caloric intake and equally tolerated compared with clear liquid diets [16–18]. An exception to these recommendations is the management of hypertriglyceridemic AP in which fasting for 24–48 h might be one of the suggested approaches for decreasing serum triglycerides [19]. Even though some patients with AP may develop intolerance to ON, strategies to improve tolerance, like the use of smaller and more frequent meals, adjustment of the dietary fat content and consistency, and use of antiemetic and prokinetic agents, should be considered before changing to EN [9].

In patients unable to tolerate ON, EN is preferred to PN and should be started early, within 24–72 h of admission according to energy requirements calculated through simplistic formulas (25–30 kcal/kg/day), published predictive equations, or indirect calorimetry [20, 21]. Numerous studies have demonstrated that early initiation of EN in patients with AP is associated with significantly improved outcomes compared to PN [21–23].

Regarding optimal type of EN, a standard polymeric diet should be used. The relatively inexpensive polymeric feeding formulations were associated with similar feeding tolerance and appeared as beneficial as the more expensive (semi-)elemental formulations in reducing the risk of infectious complications and mortality [24].

Current guidelines suggest using gastric access as the standard procedure as it is cheaper and easier to place and maintain and to implement postpyloric access only in the case of intolerance to gastric feeding or even as the first-line option in patients with a high risk of aspiration. For those patients in whom nasoenteric feeding is not

Table 1. Nutritional Risk Screening (NRS-2002): it includes an initial screening (step 1), with four questions that can be performed by any member of the multidisciplinary team, provided they are properly trained; and a final screening (step 2), performed by a nutritionist, if initial screening is positive

Step 1: Initial screening			
		Yes	No
1	Is BMI <20.5?		
2	Has the patient lost weight within the last 3 months?		
3	Has the patient had a reduced dietary intake in the last week?		
4	Is the patient severely ill? (e.g., in intensive therapy)		

Yes: if the answer is "Yes" to any question, the screening in step 2 is performed
No: if the answer is "No" to all questions, the patient is rescreened at weekly intervals

Step 2: Final screening			
Impaired nutritional status		Severity of disease	
Absent Score 0	Normal nutritional status	Absent Score 0	Normal nutritional status
Mild Score 1	Weight loss >5% in 3 months or food intake below 50–75% of normal requirement in preceding week	Mild Score 1	Hip fracture; chronic patients, in particular with acute complications (cirrhosis, COPD); chronic hemodialysis; diabetes; oncology
Moderate Score 2	Weight loss >5% in 2 months or BMI 18.5–20.5 + impaired general condition or food intake 25–60% of normal requirement in preceding week	Moderate Score 2	Major abdominal surgery; stroke; severe pneumonia; hematologic malignancy
Severe Score 3	Weight loss >5% in 1 month (>15% in 3 months) or BMI <18.5 + impaired general condition or food intake 0–25% of normal requirement in preceding week in preceding week	Severe Score 3	Head injury; bone marrow transplantation; intensive care patients (APACHE>10)

Score of impaired nutritional status + score of severity of disease = total score. Age if ≥ 70 years: add 1 to total score above = age-adjusted total score. Score ≥3: the patient is nutritionally at risk and a nutritional care plan is initiated. Score <3: weekly rescreening of the patient. BMI, body mass index; COPD, chronic obstructive pulmonary disease; APACHE, acute physiology and chronic health evaluation.

tolerated and/or in whom long-term EN (>30 days) is anticipated, endoscopic placement of a feeding tube should be considered. Patients who can tolerate feeding through nasogastric tube are candidates for a percutaneous endoscopic gastrostomy, while in those who are unable to tolerate it and/or who are at high risk for aspiration, direct percutaneous endoscopic jejunostomy or percutaneous endoscopic gastrostomy with jejunal extension are reasonable options [20, 21, 25].

Intolerance to EN is common in moderately severe to severe AP, and strategies to improve tolerance include changing gastric to postpyloric access, changing polymeric formula to a (semi-)elemental formula, and switching from bolus to continuous infusion. Additionally, supplementing enteral formula with soluble dietary fiber might be an option for those patients in whom diarrhea is a bothersome symptom [20, 26]. When these methods have failed to improve EN tolerance, use of medication,

like antiemetics and/or prokinetics, can improve tolerance [9, 27, 28].

PN should be administered to patients with AP who do not tolerate EN, are unable to reach targeted nutritional requirements, or if contraindications for EN exist. Contraindications to EN include critically ill patients with uncontrolled shock, uncontrolled hypoxemia and acidosis, uncontrolled upper gastrointestinal bleeding, gastric aspirate >500 mL/6 h, bowel ischemia, bowel obstruction, abdominal compartment syndrome, and high-output fistula without distal feeding access [20, 29, 30]. The optimal timing for initiating PN is not clear but is suggested to be within 3 to 7 days after admission with the decision made on a case-by-case basis.

Regarding PN prescription, a central venous access should be preferred delivering route. Glucose should be the preferred carbohydrate energy source, and its administration should not exceed 5 mg/kg/min. Lipids provide an efficient source of calories as well, and use of intravenous lipids in AP is safe as far as hypertriglyceridemia is avoided. Even though the benefit of protein supplementation during critical illness is not clear, guidelines recommend that 1.2–2.0 g/kg protein equivalents per day can be delivered progressively. As in all critically ill patients, a standard daily dose of multivitamins and trace elements is recommended [19, 20, 29, 30]. Glutamine is a nonessential amino acid that has been studied for its antioxidant properties and should be considered as a supplement only in AP patients with total PN as it may reduce complications and mortality [21, 31].

Even though there is evidence demonstrating high prevalence of pancreatic exocrine insufficiency (PEI) in AP patients both during their initial hospitalization and in long-term follow-up, the clinical benefit of treatment of AP-associated EPI with pancreatic enzyme replacement therapy (PERT) is unknown. Therefore, PERT should only be considered in AP when proven or obvious PEI is present, most likely occurring in patients with pancreatic necrosis and those with alcohol-related AP [32, 33].

Table 2. Malnutrition Universal Screening Tool (MUST): a five-step screening tool to identify adults, who are malnourished, at risk of malnutrition (undernutrition), or obese; it also includes management guidelines which can be used to develop a care plan

Step 1: BMI score		
BMI kg/m^2		
BMI >20		Score 0
BMI 18.5–20		Score 1
BMI <18.5		Score 2
Step 2: Weight loss score		
Unplanned weight loss in past 3–6 months		
<5%		Score 0
5–10%		Score 1
>10%		Score 2
Step 3: Acute disease effect score		
If patient is acutely ill and has been or is likely to be no or nutritional intake for >5 days, add a score of 2		
Step 4: Overall risk of malnutrition		
Add scores together to calculate overall risk of malnutrition		
Step 5: Use of management guidelines		
Score 0	Low risk	Routine clinical care Repeat screening • Hospital – every week • Care homes – every month • Community – every year for special groups, e.g., those >75 years
Score 1	Medium risk	Observe • Hospital – document dietary and fluid intake for 3 days • Care homes (as for hospital) • Community – repeat screening, e.g., from 6 months (with dietary advice if necessary)
Score ≥2	High risk	Treat • Hospital – refer to dietitian or implement local policies. Generally food first followed by food fortification and supplements • Care homes (as for hospital) community (as for hospital)

BMI, body mass index. MUST is reproduced here with the kind permission of BAPEN (British Association for Parenteral and Enteral Nutrition); for further information on "MUST" see www.bapen.org.uk.

Nutrition in Chronic Pancreatitis

CP refers to a syndrome that involves chronic progressive inflammation, fibrosis, and scaring of the pancreatic tissue, resulting in permanent damage to ductal, acinar, and islet cells, with consequent loss of exocrine and endocrine functions [34]. It is a serious condition that can have a severe impact on the quality of life in addition to life-threatening long-term sequelae, such as malnutrition, diabetes mellitus, and PC [35].

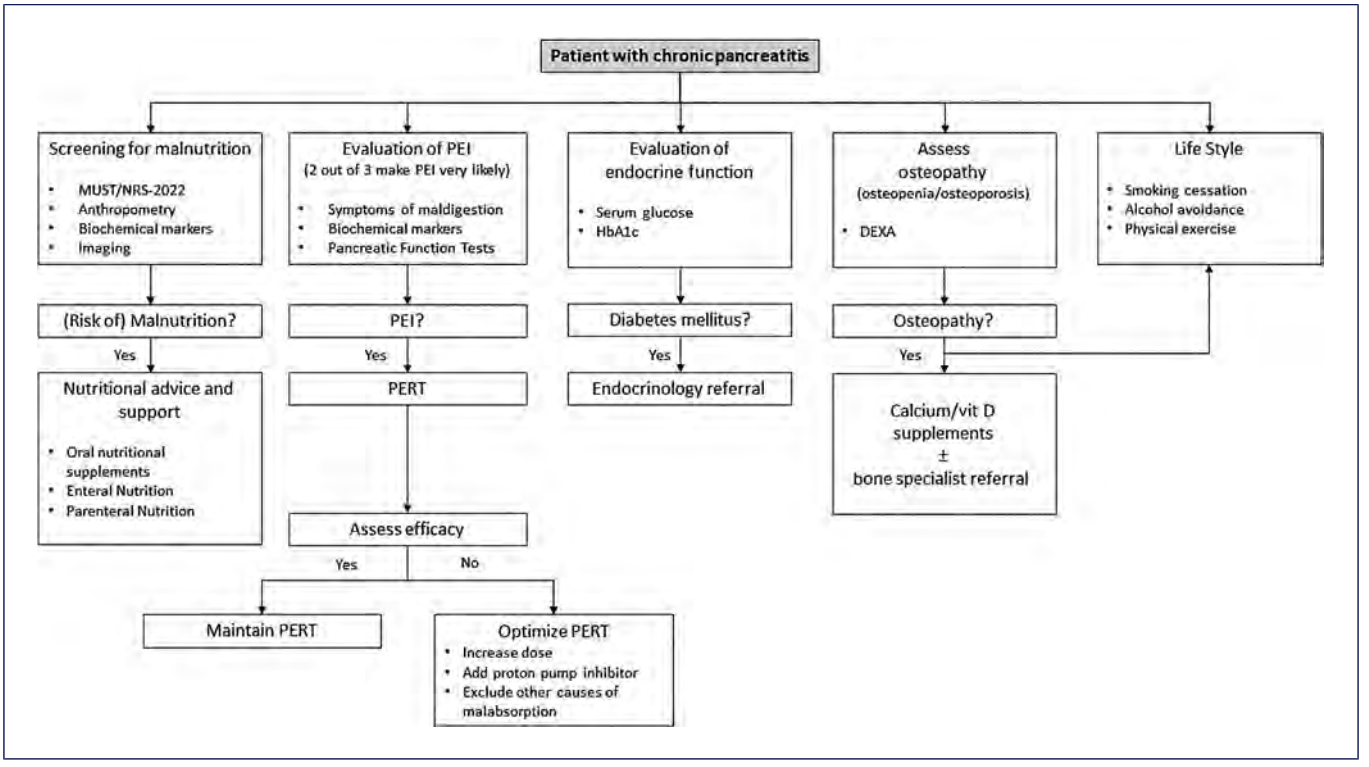

Fig. 2. Algorithm suggesting nutritional management in CP (adapted with permission from Pezzilli R, et al. [42]). DEXA, dual-energy X-ray absorptiometry; MUST, malnutrition universal screening tool; NRS-2002, Nutrition Risk Screening-2002; PEI, pancreatic exocrine insufficiency; PERT, pancreatic enzyme replacement therapy; CP, chronic pancreatitis.

Malnutrition in patients with CP is common but often a late manifestation of the disease [36]. Consequences of malnutrition include decreased functional capacity and quality of life and increased risk of developing significant osteopathy, postoperative complications, hospitalization, and mortality [21, 37]. Multiple causes contribute to nutrient deficiency and malnutrition in patients with CP, namely pancreatic insufficiency (both exocrine and endocrine), abdominal pain and related anorexia, delayed gastric emptying (from duodenal stenosis or extrinsic compression from pseudocysts), alcohol abuse, and smoking [38]. Additionally, increased resting energy expenditure has been reported in up to 50% of patients with CP, which leads to a negative energy balance and malnutrition [39].

Malnutrition Risk Screening and Assessment in Chronic Pancreatitis

Patients should undergo initial screening either with the community malnutrition universal screening tool (Table 2) or hospital NRS-2002 (Table 1) [19]. Nutritional assessment should be completed with symptoms, anthropometry (body mass index, triceps skin-fold, midarm circumference, and hand-grip strength), biochemical evaluations, and body composition (using bioelectrical impedance analysis of CT scan), ideally in the setting of a multidisciplinary group, including dieticians [21]. Body mass index alone is an unreliable marker of malnutrition as sarcopenia may be present in obese patients [40]. Active screening for micro- and macronutrient deficiencies (i.e., folate, vitamins A, D, E, and B12, calcium, selenium, zinc, magnesium, iron, albumin, prealbumin, retinol-binding protein, transferrin) should be performed regularly, at least once a year, or more frequently in those with severe disease and uncontrolled malabsorption, with prompt supplementation according to recent micronutrient guidelines in case of low concentrations or if clinical signs of deficiency occur [21, 35, 41]. An algorithm regarding the nutritional management of patients with CP is suggested (Fig. 2).

Nutritional Therapy in Chronic Pancreatitis

In patients with CP, a low-fat diet is unnecessary and may even predispose to malnutrition, weight loss, and deficiencies of lipid-soluble vitamins [35]. Therefore,

while patients with an adequate nutritional status should adhere to a well-balanced diet, those with malnutrition should be advised to consume a high-protein (1–2 g/kg/day) and high-energy diet (at least 35 kcal/kg/day), divided into 5–6 meals per day [21]. The only restrictions to be considered are to avoid diets with high content of fiber (as it may increase symptoms of flatulence and decrease the action of PERT) and to adhere to low-fat diet as a last resort when symptoms of steatorrhea cannot be controlled with optimized PERT [43].

When ON is insufficient for reaching caloric and protein goals, oral nutritional supplements (ONSs) should be prescribed, a practice that is only necessary in about 20% of the patients [21]. As medium-chain triglycerides are less dependent on lipase activity for their absorption, their use in patients with CP has been studied. However, not only do they have an unpleasant taste and gastrointestinal adverse events, but their benefits have not been consistently proved, so they are not routinely recommended [44].

In patients in whom ON with dietary counseling and ONS are unable to improve nutritional status and correct malnutrition, EN is indicated, which occurs in approximately 5% of the patients with CP [19]. In those patients with pain, delayed gastric emptying, persistent nausea or vomiting, or gastric outlet obstruction, the nasojejunal route is the preferred for EN administration. When long-term EN (>30 days) is anticipated, percutaneous endoscopic gastrostomy with jejunal extension, percutaneous endoscopic jejunostomy, endoscopic ultrasound-guided gastroenterostomy, or surgical jejunostomy should be considered [21]. Despite being more expensive, (semi-)elemental formulas with medium-chain triglycerides are more adapted to jejunal nutrition and can be used when standard polymeric formulas are not tolerated. When EN is needed and concurrent PEI is present, pancreatic enzymes can be administered with the formula by opening the capsules and suspending the enzyme microspheres in thickened acidic fluid (such as "nectar-thick" fruit juice) for delivery via the feeding tube [21].

PN can be associated with catheter-related infections, septic complications, hyperglycemia, and disruption of the gut mucosal barrier but is needed in <1% of patients with CP [19, 45]. It may however be indicated in patients with gastric outlet obstruction, need for gastric decompression, impossibility to introduce a tube into the jejunum, complex fistulating disease, or in case of intolerance of EN, preferably using a central venous access [35].

Pancreatic Exocrine Insufficiency

PEI is defined as an insufficient production or secretion of pancreatic enzymes (acinar function) and/or sodium bicarbonate (ductal function) and affects over 70% of patients with CP during their lifetime [35, 46]. Despite the fact that overt steatorrhea is not expected unless the secretion of pancreatic lipase decreases below 10% of normal, nutritional deficiencies with respective clinical consequences can occur earlier in cases of mild to moderate exocrine insufficiency. Other common symptoms of PEI include flatulence, abdominal bloating, cramping, or unexplained weight loss. As patients may voluntarily change their dietary habits to avoid or minimize symptoms, PEI is often asymptomatic [38].

In the clinical practice, a noninvasive pancreatic function test should be performed to aid in the diagnosis of PEI. Fecal elastase-1 (FE-1) is a noninvasive simple test, widely available, requiring only a random sample of formed stool for analysis and is therefore the most frequently used test in this context. Lower concentrations of FE-1 are correlated with higher probability of PEI, but FE-1 may not be suitable for excluding mild to moderate PEI. Despite being less available, the ^{13}C-mixed triglyceride breath test and coefficient of fat absorption are valid alternatives [21]. The presence of two out of three criteria (presence of symptoms of maldigestion, biochemical nutritional deficiencies, and altered pancreatic function tests) makes the diagnosis of PEI very likely [38].

PERT is the cornerstone in the treatment of PEI and should be initiated as soon as PEI is diagnosed or suspected as it has been shown to improve serum nutritional parameters, weight, gastrointestinal symptoms, and quality of life without significant adverse events [47]. PERT should be administered along with snacks and larger meals, with a minimum lipase dose of 20,000–25,000 units before snacks and 40,000–50,000 units in larger meals (in this situation, taking one half of the total dose before the meal and the other half in the middle of the meal) [35].

Efficacy of PERT is commonly evaluated by the relief of gastrointestinal symptoms and the improvement of both anthropometric and biochemical nutritional parameters, which occurs in more than a half of patients [47]. When there is no response to PERT, several strategies may be used, namely increasing PERT dosage or adding a proton pump inhibitor and excluding other causes of malabsorption such as lactose intolerance, bile salt diarrhea, or small intestinal bacterial overgrowth, which can be present in up to one-third of the patients [48–50].

Pancreatic Endocrine Insufficiency in Chronic Pancreatitis

Annual monitoring of serum glucose and glycosylated hemoglobin levels, even in the absence of diabetes mellitus symptoms, is also appropriate because of the high incidence of pancreatogenic (type 3c) diabetes mellitus in patients with CP, the frequent association of diabetes and PEI, and the impact of undiagnosed diabetes on their nutritional status [38]. Criteria for a diagnosis of T3cDM are fasting plasma glucose ≥126 mg/dL or HbA1c ≥6.5%. An HbA1c <6.5% does not rule out T3cDM due to the limitations of this test in this patient population. Therefore, normal HbA1c (<6.5%) should always be confirmed by fasting plasma glucose. In the absence of unequivocal hyperglycemia (random plasma glucose ≥200 mg/dL) or in doubtful cases, results should be confirmed by repeat testing or by the evaluation by a standard 75 g oral glucose tolerance test (2 h fasting glucose ≥200 mg/dL) [35]. This is generally an underappreciated subtype of the disease and can be challenging to manage, particularly by the increased risk of potential life-threatening acute complications and the presence of brittle diabetes with rapid swings in glucose levels in up to 25% of the patients [35, 51, 52]. For these reasons, when diabetes mellitus is diagnosed, prompt referral to endocrinology is advised.

Bone Health and Osteopathy

Another important issue in the nutritional management of patients with CP is the evaluation of bone health as almost 25% of patients are at risk for osteoporosis and about 65% are at risk for osteopathy (either osteoporosis or osteopenia) [53]. There are multiple factors contributing to osteopathy in CP, such as chronic inflammation, smoking and alcohol intake, low physical activity, impaired absorption of vitamin D, and poor dietary intake and sunshine exposure.

The method of choice to identify patients with osteopathy is the dual-energy X-ray absorptiometry. While baseline bone density assessment for all patients with CP should be considered, it is certainly indicated in patients with an additional risk factor such as postmenopausal women, those with previous low-trauma fractures, men over 50 years, and those with malabsorption [35].

General measures to prevent osteopathy include adequate consumption of calcium/vitamin D, avoidance of smoking and alcohol, regular exercise, and PERT if indicated. Additionally, daily supplement of vitamin D (800 UI) and calcium (500–1,000 mg) should be considered in patients with osteopenia, in whom dual-energy X-ray absorptiometry should be repeated every 2 years. When osteoporosis is present, referral to a bone specialist with expertise in more specific treatments should be considered [21, 35].

Nutrition and Pancreatic Cancer

PC remains one of the most lethal tumors, being the fourth most frequent cause of cancer-related death and having a 5-year survival well below 10% [54]. Curative treatments, which involve surgery and chemotherapy, are only possible in a minority of patients as localized forms of the disease are diagnosed in just about 20% of the cases [55].

Malnutrition has been described in up to 70% of the patients with PC, with about 40% reporting significant weight loss at the diagnosis [56, 57]. The development of malnutrition in PC is multifactorial and involves different mechanisms: reduced food intake caused by abdominal pain, gastric outlet obstruction, or anorexia; a pro-inflammatory response and activation of several molecular pathways resulting in elevated resting energy expenditure and leading to sarcopenia and cachexia; malabsorption of nutrients related to PEI; and finally, depression, side effects of the chemotherapy, and anatomical changes due to surgery can greatly affect food intake [58]. Cancer-related malnutrition origins a cascade of consequences, namely increased risk of infections, postoperative complications, and prolonged hospitalization, reduced tolerance or response to chemo- or radiotherapy, and reduced performance status, ultimately decreasing quality of life [59].

It is now well recognized that early nutritional support in patients with PC can favorably impact survival not only by increasing tolerance and response to disease treatments but also by improving quality of life and decreasing postoperative complications [60, 61]. An algorithm with an approach to nutritional assessment of patients with PC is presented (Fig. 3).

Malnutrition Risk Screening and Assessment in Pancreatic Cancer

Latest guidelines on nutritional care in cancer patients recommend that nutritional screening be performed in all cancer patients from the beginning of the disease course, in order to implement nutritional intervention in the form of personalized plans [62]. However, although many nutritional screening tools are available, none of them have been specifically validated for use in PC patients [58]. Some of the suggested tools are the previously referred NRS-2002 (Table 1) and malnutrition universal screening tool (Table 2). Several other tools to assess the nutritional status of patients with PC are available, including bioelectrical impedance analysis or serum proteins, which are frequently used as markers of poor protein and energy intake,

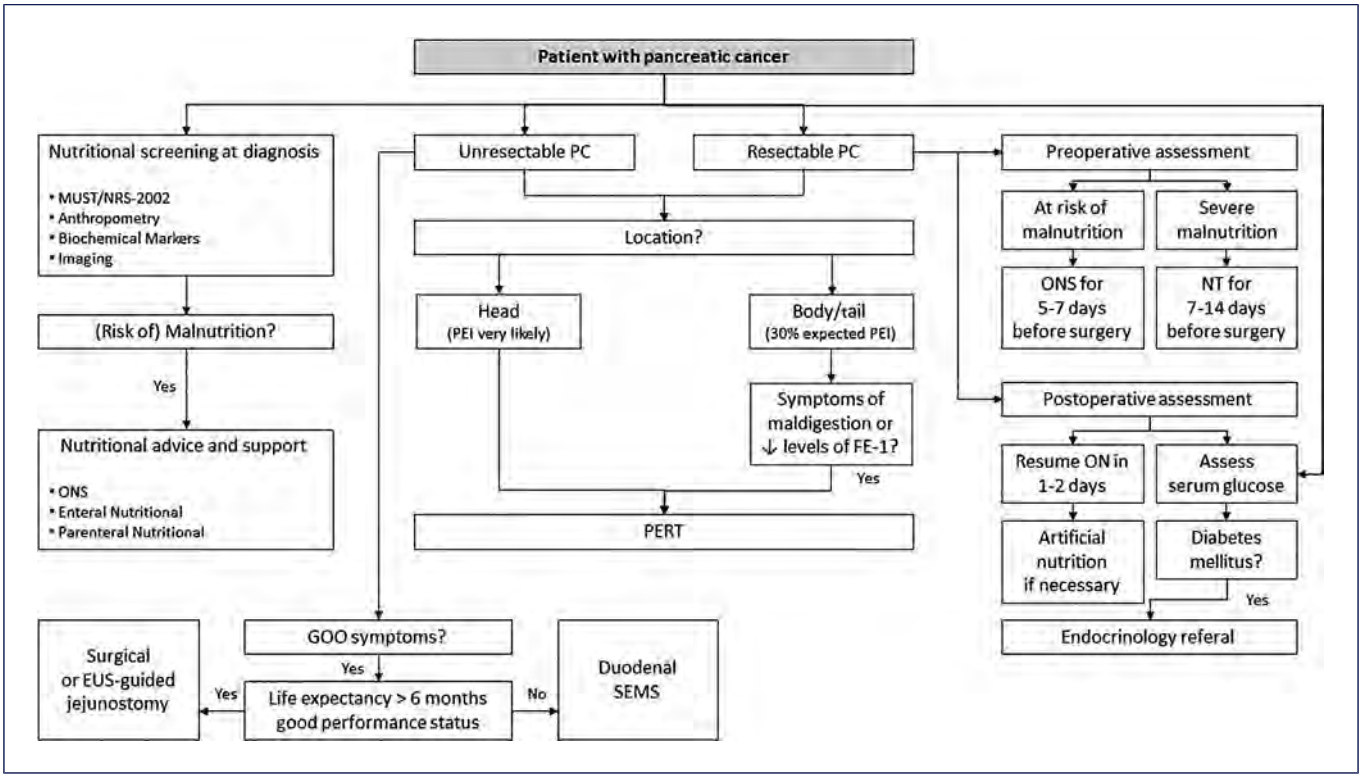

Fig. 3. Algorithm suggesting nutritional management in pancreatic cancer. EUS, endoscopic ultrasound; FE-1, fecal elastase-1; GOO, gastric outlet obstruction; MUST, malnutrition universal screening tool; NRS-2002, Nutrition Risk Screening-2002; NT, nutritional therapy; ON, oral nutrition; ONS, oral nutritional supplements; PC, pancreatic cancer; SEMS, self-expandable metal stent.

impaired liver synthesis, and a pro-inflammatory status [58].

Patients with a positive screening test for nutritional dysfunctions should then be offered a comprehensive assessment of nutritional intake, symptoms, muscle mass, degree of systemic inflammation, and physical activity. If a deficit in one or more of those topics is recognized, a multidisciplinary team should work together to correct it [63].

Nutritional Therapy in Pancreatic Cancer

Although a cachexic patient is likely to consume a diet that would be insufficient to maintain weight in a healthy individual, it is recognized that in many patients there is an increase in the metabolism that is responsible for higher caloric needs [64]. When energy expenditure is not individually measured, current guidelines suggest a caloric intake of 25–30 kcal/kg/day and a protein intake of 1.2–1.5 g/kg/day [62].

Nutritional counseling is generally the first step to take and involves increasing the size of meals, the number of snacks, or the energy value of existing meals [64]. If a patient continues to lose weight despite these dietary changes, then ONS may be of value, and despite the low quality of the available evidence, several studies have reported the likely benefit of omega-3 fatty acids on PC cachexia, showing a trend toward stabilization or an increase in weight and in lean body mass [64, 65].

In patients who are unable to tolerate sufficient oral food intake, prompt artificial nutrition is recommended. While EN should be preferred to PN due to lower costs, fewer complications, and ability to maintain the gut barrier, PN has been shown to be of benefit to the majority of patients with pancreatic or advanced cancers [66–68].

Clinical history is essential in identifying obstructive symptoms causing weight loss. Refractory vomiting is the cardinal symptom of gastric outlet obstruction, generally due to malignant infiltration of the duodenum or stomach. In patients with a better life expectancy (>6 months) and good functional status, a surgical or endoscopic ultrasound-guided gastrojejunostomy should be performed, while endoscopic placement of a duodenal

self-expandable metal stent should be limited to patients with a worse prognosis [69, 70]. Gastroparesis in the absence of anatomical abnormality on CT scan is common, possibly due to direct cancer infiltration of the autonomic nerve fibers and neurohormonal changes. In this setting, prokinetics such as erythromycin or metoclopramide may be useful.

Particularities of Pancreatic Cancer Treatments

In the preoperative setting, patients at risk of malnutrition should be given ONS for at least 5–7 days before surgery [71]. However, patients with severe nutritional risk (NRS-2002 >5, weight loss >10% within 6 months, or serum albumin <30 g/L) should receive nutritional therapy for a period of 7–14 days prior to major surgery even if cancer operations have to be delayed [72].

In the postoperative period, patients can generally resume eating solid food from the first or second day after surgery, but a significant percentage fail to reach caloric and protein requirements due to the occurrence of complications [58]. Early implementation of artificial nutritional support should be considered in malnourished patients, in those at high risk of developing malnutrition or with postoperative complications, and in any patients who cannot tolerate at least 50% of their caloric and protein requirement by postoperative day 7 [72].

Regarding chemotherapy, the rate of patients able to complete planned adjuvant treatments ranges from 54% to 72%, having prognostic impact for disease recurrence and survival [58]. While a worse nutritional status is associated with an increased rate of incomplete adjuvant chemotherapy, a better nutritional status is predictive of an enhanced local response to primary tumor as well as a reduced rate of acute complications [73, 74]. Common use of multidrug chemotherapy regimens can certainly impact patients' nutritional status. If, on one hand, their use may increase toxicity that may impair patients' feeding ability, on the other hand, more intense chemotherapy can induce better tumor response and, as a consequence, improvement in tumor-related symptoms, inflammatory status, body composition, and nutritional status [75].

Pancreatic Exdocrine Insufficiency and Pancreatic Cancer

Prevalence of PEI in operable PC has been reported as 50–100% [76] and after cancer-related pancreatic surgery as 64–100% [77]. The likelihood of developing PEI in patients with PC depends on different aspects, namely the disease site (head vs. body/tail of the pancreas), the disease stage (local vs. advanced), and the received treatments (surgical resection of the pancreatic head or of body/tail vs. none) [42]. There are several factors contributing to PEI in PC as follows: obstruction of pancreatic ducts due to cancer progression with impaired enzyme and bicarbonate delivery, primary parenchymal loss/resection related to surgery, reduced cholecystokinin-mediated secretion due to duodenal resection, and asynchrony between gastric emptying and bile and enzyme secretion due to surgical denervation and reconstruction [78].

As stated before, several noninvasive methods to diagnose PEI have been described, but in the context of PC, coefficient fat absorption and ^{13}C-mixed triglyceride breath test have the highest accuracy. However, their lack of availability is a barrier for their use in the clinical practice [79]. When the pretest probability of PEI is very high, the presence of symptoms or clinical and laboratory evidence of maldigestion should lead to the decision to start PERT, irrespective of the result of a diagnostic test. Therefore, in patients with pancreatic head cancer, either unresectable or submitted to surgical resection, the expected PEI prevalence is so high that PERT should be started immediately. Conversely, in patients with pancreatic body/tail cancer, PEI should be tested by FE-1 and PERT be started only in the presence of low FE-1 levels or symptoms of maldigestion [42].

While some recent studies showed that PERT significantly impacts quality of life and survival even in the setting of metastatic disease [80, 81], others reported worrying analysis, in which only about 20% of the patients were adequately treated with PERT [82]. In the setting of PC, PERT should be started with higher doses than those used in CP (50,000–75,000 units of lipase with meals and 25,000–50,000 with snacks or supplements). Moreover, as after pancreaticoduodenectomy the secretion of bicarbonate may be impaired and the acidic environment of the duodenum and proximal jejunum may lead to inefficient activation of pancreatic enzymes, concurrent use of proton pump inhibitors is suggested in operated patients [42].

Pancreatic Endocrine Insufficiency and Pancreatic Cancer

Due to ductal obstruction associated with acinar inflammation and fibrosis replacement of the exocrine pancreas, patients with PC can also exhibit pancreatic endocrine insufficiency, resulting in diabetes mellitus [51]. Plasma glucose should be regularly monitored and if diabetes is diagnosed, endocrinological evaluation should be sought. Importantly, hypoglycemia may occur on glucose-lowering treatment if the patient

develops upper intestinal obstruction, cachexia, or steatorrhea, all of which may necessitate dose reduction. On the contrary, hyperglycemic states can be precipitated by chemotherapy infusions in dextrose solutions, by steroids such as dexamethasone used for appetite stimulation, or by PERT which facilitates sugar absorption [83]. Surgical resections for the treatment of PC can also impact endocrine function, which has been described to be worsened, improved, or unchanged after surgery [55]. New onset of diabetes mellitus after surgery may occur after duodenopancreatectomy in up to 40% but is more frequent after distal pancreatectomy [55].

Conclusion

The incidence of pancreatic disorders such as AP, CP, and PC is currently increasing, and adequate nutritional care has been shown to improve patients' outcomes in all of them. In an era of personalized medicine, tailoring of nutrition care for each patient should be pursued as soon as the diagnostic is established, leading to an appropriate nutritional care plan. As awareness of nutritional issues in pancreatic diseases increases among gastroenterologists, they should become prepared to lead multidisciplinary teams with surgeons, dieticians, endocrinologists, and oncologists involved in the management of these patients.

Conflict of Interest Statement

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Data Availability Statement

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

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The Growing Landscape of NAFLD-Associated Hepatocellular Carcinoma and Its Impact in Surveillance

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Keywords
Nonalcoholic fatty liver disease · Hepatocellular carcinoma · Screening

Abstract
Liver cancer is globally the third leading cause of death from cancer. Hepatocellular carcinoma (HCC) develops in patients with underlying liver disease. The fraction of HCC attributed to nonalcoholic fatty liver disease (NAFLD) shows an accelerated increase in the last decades, being already responsible for 15% of all HCC cases. Similar to other causes of liver cirrhosis, patients with NAFLD-associated cirrhosis should be enrolled in HCC-screening programs, yet these patients are under-screened, and currently are less than half likely to be proposed for HCC screening as compared to patients with HCV-associated cirrhosis. NAFLD-associated HCC has the peculiarity of occurring in precirrhotic phases in 20–50% of the cases. Currently, HCC screening in precirrhotic NAFLD patients is not routinely recommended, since the risk of developing HCC is very low. However, because NAFLD affects one-third of the worldwide population, noncirrhotic NAFLD already accounts for 6% of HCC cases. As such, it is pressing to develop stratification tools, in order to personalize the individual risk of HCC development in a patient with NAFLD, allowing precision HCC-screening programs. This review summarizes the epidemiology of NAFLD-associated HCC with a critical analysis of current HCC-screening recommendations.

O crescente panorama do carcinoma hepatocelular associado ao fígado gordo não alcoólico e o seu impacto no rastreio

Palavras Chave
Fígado gordo não alcoólico · Carcinoma hepatocellular · Rastreio

Resumo
O cancro do fígado é, globalmente, a terceira causa de morte por cancro. O carcinoma hepatocelular (CHC) desenvolve-se em doentes com doença hepática crónica subjacente. A fracção de CHC atribuível ao fígado gordo não alcoólico (FGNA) tem vindo a aumentar com uma aceleração no seu crescimento nas últimas décadas, sendo atualmente responsável por 15% dos casos de CHC. À semelhança do que ocorre com outras causas de cirrose hepática, os doentes com cirrose associada a

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FGNA devem ser inseridos em programas de rastreio de CHC. Contudo, esses doentes são sub-rastreados, já que a probabilidade de serem incluídos em programas de rastreio de CHC é menos de metade comparando com doentes com cirrose associada a hepatite C crónica. O CHC associado ao FGNA tem a particularidade de ocorrer em fases pré-cirróticas em 20 a 50% dos casos. O rastreio de CHC em doentes com FGNA em fase pré-cirrótica não está recomendado por rotina, uma vez que, ainda assim, o risco destes doentes desenvolverem CHC é muito baixo. No entanto, uma vez que um terço da população mundial tem FGNA, o FGNA em não cirróticos corresponde a 6% de todos os casos de CHC. Assim sendo, é urgente o desenvolvimento de métodos de estratificação, por forma a personalizar o risco individual de desenvolvimento de CHC em doentes com FGNA, permitindo maior precisão nos programas de rastreio de CHC. Esta revisão sumariza a epidemiologia de CHC associado ao FGNA, com uma análise crítica das atuais recomendações de rastreio de CHC.

Introduction

Liver cancer is the sixth cancer and the third cause of death from cancer worldwide, according to the 2020 GLOBOCAN report. The higher ranking of liver cancer in mortality over incidence reflects its dismal prognosis, with almost matching incidence and mortality rates [1].

Hepatocellular carcinoma (HCC) develops in the context of chronic liver disease (CLD), the main causes being B/C viral hepatitis, alcohol-associated liver disease (ALD), and nonalcoholic fatty liver disease (NAFLD). The epidemiology of CLD is changing and shaping the epidemiology of HCC. Hepatitis B (HBV)-associated HCC, which is still highly prevalent in Asia and Africa, is decreasing with the widespread HBV vaccination [2]. The breakthrough on hepatitis C (HCV) treatment is decreasing HCV-associated HCC. Instead, the obesity pandemic justifies the 5% increase in NAFLD prevalence in the last 5 years to 30% worldwide, even in regions classically with low prevalence such as Asia and East-North Africa [3]. The aggregate data result in NAFLD being the fastest-growing etiology for HCC [4, 5]. This review summarizes the available data on epidemiology of NAFLD-associated HCC and the rationale for its screening algorithms.

Epidemiology of NAFLD-Associated HCC

NAFLD accounts for 15% of HCC cases worldwide [6]. In the USA, the prevalence of NAFLD-attributable HCC in patients transplanted for HCC increased 8-fold: 2% in 2002 and 16% in 2016 [4]. Similarly, the prevalence of HCC in patients transplanted for NAFLD increased 12-fold (twice the increase in patients transplanted for HBV, three times the one in ALD, and 6 times in HCV) [4].

Regarding Europe, in France, NAFLD-attributable HCC increased from 2.6% in the period of 1995–1999 to 19.5% in 2010–2014, whereas HCV decreased from 43.6% to 19.5% [7]. In the UK, where historically the prevalence of HCV-attributable HCC is low, the mortality of HCC is increasing, with a particular rise in the referrals for NAFLD-associated HCC as compared to HCV- or ALD-associated HCC [8]. In the Newcastle-upon Tyne Hospitals NHS Foundation 2010 register, 35% of HCC cases were attributable to NAFLD [8].

In Latin America, NAFLD-attributable HCC in transplanted patients increased 6-fold from 2005 to 2012 (from 2% to 13%), in contrast with only 1.5-fold increase in ALD and 2-fold decrease in HCV [5]. Regarding Asia, in Japan, nonviral etiology of HCC, including NAFLD and ALD, accounted for 10% of the cases in 1991, 24% in 2010 (representing 10% relative increase each year), and 32.5% in 2015 (representing an acceleration for 30% relative increase per year) [9]. One study from Japan described an even higher 46% NAFLD-attributable HCC, in 2018 [10]. Similar figures are observed in Korea, where NAFLD-attributable HCC increased from 3.8% during 2001–2005 to 12.2% in 2006–2010 [11].

Considering only cirrhotics, the trend sustains. A study with around 100,000 cirrhotic patients from the Veterans Administration healthcare system showed a 60% increase in the incidence of HCC in patients with cirrhosis diagnosed in 2008–2014, as compared to 2001–2007. The greatest increase, 88%, occurred in NAFLD-associated cirrhosis [12].

Meta-analyses showed an annual HCC incidence rate of 1.44% and 3.78% in patients with NAFLD-associated advanced liver fibrosis and cirrhosis, respectively, which seems similar to non-NAFLD-associated cirrhosis [13, 14], except for HCV-associated cirrhosis [12, 15]. The risk was 100 times lower in precirrhotic NAFLD: 0.03% per year [14]. Importantly, despite the low incidence of HCC in precirrhotic NAFLD, a retrospective study on around 300,000 NAFLD patients from the Veterans Health Administration showed an 8-fold higher risk for HCC compared with non-NAFLD controls, after adjusting to race and metabolic traits [16].

In noncirrhotic HCC, the proportion of NAFLD-attributable HCC is even higher. Indeed, the absence of cirrhosis is 5-fold more likely in NAFLD-associated HCC compared to non-NAFLD HCC [16].

NAFLD-associated HCC, compared to other etiologies, tends to occur in older patients, with more metabolic and cardiovascular comorbidities, and more frequently without liver cirrhosis (38% vs. 15%) [6]. NAFLD-associated HCC is more often detected outside specific surveillance [6], which could not be fully explained by the higher proportion of noncirrhotic HCC, since it also occurs in NAFLD-associated cirrhosis [17], even though HCC incidence is similar to other etiologies of cirrhosis [14, 15]. Indeed, HCC screening is less than half likely to be offered to a patient with NAFLD-associated cirrhosis as compared to HCV-associated cirrhosis, even though those patients do not comply less [18]. NAFLD-associated HCC tends to be larger, uninodular, with a more infiltrative pattern but more frequently well-differentiated, and with similar tumor stages at diagnosis [6]. Larger tumor size and uninodular involvement may be associated with the absence of cirrhosis, which confers lower resistance to expansive tumor growth [6]. Interestingly, despite overall survival in NAFLD-associated HCC patients seems similar compared to HCC from other causes [8], considering only cirrhotic patients, mortality from HCC seems 70% higher in NAFLD-associated cirrhosis [6], which may reflect treatment limitations due to comorbidities. Furthermore, preliminary data suggest that immunotherapy may be less efficient in NAFLD-associated HCC due to immune exhaustion and impaired immune-surveillance [19].

Risk Factors for NAFLD-Associated HCC

NAFLD-associated HCC occurs more frequently in noncirrhotic livers, as compared to other etiologies. A meta-analysis of 19 studies including over 150,000 patients showed that in precirrhotic CLD, NAFLD associates with 2.5-fold increased risk of developing HCC compared to other etiologies [20]. The presence of NASH further increases the risk for HCC [21]. Furthermore, 40% patients with NAFLD-associated HCC are precirrhotics, ranging from 10 to 75% among studies [16, 20]. Importantly, the prognosis of HCC depends on its stage and treatment approaches, whereas the presence of cirrhosis does not seem to independently associate with survival in NAFLD-associated HCC [22].

In NAFLD patients, the presence and severity of liver fibrosis are the most important risk factors for HCC development, whereas steatosis, ballooning, or lobular inflammation are not associated [23]. Despite the lack of association with histological inflammation, increased aminotransferase levels seem to increase the risk for cirrhosis and to double the risk for HCC [24]. High scores in noninvasive fibrosis tools, such as APRI, FIB-4, and NAFLD fibrosis score (NFS), are associated with an increased risk for HCC [23], even in the noncirrhotic range [10].

Liver stiffness measurement (LSM) may add in HCC risk stratification. While there is no clear LSM cutoff that accurately predicts the risk for HCC [25], there is a dose-dependent increase in the risk with higher LSM, in noncirrhotic and cirrhotic ranges [23]. For example, the 2-year risk was estimated as 9% if higher than 18 kPa and 13% if higher than 38 kPa [25]. The kinetics of LSM might also be predictive, as a retrospective study on 1,039 NAFLD patients showed that an increase in LSM was associated with a 70% increase in HCC risk, particularly for increases higher than 20% [26].

Older patients are more likely to develop HCC, even without cirrhosis, due to a defective cancer immune-surveillance and DNA damage with accumulation of gene mutations. Regarding metabolic dysfunction, type-2 diabetes mellitus (T2DM) is the strongest risk factor for HCC in NAFLD, increasing 3-fold the risk [16]. Smoking is another risk factor, with a synergic effect with T2DM. In cirrhotics, current smokers have a 50–80% increased HCC risk compared to never smokers [27].

Concerning alcohol, any alcohol consumption, even social intake (i.e., less than 3 drinks per day or 3–6 drinks daily on weekends), increases 3.5-fold the HCC risk in NAFLD-associated cirrhosis [15], whereas in noncirrhotic patients, the effect of moderate alcohol consumption remains controversial. However, we should take into consideration that alcohol and body mass index (BMI) present a synergic effect on the risk for HCC, with obese patients with mild alcohol consumption (defined as more than 3 drinks per week), presenting an almost 4-fold increased risk [28].

In NAFLD-associated cirrhotics, the known risk factors for HCC are male sex, older age (80% increased risk per decade), T2DM (2–4 times increased risk), decreased platelets count (translating portal hypertension), and low serum albumin (2 times increased risk) [23, 29–31]. Conversely, BMI, hypertension, or dyslipidemia does not seem to be risk factors, probably rendering the reversal of those metabolic factors as cirrhosis progresses [29]. Clinical decompensation further increases HCC risk in NAFLD-associated cirrhosis [30]. Also, even in compensated cirrhotics, 6 points on Child-Pugh-Turcotte score increase 2-fold the risk compared with 5 points [31].

Physiopathology of NAFLD-Associated HCC

European primary care healthcare records showed that, compared to the general population, NAFLD patients had a 3-fold higher chance of developing HCC. That risk increased by 8-folds in patients with steatohepatitis [21].

The increased risk for HCC in NAFLD may depend on the hepatic steatosis and liver injury per se, or on the metabolic conditions that led to hepatic steatosis, such as T2DM and obesity. Indeed, T2DM and/or obesity represented over one-third of the attributable fraction for HCC in the elderly, in a SEER-Medicare database [32]. Furthermore, in the general population, the number of metabolic abnormalities, such as T2DM, obesity, arterial hypertension, and dyslipidemia, has an additive effect on HCC risk [33].

Liver steatosis is, by itself, potentially carcinogenic, being a source of oxidative stress [34]. Oxidative stress induces DNA damage and the accumulation of methylated, hence silenced, tumor-suppressor genes. Accordingly, NASH patients with HCC present higher oxidative damage in hepatocytes [35]. Cholesterol and ceramides-related lipotoxicity may also favor carcinogenesis [34].

T2DM is potentially carcinogenic through different mechanisms: (a) activation of proinflammatory pathways and oxidative stress leading to genomic instability and apoptosis inhibition, (b) hyperinsulinemia and insulin-like growth factor [29], (c) T2DM-induced dysbiota and bacterial translocation, and (d) iron deposition. T2DM is consistently the strongest risk factor for HCC, in the general population [32], in patients with NAFLD [21, 33] and NAFLD-associated cirrhosis [29], and even in patients with non-NAFLD cirrhosis [36]. The effect of T2DM on HCC risk seems to be time-dependent, as T2DM duration less than 10 years is associated with a 3-fold increased risk, but duration longer than 10 years with a 5-fold increased risk as compared with the absence of T2DM [37]. Also, diabetic retinopathy seems a stronger predictor for HCC as compared to T2DM alone, which may translate a longer duration of T2DM or a disruption on VEGF physiology [38].

Epidemiological studies suggested that metformin was associated with 50% decreased risk for HCC [39], with a time-dependent effect: 7% decreased risk per year on metformin [40]. Reversely, insulin or sulfonylureas were associated with 2-fold and 50% increased risk, respectively [39]. Insulin may have carcinogenic effects promoting cell proliferation. Sulfonylureas promote insulin secretion potentially being indirectly carcinogenic. Accordingly, sulfonylureas' potential carcinogenic effect seems to be restricted to first- and second-generation sulfonylureas, but not third-generation drugs such as glimepiride, which have lower insulin secretagogue effects [41]. Anti-HCC effects of metformin seem to be insulin-dependent and -independent: increases insulin sensitivity decreasing insulin levels, but also directly activates intracellular AMPK, leading to decreased protein synthesis and cell proliferation [40], decreases the stem cell population, and inhibits an epithelial-to-mesenchymal transition. The effect of thiazolidinediones is less clear, as a meta-analysis of 4 studies did not show a significant effect, even though all studies individually found a beneficial effect [39]. Thiazolidinediones present potentially anticancer effects by inducing cell growth arrest and apoptosis, while being able to inhibit cell invasion [42]. A study from Taiwan not included in that meta-analysis, on around half a million T2DM patients followed for 7 years, did find a dose- and time-dependent beneficial effect of both pioglitazone and rosiglitazone on the risk of developing HCC [42].

Obesity seems to double the risk for HCC [43], accounting for 16% of its attributable risk [44]. There is dose-dependent increased risk for HCC according to the BMI category: 36% increase in overweight, 80% in class I obesity, and 300% in type II [45]. Even though lifestyle factors are difficult to dissect as risk factors for HCC, high physical activity seems to decrease in 25% the risk for HCC as compared to low physical activity [46].

Dyslipidemia is a risk factor for NAFLD/NASH, but its association with HCC is controversial [47]. However, consistent epidemiological data point out statins treatment to decrease 40–70% the risk for HCC [48], which may translate the pleiotropic effects of statins besides its cholesterol-lowering effect.

Genetic polymorphisms known to promote NAFLD have also been associated with increased risk for HCC. PNPLA3 (patatin-like phospholipase domain-containing-3) rs738409 variant impairs mobilization of triglycerides from lipid droplets and is associated with a 3-fold increased risk for HCC, independently of age, gender, BMI, presence of T2DM, or advanced fibrosis/cirrhosis [49]. TM6SF2 (transmembrane-6 superfamily member-2) rs58542926 variant hampers trafficking of pre-VLDL particles and is associated with a 2-fold increased risk for HCC when on homozygosity [50]. APOB (apolipoprotein B) variants are associated with increased HCC risk despite favorable lipid profile [51]. MBOAT7 (membrane-bound O-acyl transferase-7) ensures adequate cell membranes' desaturation level by catalyzing the transfer of polyunsaturated fatty acids such as arachidonoyl-CoA to lysophosphatidylinositol. MBOAT7 rs641738 variant results in decreased MBOAT7 expression and is associated with a 2-fold increased HCC risk in NAFLD patients without advanced fibrosis [52].

Conversely, HSD17B13 (hydroxysteroid-17-beta dehydrogenase-13) rs72613567 variant is associated with a 40% protection for HCC [53].

Accuracy of Screening Methods for NAFLD-Associated HCC

Ultrasound (US) is the imaging modality recommended for HCC screening. However, US is operator-dependent, and 20% US examinations do not have adequate quality for the evaluation of hepatic lesions [54], rising to 33% in Child-Pugh-Turcotte class C patients, with BMI over 35 kg/m^2, or with NAFLD-associated cirrhosis [55]. US detects HCC lesions with 84% sensitivity and 91% specificity; however, sensitivity drops to 47% for early HCC [56]. Interestingly, only 40% of HCC is detected at an early stage, and inadequate US sensitivity is the main reason for HCC being diagnosed at advanced stages during surveillance [57]. Patients with Child-Pugh-Turcotte class B/C cirrhosis have a 90% increased risk of inadequate US, due to lower accessibility of a severely atrophic liver retracted under the rib cage [55]. US performs particularly worse in NAFLD-associated cirrhosis, with an almost 3-fold increased risk of US diagnostic inadequacy [55]. Steatosis can impair visualization of deep liver nodules through increased attenuation of the US pulse [55]. To standardize the evaluation of the HCC-screening US accuracy, the American College of Radiology developed the Ultrasound Liver Imaging Reporting and Data System (US LI-RADS) algorithm that has 2 components: detection scores and visualization scores. The visualization score allows standardization of the US report regarding expected sensitivity, in 3 categories: A (no or minimal limitations), B (moderate limitations), and C (severe limitations to allow accurate visualization).

The diagnostic accuracies of CT and MRI are superior to US, particularly in patients with worse US LI-RADS visualization scores [58]. However, CT scans impose potential harms such as radiation exposure and contrast-induced nephropathy, and MRI is time consuming and costly. Recently, application of abbreviated MRI protocols to HCC screening presented higher sensitivity than US (82% vs. 53%), even though the performance declined for tumors smaller than 2 cm (69% vs. 86%) [59]. There are different abbreviated MRI protocols that consist of a limited number of sequences, not requiring contrast administration, hence allowing reduced acquisition and interpretation time [59].

Alpha-fetoprotein (AFP) is the best-studied HCC tumor marker, with the best cutoff, 20 ng/mL, presenting, in cirrhotics, a sensitivity of 41–61% at any stage (32–49% for early HCC) and specificity of 80–94% [60]. In combination with US, it increases 20% HCC-screening sensitivity versus US alone [56]. It can present false positives in cirrhotics particularly when aminotransferases are elevated, and in non-HCC malignancies such as cholangiocarcinoma and embryonal carcinoma of the testes. A different cutoff, 11 ng/mL, was proposed for non-HCV HCC [61]. Assessment should be longitudinal as increasing or fluctuating AFP levels might elicit intensive monitoring [62].

Lens culinaris agglutinin-reactive AFP (AFP-L3), des-gamma-carboxy-prothrombin (DCP), and protein induced by vitamin K absence or antagonist-II (PIVKA-II) are other biomarkers. A small study on NAFLD showed PIVKA-II to present best accuracy (AUROC 0.86), while AFP-L3 lower (AUROC 0.689), compared to AFP (AUROC 0.763) [63]. DCP seems to outperform AFP in tumor recurrence after curative treatment in NAFLD (but not ALD)-associated HCC [64].

Clinical-laboratorial scores are being developed. GALAD score incorporates 5 parameters – sex, age, AFP, AFP-L3, and DCP – and seems promising in phase 2 studies for HCC screening [65]. GALAD score was validated in 2 NAFLD cohorts (from Germany and Japan), with better accuracy (AUROC >0.90) as compared to tumor markers alone, at any stage but particularly within the Milan criteria and in patients with precirrhotic NAFLD (AUROC 0.98). A GALAD score higher than −0.63 could be detected up to 1.5 years before the development of HCC [66] and hence could be used to stratify patients to intensive HCC-screening programs.

Novel tumor markers have been proposed, but need further validation. WTA$^+$-M2BP (*Wisteria floribunda* agglutinin-positive Mac2-binding protein) or M2BPGI (Mac2-protein glycosylated isomer) is a noninvasive marker of liver fibrosis that seems promising as a NAFLD-associated HCC tumor marker [67]. M2BP is a secretory glycoprotein that, during fibrogenesis, undergoes modifications in N-glycosylation specifically recognized by WTA, resulting in WTA$^+$-M2BP/M2BPGI. Among NAFLD patients with advanced fibrosis, the 1.25 cutoff presented 70% sensitivity, 78% specificity, and AUROC 0.806 for HCC. NAFLD patients with high versus low WTA$^+$-M2BP/M2BPGI presented 21% versus 1.7% probability of HCC in 10 years [67]. ITIH4 (inter-alpha-trypsin inhibitor heavy chain-4) is upregulated by IL-6 and regulates the extracellular matrix. In preclinical and human NAFLD-associated HCC studies, higher ITIH4 levels are associated with NAFLD-attributable HCC, independently of liver fibrosis [68].

Table 1. Summary of HCC-screening guidelines for patients with NAFLD

	EASL, 2018	AASLD, 2018	AGA, 2020	Japanese guidelines, 2021
Who to screen?	F4 and F3 (can be assessed by LSM)	F4	F4 and F3 2 concordant noninvasive methods: FIB-4 or ELF+ LSM ≥16 kPa or MRE ≥5 kPa	F3-F4 and F2 in male 2-step risk stratification 1st: markers of fibrosis*, platelet counts, FIB-4 or NFS 2nd: elastography or biopsy
How to screen?	US	US±AFP Consider CT/MRI if inadequate US	US or CT/MRI if US quality category C (and some B)±AFP	Tumor marker + US If difficult US, CT, or MRI
Screening frequency	Every 6 months	Every 6 months	Every 6 months	Every 6 months

AASLD, American Association for the Study of Liver Disease; AGA, American Gastroenterology Association; EASL, European Association for the Study of the Liver; NFS, NAFLD fibrosis score. *Serum markers of fibrosis include hyaluronic acid, type III collagen 7s, and MAC-2-binding protein.

Lastly, AIM (apoptosis inhibitor of macrophages) is produced by macrophages and hepatic Kupffer cells and circulates in the bloodstream in two ways: inactive IgM-bound and active IgM-unbound, which helps in mediating the removal of excess fat, bacteria, cancer cells, and dead cell debris. In a small study with NAFLD patients, serum IgM-unbound AIM >1.6 μg/mL presented higher sensitivity for HCC detection than AFP and DCP (88.5% vs. 26.9% and 53.8%, respectively) [69]. Increased serum IgM-unbound AIM was detected up to 5 years before the diagnosis of NAFLD-associated HCC, which may represent a useful tool to select patients for HCC surveillance [70].

Current HCC-Screening Algorithms for NAFLD-Associated HCC

Cost-effectiveness of HCC screening in cirrhotics requires an annual incidence rate of at least 0.8–1.5%. In NAFLD-associated cirrhosis, similar to non-NAFLD cirrhosis, the HCC annual incidence rate is 1.5–4% [14, 15]; hence HCC screening is worthwhile. However, less than one-fourth of all patients with cirrhosis, and even less if NAFLD-associated cirrhosis, are enrolled in a HCC-screening program [57]. In the decision to enroll a patient in a HCC-screening program, other factors should be evaluated, such as age, overall health, functional status, willingness and ability to comply with screening, and eligibility for HCC treatment. International HCC-screening guidelines are consensual in supporting HCC screening for patients with NAFLD-associated cirrhosis (Table 1).

Cirrhosis can be assessed through noninvasive tools such as LSM. The Baveno Working Group proposed LSM higher than 15 kPa as the threshold for compensated advanced CLD and hence for starting HCC screening. Screening should be performed twice a year with AFP and US. NAFLD-associated cirrhotics with an inadequate US [55] might be offered other imaging modalities such as CT scan, MRI, or, more recently, abbreviated MRI [71], which will increase the screening costs. Ioannou et al. [72] proposed a risk-stratification model for patients with NAFLD-associated cirrhosis to optimize HCC screening. The model is available online (www.hccrisk.com) and integrates age, gender, BMI, T2DM, platelet count, AST, ALT, and albumin. It predicts a 3- and 5-year risk for HCC and categorizes in 3 risk groups: high risk with annual incidence >3%, medium risk 1–3%, and low risk <1%. Only patients with high or medium risk should be on HCC-screening programs, with the former probably benefiting from intensive strategies such as using abbreviated MRI [72].

Regarding precirrhotic NAFLD, guidelines do not recommend universal screening, since the annual risk of HCC development is 0.03–0.6% [14], lower than the accepted cost-effective 1.5%/year cutoff for cirrhotics. However, the 1.5% cutoff was delineated for cirrhotic patients, and cost-effective risk for HCC screening in noncirrhotic NAFLD patients could be lower. For example, in noncirrhotic HBV, an annual risk >0.2%/year is cost-effective [73], probably because those patients are eligible to different treatment modalities compared to cirrhotics, being able to tolerate large hepatectomy surgeries, and with higher life expectancy outside the tumor burden. Furthermore, because 6% of HCC occurs in

precirrhotic NAFLD [6], an estimated global incidence of over 1 million cases by 2025 [74] results in 60,000 cases of HCC in noncirrhotic NAFLD that would be missed from HCC-screening programs each year.

HCC risk is heterogeneous among noncirrhotic NAFLD patients. For example in precirrhotic patients, high FIB-4 associates with 10 times higher HCC incidence compared to low FIB-4 [16]. Of note, the most recent guidelines already advise HCC screening in NAFLD patients with F3 fibrosis. An European cohort found that 90% of HCC in noncirrhotic NAFLD occurred in patients older than 65 years-old, suggesting that screening should not be considered in younger patients [17]. Preliminary evidence also suggests that noncirrhotic NAFLD patients 55 years old or older, with increased ALT and/or T2DM, are at particularly high risk [25]. Indeed, a study from Taiwan with a long-term follow-up of around 30,000 patients showed a 0.04% annual HCC incidence in young patients with normal ALT but 1.24% in older than 55 years with increased ALT [75]. Additionally, a population-based study from the USA suggested that noncirrhotic NAFLD patients that were male, older than 65 years old, smokers, diabetics, with increased ALT, had a 10-fold increased risk as compared to the whole noncirrhotic NAFLD patients, with a 0.45% annual incidence rate [30]. In NAFLD diabetic patients, the presence of diabetic retinopathy presented an AUROC 0.731 for HCC, being present in 15% of the diabetic population, but in 80% diabetic patients with HCC [38].

Two polygenic risk scores may help identifying high-risk NAFLD patients to guide a personalized HCC-screening program: (1) hepatic fat polygenic risk score (PRS-HFC) that combines known polymorphisms on PNPLA3, TM6SF2, GCKR, and MBOAT-7; and (2) polygenic risk score 5 (PRS-5) adjusted to HSD17B13 splice variant [76]. Both performed similarly: PRS-HFC ≥0.532 and PRS-5 ≥0.495 associated with 15 times higher HCC risk in the general population, 3 times in NAFLD patients (2 times in noncirrhotic patients), 5 times in obese, and 4.5 times in T2DM patients. Those scores presented very high specificity of 90%, but sensitivity below 30%. As such, those scores may help selecting patients to HCC screening, but should not be used to exclude patients from HCC screening.

A 133-gene signature in the hepatic transcriptome was proposed as a prognostic liver signature in NAFLD patients (PLS-NAFLD), which stratifies patients in high risk (23% 15 years HCC rate) and low risk (15 years HCC rate of 0) [77]. This score performs well even in patients with minimal liver fibrosis. Interestingly, high-risk genes were associated with immune cells activation, induction of tolerogenic IDO1^{+}-dendritic cells and T-cell exhaustion (a known feature of NAFLD-associated carcinogenesis [19]), whereas low-risk genes were associated with FXR and FGF-19/21 pathways. Furthermore, a 4-protein secretome signature (PLSec-NAFLD) also stratified in high risk for HCC (38% 15-years incidence) and low risk (none developing HCC) [77]. High-risk proteins were lymphoprotectin and progranulin, and low-risk proteins angiopoietin-2 and hepatocyte growth factor receptor. These scores might help excluding patients from HCC screening.

Extrahepatic cancer screening programs should also be encouraged to NAFLD patients, since extrahepatic cancers are 8 times more frequent than HCC and not associated with liver fibrosis [13]. A meta-analysis showed an annual incidence rate of 1.16%, being the most frequent ones uterine, breast, prostate, colorectal, and lung cancers [13].

Conclusion

A HCC-screening program requires 3 premises: (1) the population on surveillance must have high risk for HCC; (2) screening tools must be effective in diagnosing treatable HCC in that population; and (3) those patients must be eligible for effective treatments with expected impact on survival and/or quality of life.

Regarding the first premise, patients with NAFLD-associated cirrhosis have a HCC incidence rate superior to the cost-effective 1.5% cutoff and should undergo HCC screening. However, 20–50% of NAFLD-associated HCC occurs in patients with precirrhotic disease. The actual cost-effective cutoff in this population is yet to be determined. Furthermore, the risk of HCC in NAFLD patients is highly variable, being only significant in older patients, and screening should not be proposed in younger than 65 years old. Research is moving toward precision-medicine, and tools to thoroughly stratify patients are in development. One example is polygenic risk scores, which showed promising results.

The second premise, effective screening tools, has some specific limitations in NAFLD patients. Indeed, the accuracy of US decreases in obese and patients with liver steatosis, rendering usual screening programs less accurate for NAFLD patients. Abbreviated MRI is appealing for patients with unreliable US.

The third premise, effective HCC treatment, also has its caveats in patients with NAFLD-associated HCC, which tend to be older and with comorbidities that may limit treatment options, as well as preliminary data showing less efficacy of first-line systemic therapies in NAFLD-associated HCC. HCC screening in patients with NAFLD is challenging but should be improved, so

we can change current statistics in which NAFLD is the underlying etiology with the highest proportion of HCC diagnosed outside screening programs.

Statement of Ethics

This work is a literature review, and as such, it does not involve study on human subjects or animals.

Conflict of Interest Statement

The author has no conflicts of interest to declare.

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Ultrarapid Iron Polymaltose Infusions Are Safe for Management of Iron Deficiency

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Keywords
Iron deficiency · Iron infusion · Safety · Treatment and hospital

Abstract

Introduction: Iron deficiency is a common condition, especially among patients with kidney and heart failure and inflammatory bowel disease. Intravenous iron is the preferred method of treatment in these patients, but it usually requires prolonged iron polymaltose infusions or multiple administrations of alternative preparations. The aim of the study was to confirm the safety and patient acceptance of ultrarapid iron polymaltose infusions as an alternative to slower treatments and ferric carboxymaltose. ***Method:*** An open-label, phase 4 safety study was conducted at a tertiary hospital, with consenting participants diagnosed with iron deficiency and requiring iron polymaltose up to 1,500 mg receiving the infusion over 15 min. The acute adverse event (AE) rates and their severities were compared to historical controls of 1- and 4-h iron polymaltose infusions from a retrospective study of 648 patients from the same study site. Delayed AEs as well as participant infusion acceptability were also studied. ***Results:*** Three hundred participants over a 2-year period received ultrarapid infusions of iron polymaltose with an acute AE rate of 18.7% and severe AE rate of 1.0%. The total and mild infusion AE rates were higher compared to those of slower infusions ($p < 0.001$), but comparable for moderate and severe AEs. Delayed reactions occurred in 12.5% of participants, with over 95% of them preferring repeat ultrarapid infusions if required again. ***Conclusion:*** Iron polymaltose can be safely infused at ultrarapid rates when compared to slower infusions, with similar safety to ferric carboxymaltose, offering greater convenience for patients and reduced healthcare costs.

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As infusões de ferro polimaltose ultra-rápidas são seguras na anemia ferropénica

Palavras Chave
Deficiência de ferro · Anaemia · Ferropenia · Infusão de ferro · Segurança · Tratamento

Resumo
Introdução: A deficiência de ferro é uma condição comum, especialmente nos doentes com insuficiência renal e cardíaca e doença inflamatória intestinal. O ferro intravenoso é o método de tratamento preferido nestes doentes, mas normalmente requer infusões prolongadas ferro-polimaltose ou múltiplas administrações de preparações alternativas. O objectivo deste estudo foi confirmar a segurança e a aceitação das infusões de ferro polimaltose ultrarápidas como alternativa às infusões mais lentas e à carboximaltose férrica. ***Métodos:*** Estudo de segurança aberto, fase 4, num hospital terciário, incluindo doentes com ferropenia com necessidades de ferro-polimaltose até 1500 mg, que receberam a infusão durante 15 minutos. As taxas de eventos adversos (AE) agudos e as suas gravidades foram comparadas com controlos históricos de infusões de ferro-polimaltose de uma e quatro horas de duração, a partir de um estudo retrospectivo de 648 pacientes do mesmo centro. Foram também avaliados os EA diferidos, bem como a aceitabilidade da infusão dos participantes. ***Resultados:*** Trezentos participantes receberam infusões ultrarápidas de ferro-polimaltose durante um período de 2 anos, com uma taxa de EA agudos de 18,7%, e uma taxa de EA graves de 1,0%. As taxas globais de AE e de AE ligeiros foram superiores às da infusão lenta ($p < 0,001$), mas comparável para os AEs moderados e graves. Reações tardias ocorreram em 12,5% dos participantes. Mais de 95% deles manifestaram preferência por repetir as infusões ultrarápidas, se necessidade subsequente de terapêutica. ***Conclusão:*** A infusão ultra-rápida de ferro-polimaltose é segura quando comparada com infusões mais lentas, com segurança também semelhante à carboximaltose férrica, oferecendo maior comodidade e menores custos de saúde.

Introduction

Iron deficiency is a common condition among the general population and patients admitted to hospitals [1–4]. Correction of iron deficiency improves quality of life by reducing symptoms of anaemia, increasing sensitivity to erythropoietin stimulating agents, as well as resolution of related conditions [1–4]. Total body iron replacement is common practice in hospital settings for patients intolerant of oral iron supplements, those with malabsorptive conditions, or those with poor medication adherence [3, 4].

Previous research has demonstrated the safety of iron polymaltose (IPM) up to 1,500 mg, administered as a rapid 1-h infusion with the average replacement doses ranging from 1,300 to 1,500 mg [3–5]. However, despite increased medication cost and the 1,000 mg dose per week limit resulting in the need for multiple presentations, ferric carboxymaltose is the preferred iron infusion due to its primary advantage of ultrarapid administration over 15 min [6].

A 2017–2018 pilot study demonstrated expected rates of mild and moderate adverse events (AEs) without serious reactions for the administration of up to 1,500 mg IPM over 15- and 30-min intervals [7]. This sufficiently powered study aimed to validate the results of the pilot, comparing the safety of the ultrarapid IPM infusions to previously published results for 1- and 4-h infusions. Ultrarapid IPM infusions would yield significant benefits for patients requiring total body iron replacement in a single treatment session and reduce nursing time and direct medication costs compared to slower infusions and newer parenteral iron products.

Materials and Methods

This was an open-label, single-centre, phase 4 safety study conducted at a tertiary hospital that provides medical, surgical, women's health, and intensive care services in Victoria, Australia. Participants were recruited if they were admitted to the study site or presented to the hospital's infusion centre with a diagnosis of iron deficiency of any cause requiring replacement with intravenous IPM, with calculated doses of up to 1,500 mg inclusive.

Doses were calculated based on patients' actual body weights and haemoglobin results using the Ganzoni equation from the product information, with adjustments for any blood transfusions. Participants with history of chronic kidney disease (CKD) had their doses capped at 1,000 mg as per local guidelines.

Potential participants were identified via receipt of iron infusion orders by the hospital's pharmacy department. Consent was obtained from participants' treating teams and written informed consent from patients. Patients were excluded if their calculated

dose exceeded 1,500 mg of iron or if they were unable to provide informed consent. Study participants were administered IPM, diluted in 250 mL of sodium chloride 0.9%, intravenously over 15 min via infusion pumps by nursing staff. Nursing staff were educated on potential AEs and provided with written instructions for monitoring requirements of vital signs. These measures were performed before the infusion, at 5-min intervals during the infusion, followed by 1 h of observations at 15-min intervals, and recorded in the electronic health record system. Infusions were delayed for participants recovering from infections or surgery, until C-reactive protein (CRP) measures were under 100 mg/L and participants were afebrile. Participants who experienced AEs were able to complete the infusions at a slower rate or, if the reactions were severe, had their infusions stopped and restarted only after medical review and if it was considered safe to do so.

The primary outcome was the overall AE rate during the IPM infusions [3, 4, 7]. Secondary outcomes included delayed AE rates during the week post-infusion and the severity of acute and delayed AEs graded as mild, moderate, or severe. Mild acute AEs were defined as those that did not require a change in the infusion rate, treatment, or prolongation of hospital stay; moderate AEs required an interruption or change to the infusion rate, minor treatment such as analgesia, or additional monitoring; and severe AEs included those that required cessation of the infusion without intention to restart and where patients required urgent medical attention with administration of resuscitation or severe allergic reaction medications such as adrenaline, hydrocortisone, or parenteral antihistamine, or prolongation of hospitalization (more than 1 day) [3, 4, 7]. Delayed AEs were graded as mild for those not requiring treatment, moderate where minor treatment was required, and severe for those that required attention of a local doctor or hospital presentation [3, 4, 7]. Additional secondary outcomes were the rates of AEs as compared to historical controls of 1- and 4-h infusions from a retrospective study conducted at the same study site between June 2013 and May 2015 [4] and the participant willingness for repeat ultrarapid infusions of IPM if clinically required. In the retrospective study, the dilutions selected by clinicians included either the 1-h infusions of IPM up to and including 1,500 mg in 250 mL of sodium chloride 0.9% or the 4-h infusions of any calculated dose to be administered in 500 mL of sodium chloride 0.9%, both infused after a 15-min test dose infusion at 40 mL/h [4]. All participants who experienced severe AEs during the infusion were reviewed by an independent medical consultant to adjudicate if the AE was infusion rate related. Data collected by investigators were obtained from patients' medical records and included patient demographics, aetiology of iron deficiency, pre-infusion pathology, blood transfusions in the previous fortnight, comorbidities, preadmission medications, and any premedications used. IPM dose, risk factors for adverse effects to iron such as inflammatory bowel disease (IBD), raised inflammatory markers, and the use of concurrent immunosuppressive therapies were also recorded [3]. Bedside nursing staff recorded AEs on supplied data collection forms which included duration and time to onset, treatments used to manage the AEs, infusion rate adjustments, and whether participants required cessation or re-initiation of infusions after medical assessment. Delayed AEs data were obtained by the study investigators from the participants via telephone 1-week post-infusion or in person where participants remained hospitalized at the study site. Participants were asked about the nature and duration of delayed AEs and whether medical attention was needed. During follow-up, participants were also asked regarding their preference to receive IPM infused at the ultrarapid rate if repeat prescription was indicated.

Statistics

The study was powered to 80%, with two-sided significance set at 5%, requiring 275 patients to detect a change in severe adverse reactions of 3% from an estimated 1% to the previously set cut-off of 4% [3, 4]. This study size also powered the study to detect a total AE change of 5.7%. Allowing for loss to follow-up, 300 patients were planned for enrolment into the study.

Fisher's exact test was used to compare total AE rates and severities against previously published results for IPM 1- and 4-h infusions [3, 4]. All statistical testing was completed using SPSS Computer Program, Version 25.0. (SPSS Inc., Chicago, IL, USA).

Ethics

The study received Drugs and Therapeutics Committee approval and approval from the Human Research Ethics Committee at the study site with reference number AM/50300/PH-2019-189648(v2). The study is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12619000272190p) and Clinical Trial Notification number CT-2019-CTN-00594-1.

Results

Over the study period (June 2019 to August 2021), 789 IPM infusions were prepared by the pharmacy department, with 487 patients not meeting the inclusion criteria (see Fig. 1). Two participants withdrew from the study prior to the iron infusions being given and were excluded from the final analysis. Three hundred infusions were administered, with 13 participants receiving multiple (two or three) infusions months to years apart. The mean age of the study participants was higher (70.0 years) than that of those included in the 1- and 4-h IPM infusions (60.4 and 66.1 years, $p < 0.001$ and 0.052, respectively), and there were also fewer female participants (see Table 1). The most common causes of iron deficiency were CKD, congestive cardiac failure (CCF), and gastrointestinal bleeding. Study protocol deviations occurred for 4 participants, where infusions were stopped without resumption at a slower rate after the resolution of mild or moderate AEs. The average dose of IPM administered was 1,099.3 mg (95% CI 1072.8–1,125.9), with 109 (36.3%) infusion doses within the range of 1,100–1,500 mg. These doses were lower compared to 1- and 4-h IPM infusions ($p = 0.185$, <0.001, respectively). Eighty-nine (29.7%) participants received blood transfusions due to severe anaemia, with an average of 2.7 units (95% CI 2.4–3.0) of blood being transfused within 2.9 days (95% CI 2.4–3.4) before the IPM infusion. Identified risk factors for AEs to

Table 1. Participant demographics and risk factors

Characteristics	Ultrarapid infusion (*N* = 300)	1-h infusion[4] (*N* = 354)	4-h infusion[4] (*N* = 294)	Significance (*p*)
Age (mean), years	70.0 (95% CI 68.1–71.9)	60.4 (95% CI 58.1–62.7)	66.1 (95% CI 63.8–68.4)	<0.001*,0.052#
Gender: females, *n* (%)	146 (48.7)	241 (68.1)	176 (59.9)	<0.001*,0.006#
Length of stay (mean), days	9.8 (95% CI 8.7–10.9)	5.0 (95% CI 4.1–5.92)	6.6 (95% CI 5.3–7.9)	<0.001*, <0.001#
Weight (mean), kg	81.0 (95% CI 78.4–83.6)	76.9 (95% CI 74.4–79.4)	78.4 (95% CI 76.0–80.8)	0.002*, 0.473#
Causes of anaemia				
Gastrointestinal bleeding	64 (21.3%)	89 (25.1%)	104 (35.4%)	0.252*, <0.001#
Unknown	30 (10.0%)	135 (38.1%)	86 (29.3%)	<0.001*, <0.001#
CKD	130 (43.3%)	51 (14.4%)	36 (12.2%)	<0.001*, <0.001#
Heart failure	133 (44.3%)	n/a	n/a	n/a
IBD	17 (5.7%)	n/a	n/a	n/a
Menorrhagia	5 (1.7%)	26 (7.3%)	12 (4.1%)	0.001*, 0.078#
Malnutrition	13 (4.3%)	7 (2.0%)	5 (1.7%)	0.081*, 0.061#
Postoperative	13 (4.3%)	7 (2.0%)	4 (1.4%)	0.081*, 0.030#
Pregnancy	4 (1.3%)	n/a	n/a	n/a
IPM mean dose, mg	1,099.3 (95% CI 1,072.8–1,125.9)	1,103.7 (95% CI 1,070.3–1,137.1)	1,324.5 (95% CI 1,281.6–1,367.4)	0.185*, <0.001#

* Ultrarapid versus 1-h infusions. # Ultrarapid versus 4-h infusions.

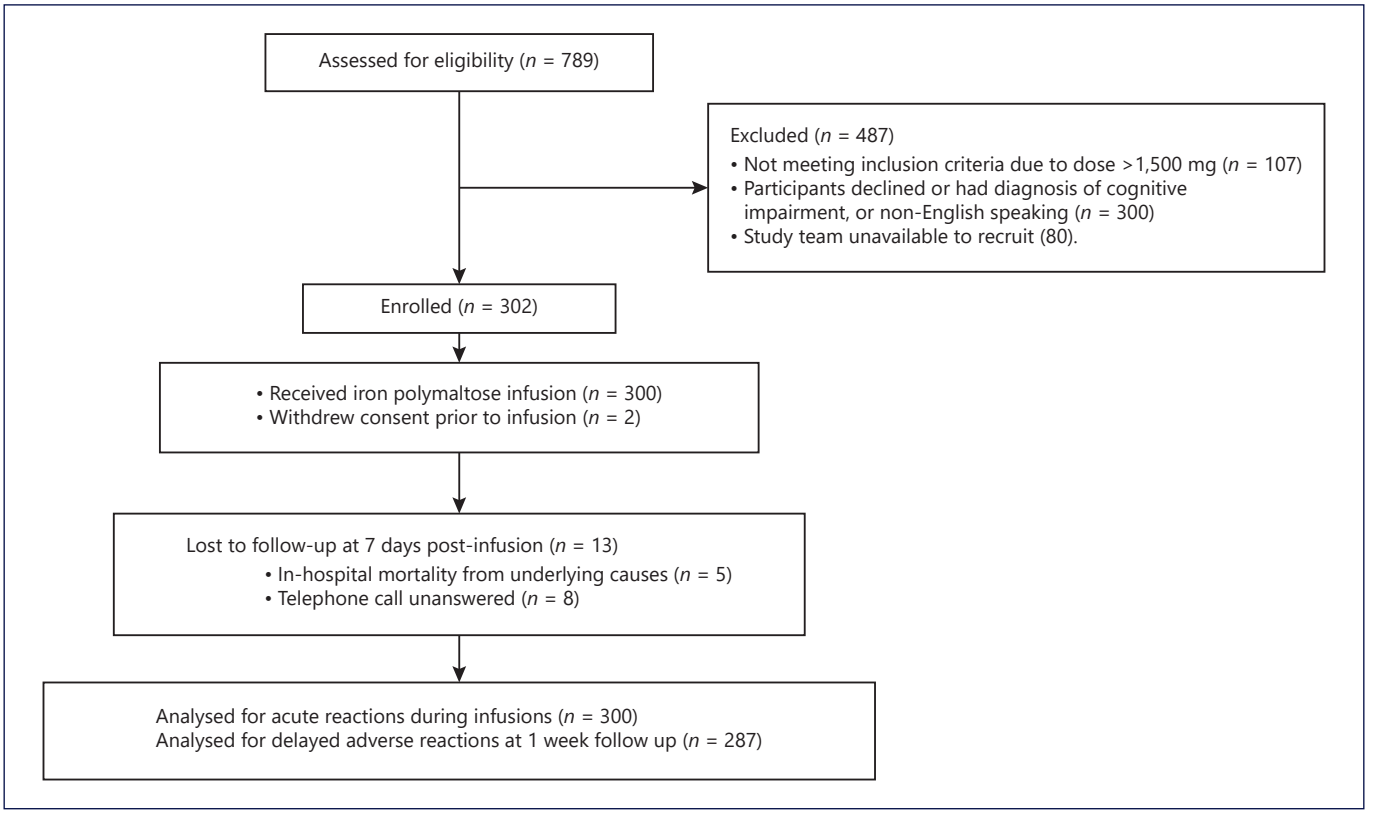

Fig. 1. Patient recruitment.

Table 2. AE rates and severities

AEs	Ultrarapid infusion (*N* = 300)	1-h infusion[4] (*N* = 350[#])	4-h infusion[4] (*N* = 290[#])	Significance, *p* value
Mild, *n* (%)	40 (13.3)	7 (2)	4 (1.4)	<0.001 versus 1-h* <0.001 versus 4-h*
Moderate, *n* (%)	13 (4.3)	17 (4.9)	18 (6.2)	0.751 versus 1-h 0.308 versus 4-h
Severe, *n* (%)	3 (1.0)	4 (1.1)	3 (1.0)	0.860 versus 1-h 0.967 versus 4-h
Total AEs, *n* (%)	56 (18.7)	28 (8.0)	25 (8.6)	<0.001 versus 1-h* <0.001 versus 4-h*
Infusion stopped, *n* (%)	11 (3.7)	12 (3.4)	14 (4.8)	0.870 versus 1-h 0.484 versus 4-h
Infusions restarted*, *n* (%)	4 (36.4)	6 (50.0)	8 (57.1)	0.510 versus 1-h 0.428 versus 4-h

* Among participants who stopped the infusion. [#] Four patients did not receive their infusions and were excluded from analysis.

iron infusions were: raised inflammatory markers in 149 (49.7%), immunosuppression in 54 (18%), and IBD in 17 (5.7%) participants.

The primary outcome of acute AEs occurred during 18.7% of infusions. The secondary outcome of acute AEs severity comprised of mostly mild reactions (13.3%) with 1.0% graded as severe (see Table 2). The majority of acute AEs did not require treatment, with the most common events being: headaches, cannula site reactions, rashes and itch, as well as chest pain (see Fig. 2). Compared to the slower infusions, the total and mild AE rates were higher ($p < 0.001$) but similar for moderate and severe reaction rates (see Table 2) [4]. Acute infusion reactions were managed with antihistamines in 2.0%, hydrocortisone in 0.7%, adrenaline in 0.3%, and analgesics in 1.3% of infusions. One participant required antihistamine premedication on their second infusion after experiencing a rash during their first infusion a year earlier. There were no AEs during the second infusion. Three participants experienced a severe reaction during the infusion; two were considered allergic reactions with 1 patient experiencing a rash and the other experiencing dyspnoea and a seizure within 15 s of starting the infusion. The third was considered a rate-related reaction with fast onset and resolution of chest pain, back pain, and dyspnoea with infusion cessation. No treatment for the reaction or prolongation of hospital stay was required.

Thirteen (4.3%) participants, including three participants who experienced acute infusion AEs (one severe and two moderate), were lost to follow-up (see Fig. 1). The secondary outcome of delayed AEs occurred in 36 (12.5%) participants. Similar to the acute reactions, mild reactions accounted for the majority of delayed AEs (7.3%), with a severe reaction reported in one participant (0.3%). The majority of participants (95.1%) available for follow-up indicated they would accept IPM infusions at ultrarapid rates, if required again.

Participants with a history of IBD had an association for a higher rate of acute AEs compared to those without IBD (29.4% vs. 18.0%, respectively, $p = 0.331$), but this was not statistically significant. Those with raised inflammatory markers had non-statistically significant lower AE rates (15.4% vs. 21.9%, respectively, $p = 0.183$). Similarly, associations between AEs and participants on immunosuppressive therapy (including corticosteroids), angiotensin-converting enzyme inhibitors or angiotensin 2 receptor blockers, and who received blood transfusions within a fortnight prior to iron therapy were not identified (see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000527794). Participants with CCF or CKD experienced less frequent AEs compared to the rest of the study population (12.0% vs. 24.7%, $p = 0.005$ for CCF; 12.3% vs. 24.1%, $p = 0.011$ for CKD). There was no age difference between participants who experienced AEs and those who did not (70.2 vs. 70.0 years, respectively).

Post hoc analysis identified a correlation between iron dose and the rate of acute AEs: 25.7% of participants re-

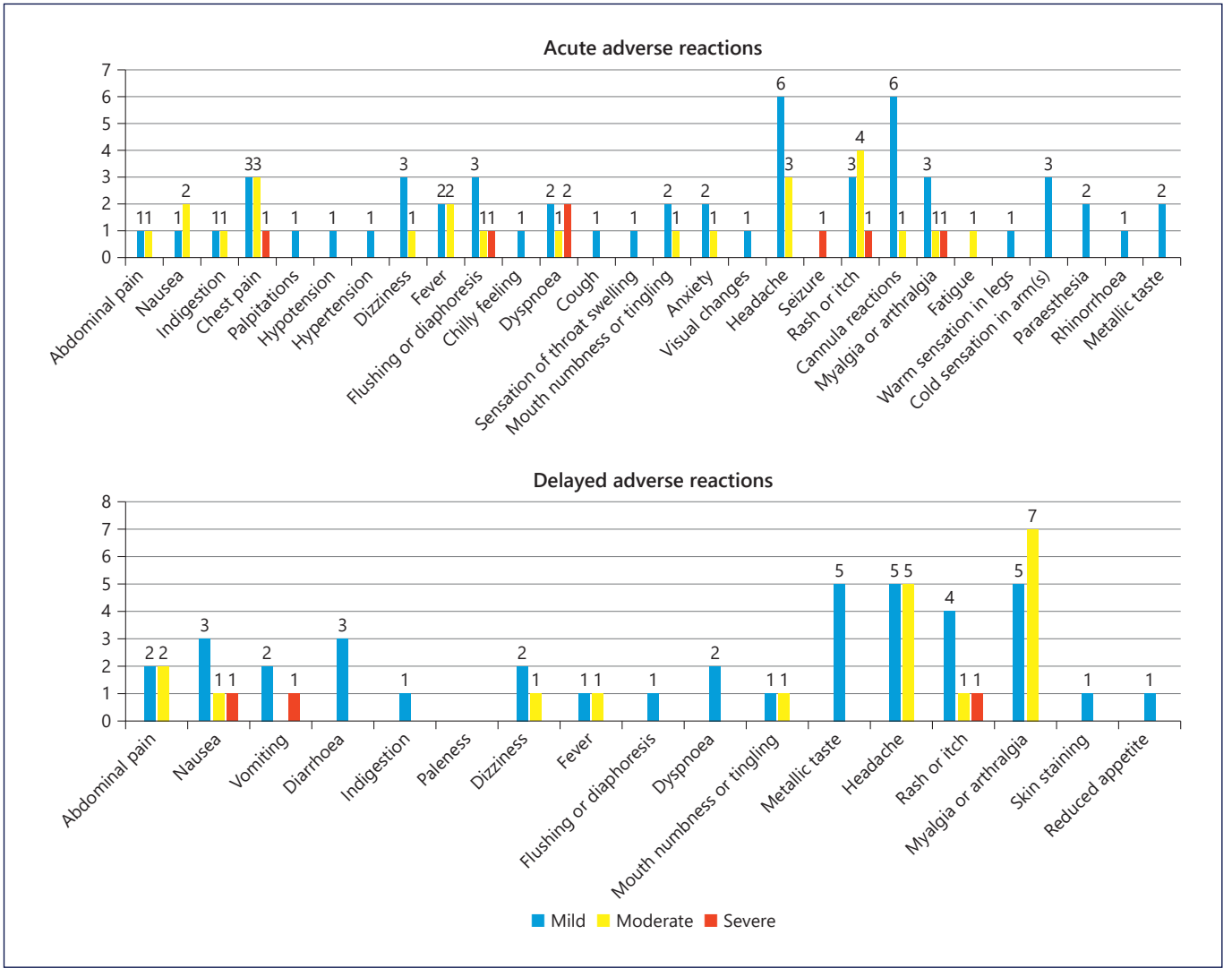

Fig. 2. Types of adverse reactions during ultrarapid infusions.

ceiving doses greater than 1,000 mg versus 14.7% of participants receiving between 500 and 1,000 mg ($p = 0.021$). Severe reactions were also higher where doses were greater than 1,000 mg at 1.8% versus 0.5% among participants receiving between 500 and 1,000 mg ($p = 0.299$) but not statistically significant.

Additionally, in post hoc analysis, another iron infusion-related AE of hypophosphataemia (<0.75 mmol/L) was identified in 34 out of 128 (26.6%) participants with available post-infusion levels (see Fig. 3). The average time to hypophosphataemia post-infusion was 7.8 days (range 1–24 days), with most reaching nadir within 15 days and only three participants experiencing nadir between days 20–24. Normalization of phosphate levels was achieved on average 3.0 days (range 0–8 days) after the nadir, with 22 (17.2%) participants requiring phosphate replacement.

Discussion

The results of this study have demonstrated similar outcomes to the original rapid (1-h) infusion study of IPM, with acute infusion reactions reported at a rate of 18.7% versus 24.0% [3]. However, delayed reaction rates were significantly lower in our cohort with a reported rate of 12.5% versus 26.3% [3]. These differences may be related to a wider spectrum of doses used in the current

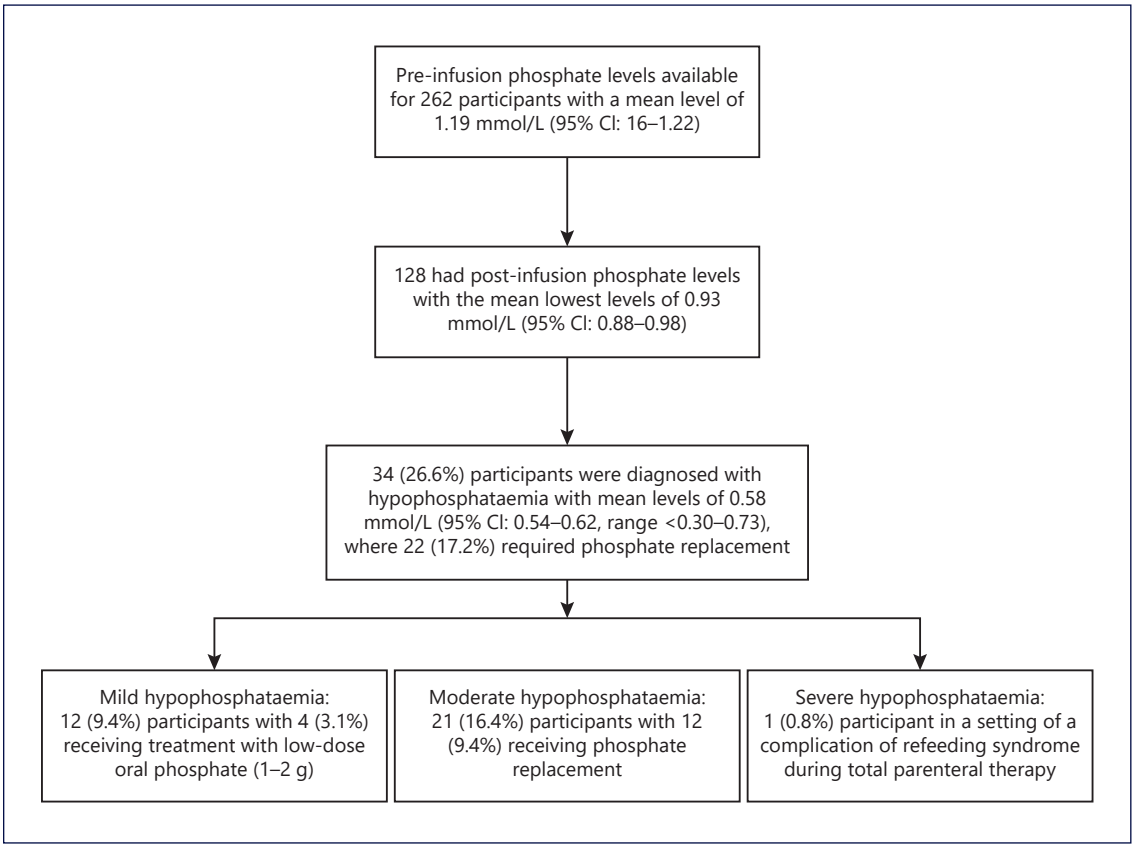

Fig. 3. Hypophosphataemia and treatment after IPM infusions.

study, as the rate of acute reactions was 25.7% in patients who received dose above 1,000 mg, which approximates the results from the 1-h infusion study of doses between 1,000 and 1,500 mg [3]. The rates of moderate-to-severe AEs were comparable to both 1-h and 4-h infusions, despite the differences in the population ages, gender, and comorbidity profiles [4].

A similarly designed study of ferric carboxymaltose among patients with iron deficiency anaemia, aged on average 42.4 years, with 87.5% female patients, 12.5% with CKD, 11.3% with IBD, and 21.3% with uterine haemorrhage, provides an effective comparator population [8]. The AE rates were not significantly higher (18.7% vs. 15.0%) and almost identical when comparing doses between 500 and 1,000 mg (14.7% vs. 15.0%) [8]. Importantly, the rate of delayed adverse reactions with ultrarapid IPM was less than half of that reported in ferric carboxymaltose-treated patients (12.5% vs. 29.3%, respectively), including for doses between 1,100 and 1,500 mg [8].

In addition to the similar safety outcomes, this study confirmed that the use of angiotensin-converting enzyme inhibitors, angiotensin 2 receptor blockers, corticosteroids, and immunosuppressants did not increase the rate of IPM infusion AEs, as was observed in the study of slower infusions [4]. We also confirmed that participants with diagnosed CKD or CCF had significantly lower AE rates compared to the rest of the study participants, a finding that was also observed in the retrospective study of slower infusions [4]. CKD and CCF were frequently diagnosed together among the study participants, and it is unknown if the lower rate is specific to one or both conditions. CKD is associated with reduced immune system function, and this may have contributed to the lower adverse reaction rate [9].

The higher rates of overall acute AEs observed in this study compared to the retrospective study of the slower infusions were considered likely to be due to the prospective methodology. Milder reactions such as paraesthesia, warm, and cold sensations in limbs, metallic taste, and fatigue may not have been documented or even reported in usual practice. These types of AEs contributed to over 20% of all adverse reactions recorded.

The AEs of hypophosphataemia occurred at significantly lower rates using IPM (26.6%) compared to the recent study of ferric carboxymaltose (>70%) [10]. Only 0.8% of participants receiving IPM experienced severe hypophosphataemia compared to 11.3% with ferric carboxymaltose [10]. Most of the hypophosphataemia occurred within the first week after IPM administration and recovered within a few days, whereas with ferric carboxymaltose, the nadir was at 14 days posttreatment and persisted to day 35 [10].

The main study limitations are the single-centre and open-label study design, with a geriatric population, and high prevalence of CCF and CKD. However, given the prevalence of iron deficiency in patients with renal and cardiac failure, this study provides a reliable reference for managing iron deficiency in this cohort. Another limitation included bedside nursing staff recording AEs, with several deviations from the study protocol identified, including recording the adverse reactions by incorrect severity and subsequently not re-initiating infusions, which may have contributed to the results presented. Additionally, post-infusion phosphate levels were checked in less than half of participants during their hospitalization, which would require further study to evaluate the extent and severity of hypophosphataemia with IPM. Notwithstanding the limitation, the included results add to the current knowledge about the AE with this iron product, and given the size and prospective nature of the study, the results support a change in practice.

Based on the similar AE rates for moderate and severe reactions to those of the slower infusions and ferric carboxymaltose, the ultrarapid IPM infusions could be considered a safe alternative. The benefits of this option include reduced nursing time, infusion equipment, and medication cost compared to the use of ferric carboxymaltose for average doses (1,300–1,500 mg), which in Australia is fivefold that of IPM. With ferric carboxymaltose, there is also a direct cost to patients with loss of time to attend second infusions and increased risk of AEs such as extravasation and skin discolouration from additional cannulations [11, 12].

Conclusion

Ultrarapid (15-min) infusions of IPM have been shown to offer a feasible alternative to slower infusions over 1 and 4 h with comparable safety and high patient acceptability. This option would also provide a more convenient and less costly alternative to ferric carboxymaltose infusions, with fewer delayed AEs. Further research on faster administration of larger IPM doses is warranted.

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Statement of Ethics

My team has no conflict of interest to declare in relation to this study, and all the listed authors have contributed to the preparation of the manuscript. The study received Drugs and Therapeutics Committee approval and approval from the Human Research Ethics Committee at the study site with reference number AM/50300/PH-2019-189648(v2). All participants in the study described in the manuscript have provided written consent, and the study has been registered on the Australian New Zealand Clinical Trials Registry (ACTRN12619000272190p).

Conflict of Interest Statement

The authors have no conflicts of interest to declare. Iouri Banakh has previously received a research grant from the Society of Hospital Pharmacists of Australia for an unrelated study and conference attendance support from DBL.

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Author Contributions

Iouri Banakh, Martha Turek, and Lilian Vo contributed to the study design, data collection, review of the results, and manuscript preparation. Dr Daniel Niewodowski, Dr Rumes Kanna Sriamareswaran, Dr Fiona Yeaman, and Dr Travis Churchill contributed to the study design, review of the results, and manuscript preparation.

Data Availability Statement

Study data are stored at the study site and are not available for sharing, as this was not approved nor applied for in the study protocol submission to the Human Research Ethics Committee.

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Endoscopic Submucosal Dissection for Resections Larger than 10 cm: Outcomes from a Portuguese Center

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Keywords
Endoscopic submucosal dissection · Early gastrointestinal cancer · Therapeutic endoscopy

Abstract
Background: Endoscopic submucosal dissection (ESD) is a minimally invasive technique for en bloc resection of superficial neoplastic lesions, independent of their size. However, for giant gastrointestinal superficial neoplasia, the risk of invasive cancer is higher, and ESD is typically challenging. Despite the increasing literature on giant resections, data on their efficacy and safety are still lacking. ***Objective:*** The aim of this study was to describe ESD outcomes from a Portuguese center, compare them with other international studies, and analyze the possible risk factors influencing outcomes. ***Methods:*** We conducted a retrospective single-center review using a prospectively collected database, including patients with rectal ESD resections larger than 10 cm, between January 2016 and December 2021. Clinical, procedural, and pathological data were collected and analyzed. Revision of the literature for comparison with international results was done through PubMed. Data were analyzed and statistical analysis performed, using Microsoft Excel and SPSS, to identify significant risk factors. ***Results:*** The study included 15 rectal resections, with a mean diameter of 140.9 mm (range 105–270), corresponding to lesions of 125.9 mm (87–238). The overall en bloc resection rate was 100% (n = 15). According to ESGE criteria, procedure was considered curative in 53.3% (n = 8), non-curative with high risk in 13.3% (n = 2), and local-risk recurrence in 33.3% (n = 5). Adverse events occurred in 26.7% (n = 4): 1 minor perforation and 3 stenosis, most endoscopically managed. For non-curative resections with local-risk recurrence, surveillance without adjuvant therapy was performed in all cases. For high-risk non-curative resections, surgery was performed in 1 patient and adjuvant chemoradiation therapy in another. Follow-up (mean 16 months) demonstrated a recurrence rate of 0%. Statistical analysis revealed resection size ≥20 cm as a risk factor for perforation (p value 0.067), and involvement of ≥90% of the circumference and procedural time ≥4 h as risk factors for stenosis (p value 0.029 and 0.009, respectively). ***Conclusions:*** Although challenging, ESD for giant lesions seems effective and safe, with a still relevant rate of complications, which were mostly endoscopically treated. Rigorous characterization of lesions is crucial to predict and avoid complications or the need for therapy escalation.

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Disseção endoscópica da submucosa em resseções maiores que 10 cm: outcomes de um centro português

Palavras Chave
Disseção endoscópica da submucosa · Cancro gastrointestinal precoce · Endoscopia terapêutica

Resumo
Background: A disseção endoscópica da submucosa (DES) é uma técnica minimamente invasiva para resseção em bloco de tumores superficiais, independentemente do seu tamanho. No entanto, nas neoplasias superficiais gastrointestinais gigantes, o risco de cancro invasivo está aumentado e a DES é tipicamente desafiante. Apesar do incremento da literatura acerca de resseções gigantes, dados da sua eficácia e segurança são ainda escassos. ***Objetivo:*** Descrição de outcomes de DES de um centro português e comparação com estudos internacionais. Análise de eventuais fatores de risco influenciando os outcomes. ***Métodos:*** Revisão retrospetiva de um centro, usando a sua base de dados prospectivamente colhida, incluindo pacientes com resseções rectais por DES maiores que 10 cm, entre janeiro 2016 e dezembro 2021. Dados clínicos, endoscópicos e patológicos foram colhidos e analisados. A literatura foi revista através do PubMed, para comparação com resultados internacionais. A análise dos resultados e estatística foi realizada, utilizando o Microsoft Excel e SPSS, para a identificação de fatores de risco com impacto significativo nos outcomes. ***Resultados:*** O estudo incluiu um total de 15 resseções retais, com uma média de diâmetros de 140,9 mm (intervalo 105–270), correspondendo a lesões 125,9 mm (intervalo 87–238). A taxa de resseção em bloco foi de 100% ($n = 15$). Segundo os critérios da ESGE, o procedimento foi curativo em 53,3% ($n = 8$), não curativo com alto risco em 13,3% ($n = 2$) e com risco de recorrência local em 33,3% ($n = 5$). Eventos adversos ocorreram em 26,7% ($n = 4$): 1 microperfuração e 3 estenoses, a maioria geridas endoscopicamente. Os 5 casos não curativos com risco de recorrência local ficaram apenas sob vigilância. Nas ressecções não curativas de alto risco, um paciente foi submetido a cirurgia e outro a quimioradioterapia adjuvante. O follow-up (média de 16 meses) demonstrou uma taxa de recorrência de 0%. A análise estatística demonstrou o tamanho da ressecção ≥20 cm como fator de risco significativo para perfuração (p value 0.067); e envolvimento de ≥ 90% da circunferência do lúmen e tempo de procedimento ≥4h como fatores de risco significativos para estenose (p value 0.029 e 0.009, respetivamente). ***Conclusão:*** Apesar de desafiante, a DES para lesões gigantes parece eficaz e segura, com uma taxa de complicações importante, possíveis de tratamento endoscópico. A caracterização rigorosa destas lesões é crucial para predizer e evitar complicações ou a necessidade de escalada terapêutica.

Introduction

Endoscopic submucosal dissection (ESD) is a recently differentiated minimally invasive endoscopic technique used for the resection of superficial gastrointestinal lesions that cannot be completely addressed by conventional endoscopic mucosal resection (EMR) nor are invasive enough to undergo surgery. According to the updated European Society of Gastrointestinal Endoscopy (ESGE) guidelines, ESD is the treatment of choice for several gastrointestinal lesions, including large pre-carcinomatous adenomas and early (T1) cancers. Indications depend on precise characterization of the lesion and its aggressiveness, which is preferably achieved by high-definition white-light and virtual chromoendoscopy, allied to internationally validated classifications such as the Paris, NICE, and JNET ones. In general, no other imaging study is required before dissection [1].

Comparing to EMR or surgery, ESD entails numerous advantages and limitations. Compared with EMR, ESD has higher en bloc and complete resection rates and lower recurrence rates. However, it implies a higher perforation risk, technical difficulty, and procedural time. Compared with surgery, ESD is associated with lower procedural time, length of hospital stays and costs, adverse events, and procedure-related morbidity and mortality. However, a higher recurrence risk and lower disease-free survival are generally associated [1, 2]. Therefore, an accurate decision based on the lesion's resectability, the patient's performance status, and the instrumentalist's expertise is crucial [3].

This study focuses on giant ESD resections (>10 cm) located in the rectum. Currently, rectal ESD should be considered for lesions endoscopically suspected of only limited submucosal invasion (demarcated depressed area with irregular surface pattern or large protruded or bulky component) or that cannot be completely removed by EMR [1].

Giant ESD resections are usually challenging and have been associated with longer procedural time and higher

adverse event rates (bleeding and perforation). The en bloc resection and curative rate have been comparable to smaller lesions, with no posterior salvage surgeries, strictures, local recurrences, or metastasis [2]. Numerous studies have discriminated tumor size, submucosal fibrosis, invasive depth, and procedure time as risk factors for complications and incomplete resections [4].

Despite increasing literature on giant resections, data on their efficacy and safety are still lacking. Overall, we propose to analyze our outcomes for rectal resections larger than 10 cm, comparing them to other international experiences. Additionally, we propose to identify any possible risk factors significantly associated with different outcomes or complications.

Materials and Methods

This is a single-center uncontrolled study conducted by the Gastroenterology Department at *Centro Hospitalar de Lisboa Ocidental* (CHLO) in Lisbon, Portugal. Consecutive patients with rectal resections larger than 10 cm submitted to ESD from January 2016 to December 2021 were included. A total of 15 rectal ESDs were performed. All patients were informed about the risks and benefits of ESD, and provided written informed consent. Patient information, follow-up exams, and consultations were obtained from their electronic medical record or telephonic contact. Outcomes included en bloc and curative resection rates, complications, the need for future endoscopic management, chemoradiation therapy or surgery, disease recurrence, and disease-related mortality. Statistical analysis for patient and lesions' characteristics, outcomes, and identification of possible risk factors significantly related to them was done through Microsoft Excel (version 2018) and SPSS (version 29). Comparison with other international studies was obtained through search and evaluation of already published scientific articles in PubMed.

ESD Procedure

All ESD procedures were performed by the same therapeutic endoscopist (PB) in a onetime session. Patients were under general sedation and endotracheal intubation by an anesthesiologist. In longer procedures, patients were covered with blankets and warmed up to avoid hypothermia. A transparent cap on the endoscope tip and CO_2 insufflation were used. Lesions were previously analyzed by white light and narrow-band imaging to detect signs of invasiveness. Submucosal injection was done with a mixture of 4% gelatin solution (Gelafundin 4%, B. Braun Melsungen AG, Germany), indigo carmine dye, and adrenaline (1:250,000). Electrocautery marking, mucosal incision, and submucosal dissection were performed using the Flush knife (Fujinon-Toshiba ES System Co., Omiya, Japan) alone or in combination with IT knife nano (KD-612L, Olympus). The electrosurgical ERBE ICC 200 generator unit (ERBE Elektromedizin, Tubingen, Germany) was set at "Endocut" (effect 3, 60 W) for mucosal incision, "Forced Coag" (45–55 W) for submucosal dissection, and "Soft Coagulation" for hemostasis (45–55 W). The scar's visible vessels were routinely electrocoagulated to prevent delayed bleeding. By routine, multiple tunneling and patient mobilization methods were used. No traction or pocket-creation methods were used. For piece recovery, a large snare was routinely used with anal lubrification and digitation help. After the procedure, all patients stayed hospitalized for clinical surveillance according to protocol. Follow-up bloodwork or exams were requested only if complications were suspected. For endoscopic resections with more than 75% circumferential resection, prophylactic topical corticotherapy (budesonide) was used. Endoscopic reports included macroscopic description of lesions (location, size, and Paris and JNET classifications) and procedural description (time, methods, en bloc resection, early adverse events).

Histopathology Assessment

All ESD resected specimens were pinned down with needles, measured, fixed in 4% neutral buffered formalin, and sent to the pathology department. Pathology reports included dimension, histology (Vienna classification), differentiation, involvement of resection margins (RX resection), budding, and lymphovascular invasion.

Definitions

En bloc resection was considered when removal of the entire lesion in a single piece was achieved. Complete R0 resection referred to ≥1 mm tumor-free horizontal margin and negative vertical margins on histology. Resections were classified as curative, non-curative with high-risk, or non-curative with local-risk recurrence, according to the updated ESGE criteria. Adverse events assessed included intraoperative or delayed perforation, bleeding, and stenosis. Intraoperative perforation was defined as an injured muscle layer with peritoneal cavity or fat tissue visualization identified during the procedure. Delayed perforation was defined as perforation manifested clinically (such as fever, abdominal pain, clinical instability) with imaging studies showing fluid collections and/or free intraperitoneal air. Bleeding was considered major if it was not controlled by endoscopy (need for surgery or radiological intervention) or if there was a need for transfusion or clinical instability. Minor bleeding included the need for change in the procedural plan (for instance, application of hemoclips) or >5 min for endoscopic control. Delayed bleeding referred to hematochezia or hemoglobin fall of >2 g/L in the first 30 days after ESD. Stenosis was defined as a luminal narrow and inability to pass a pediatric colonoscope or clinical symptoms of sub-occlusion/occlusion.

Results

Description of Resections and Outcomes

A total of 15 patients underwent giant rectal ESD resections between January 1st, 2016, and December 31st, 2021, at our center. The clinicopathological characteristics and results are summarized in Table 1.

The mean age was 67 years (range 38–85), with a male to female ratio of 9:6. The mean larger diameter of the resection piece was 140.9 mm (range 105–270) and lesion was 125.9 mm (87–238), with 53.3% (n = 8) involving ≥75% of the lumen circumference, and 13.3% (n = 2)

≥90%. Lesions were located in >1 rectal segment (*n* = 12, 80.0%) and distal rectum (*n* = 3, 20.0%), with 60% (*n* = 9) involving the pectinate line. Macroscopic morphology demonstrated 11 LST-G (73.3%, 1 homogenous, and 10 nodular mixed) and 4 LST-NG (26.7%). In virtual chromoendoscopy, lesions were JNET 2B in 73.3% and JNET 2A in 26.7%. All lesions were naive to previous therapeutics. Figure 1 illustrates the procedure related to one of the nodular-mixed LST-G resections.

The mean procedural time was 220 min (range 80–540 min) and mean post-procedural hospital stay was 2 days (range 1–5 days). En bloc resection was achieved in 100% (*n* = 15). Procedural complications occurred in 4 patients (26.7%), being discriminated as intraprocedural microperforation in 6.7% (*n* = 1) and delayed local stenosis in 20.0% (*n* = 3). The perforation was successfully closed by endoscopic clipping. No bleeding complications were observed, early or delayed. Regarding stenosis, all lesions involved the pectinate line and ≥75% of the lumen's circumference (2 of them involved ≥90% of the circumference). Of these patients, one was submitted to surgery because of concomitant high-risk non-curative resection, and the other two were submitted to endoscopic dilation, with favorable clinical response. Fibrosis and muscle retracting sign were observed in 33.3% of cases (*n* = 5). None of the procedures was interrupted because of complications nor was converted into surgery.

Pathologically, there were 3 submucosal carcinomas (20.0%), with a mean of 1,617 micromillimeters of deep invasion. The remainder of the lesions were adenomas: 7 tubulovillous (46.7%), 3 sessile serrated (20.0%), 1 tubular (6.7%), and 1 villous (6.7%), divided into 9 with high-grade (75.0%) and 3 with low-grade (25.0%) dysplasia.

On histology, R0 resection was achieved in 8 patients (53.3%). Patients who did not achieve R0 included 5 (33.3%) with only positive horizontal margins (RX), 1 (6.7%) with only positive vertical margin (R1), and 1 (6.7%) with both margins positive (R1). Budding and/or lymphovascular invasion were noted in 2 (13.3%) patients. According to the ESGE criteria, resections were considered curative in 8 patients (53.3%), non-curative with high risk in 2 (13.3%), and local risk in 5 (33.3%). In the latter, 60% (*n* = 3) involved the pectinate line. Characterization of non-curative resections is summarized in Table 2.

Additional treatments (chemoradiation or surgery) were indicated in 2 patients (13.3%): 1 had been submitted to surgery and 1 had undergone chemoradiation, with no recurrence detected. For the other patients, endoscopic follow-up was recommended (3–6 months for RX and 1 year for R0). The mean follow-up interval was 16.0 months, where 76.9% (*n* = 10) respected the recommended surveillance, with no recurrence identified (rate, 0%).

Table 1. Clinicopathologic characteristics and treatment results

Characteristic/result	Value
Age, mean (range), years	67 (38–85)
Gender, male:female	9:6
Resection size, mean (range), mm	140.9 (105–270)
Lesion size, mean (range), mm	125.9 (87–238)
Lesion location, *n* (%)	
>1 rectal segment	12 (80.0)
Distal rectum	3 (20.0)
Pectinate line involvement	9 (60.0)
Macroscopic type, *n* (%)	
LST-G	11 (73.3)
LST-NG	4 (26.7)
Circumferential involvement, *n* (%)	
<75%	7 (46.7)
75–89%	6 (40.0)
90–99%	1 (6.7)
100%	1 (6.7)
Fibrosis/MRsign, *n* (%)	5 (33.3)
Histology, *n* (%)	
Low-grade adenoma	3 (20.0)
High-grade adenoma	9 (60.0)
Submucosal invasion	
SM1 (<1,000 μm)	2 (13.3)
SM2 (>1,000 μm)	1 (6.7)
En bloc resection, *n* (%)	15 (100.0)
Curative resection (R0), *n* (%)	8 (53.3)
Non-curative, *n* (%)	
High-risk (R1)	2 (13.3)
Local-risk (RX)	5 (33.3)
Perforation, *n* (%)	1 (6.7)
Stenosis, *n* (%)	3 (20.0)
Procedure time, min (range)	220.4 (80–540)
Hospital stay time, days (range)	2 (1–5)

MRsign, muscle retracting sign.

Statistical Analysis

Regarding curative rates and complications (perforation and stenosis), univariate analysis through Fisher's exact test in SPSS was applied in order to identify significant risk factors for these outcomes. Analysis revealed resection size ≥20 cm as significantly associated with perforation (*p* value 0.067) and involvement of ≥90% of the lumen's circumference and procedural time ≥4 h as significantly associated with stenosis (*p* value 0.029 and 0.009, respectively). No other factors were found to be significantly associated with the rate of complications or

Table 2. Description of non-curative high-risk and local-risk resections

Size, mm	Macroscopy	Location	Indicators	Follow-up
105	LST-G H	>1 R segment	HM+	No recurrence
150	LST-G N	>1 R segment	HM+	No recurrence
87	LST-G N	Distal rectum	SM2, HM+, VM+, LV+, B+	Surgery
130	LST-NG F	>1 R segment	HM+	Missed
111	LST-G N	Distal rectum	HM+	No recurrence
100	LST-NG F	>1 R segment	HM+	No recurrence
170	LST-G N	>1 R segment	SM1, VM+, B+	Chemoradiation

LST-G, granular laterally spreading tumor; LST-NG, nongranular laterally spreading tumor; N, nodular; F, flat; H, homogeneous; R, rectal; SM, submucosal; HM, horizontal margin; VM, vertical margin; LV, lymphovascular invasion; B, budding.

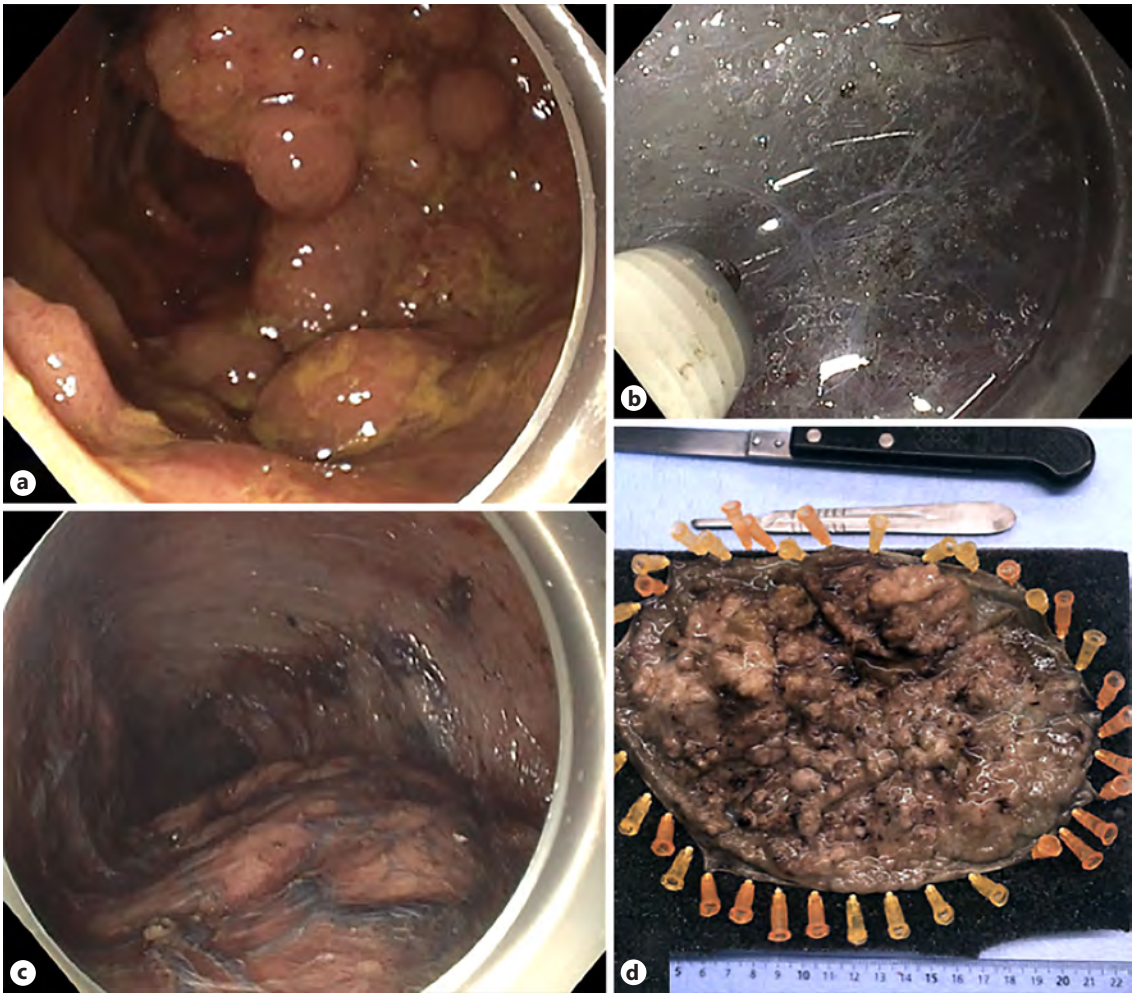

Fig. 1. Resection of a rectal nodular mixed LST-G. **a** Endoscopic appearance of a giant rectal lesion. **b** Submucosal dissection using a non-insulated tip knife. **c** Advanced phase of the procedure where the lesion lies below and the mucosal defect above. **d** Resection piece after formalin fixation.

Table 3. Univariate analysis for factors affecting non-curative resection

	Curative (*n* = 8)	Non-curative (*n* = 7)	*p* value
Curative versus non-curative resection			
Procedure time ≥4 h, *n* (%)	1 (13)	3 (43)	0.282
Resection size ≥20 cm, *n* (%)	1 (13)	0 (0)	1.000
Fibrosis/MRsign, *n* (%)	3 (38)	2 (29)	0.608
≥75% circumference, *n* (%)	5 (63)	3 (43)	0.315
JNET 2B classification, *n* (%)	6 (75)	5 (63)	0.569
Pectinate line, *n* (%)	5 (63)	4 (57)	0.608

MRsign, muscle retracting sign.

Table 4. Univariate analysis for factors affecting risk of perforation

	Perforation (*n* = 1)	No perforation (*n* = 14)	*p* value
Perforation versus no perforation			
Procedure time ≥4 h, *n* (%)	0 (0)	4 (29)	1.000
Resection size ≥20 cm, *n* (%)	1 (100)	0 (0)	0.067
Fibrosis/MRsign, *n* (%)	1 (100)	4 (29)	0.333
≥75% circumference, *n* (%)	0 (0)	8 (57)	0.467
JNET 2B classification, *n* (%)	1 (100)	10 (71)	1.000
Pectinate line, *n* (%)	1 (100)	8 (57)	1.000

MRsign, muscle retracting sign.

curative status, such as procedure time, the presence of fibrosis, JNET classification, and the involvement of the pectinate line (shown in Tables 3–5).

Table 5. Univariate analysis for factors affecting risk of stenosis

	Stenosis (*n* = 3)	No stenosis (*n* = 12)	*p* value
Stenosis versus no stenosis			
Procedure time ≥4 h, *n* (%)	3 (100)	1 (8)	0.009
Resection size ≥20 cm, *n* (%)	0 (0)	1 (8)	1.000
Fibrosis/MRsign, *n* (%)	1 (33)	4 (33)	1.000
≥90% circumference, *n* (%)	2 (67)	0 (0)	0.029
JNET 2B classification, *n* (%)	2 (67)	9 (75)	1.000
Pectinate line, *n* (%)	3 (100)	6 (50)	0.229

MRsign, muscle retracting sign.

Discussion

ESD is a technically difficult procedure, available worldwide, used for the treatment of early gastrointestinal cancers or precancerous lesions. In this study, our ESD outcomes for giant gastrointestinal lesions have been reported. The en bloc and the curative resection rates were 100.0% and 53.3%, respectively, and the adverse event rate was 26.7%, mostly managed endoscopically. Resections with risk of local recurrence (RX) accounted for 33.3%, with 0% of recurrence rate during a mean of 16 months of follow-up. Previous studies revealed better rates; however, most are not comparable as they are not related to giant lesions. In one study (n = 9), the en bloc and curative resection rates of ESD for giant colorectal LST were 88.9% and 100%, respectively, with a higher rate of adverse events (44.4%) [2]. In another study (n = 10) of ESD for giant colorectal LST, the en bloc and curative resection rates were 100% and 90%, respectively, with 40% of adverse events [5]. As shown in Table 2, ESD was considered non-curative with high-risk or local-risk recurrence because of positive horizontal and/or vertical resection margins, submucosal invasion, lymphovascular involvement, or budding. During follow-up of these high-risk non-curative resections, 1 was submitted to surgery and 1 underwent chemoradiation, without any complications or recurrence. Of the patients with significant local recurrence risk, most respected follow-up, and none suffered disease recurrence until the time of the study. However, most follow-up times were less than 2 years.

As for factors affecting the curative resection rate, our analysis was not able to show any significant difference regarding factors such as procedure time, tumor size, the presence of fibrosis, or JNET evaluation (Table 3). This is not concordant with previous studies that correlated tumor size, submucosal fibrosis, invasive depth, and procedure time with incomplete resection [4]. Differences might be related to the small number of cases in our study and to our sample's universe being filtered to >10 cm lesions, which is rare and innovative and, therefore, not comparable with results from series of all kinds of ESD.

Regarding complications, our sample analysis revealed significant association between resection size and higher risk of perforation (Table 4). This is concordant with previous studies. A user-friendly risk score model for the prediction of risk of perforation has already been delineated, named SELF, which includes factors such as tumor size, endoscopist's experience, tumor location, and submucosal fibrosis [6]. In our study, location was not a variable, as all lesions were located in the rectum, the safest

site for ESD because of its thick wall and fixed position. There was 1 microperforation, treated endoscopically without the need for additional surgery.

Regarding stenosis, our analysis showed a significant association between involvement of ≥90% of the circumference and a higher risk of stenosis (Table 5). This result is concordant with previous literature, where in different gastrointestinal locations, lesions spreading to ≥75% and ≥90% of circumference were associated with higher stenosis rates [7]. Other studies have also associated the involvement of the dentate line with higher rates of postoperative pain and strictures, which was not significant in our sample [8]. Our patients had received some kind of stenosis prophylaxis (corticosteroids), which is still controversial and currently not recommended. From the 3 stenoses, 1 was operated on since the patient had concomitant high-risk non-curative resection, and the other 2 were submitted to endoscopic dilation with favorable responses. None had incapacitating symptoms. Regarding the association between procedural time and stenosis, it might be explained by the dependency of this variable on others (such as size, circumference involvement). Previous studies have only related procedure time to post-ESD coagulation syndrome [9].

As for bleeding complications, none were reported in our cohort, which might be explained by the routine prophylactic coagulation of visible vessels. There were several limitations to this study. First, we highlight the small sample size, one endoscopist, single-centered, and retrospective nature of the study. Second, no comparison was made with surgical outcomes of giant lesions or between groups of LSTs ≥10 cm versus <10 cm. A multicentered study with several endoscopists, higher sample and follow-up time is recommended to achieve more significant and generalizable results and outcomes. Variants of ESD with tunneling and pocket-creation methods might also be studied [10].

Moreover, according to our previous studies, a minimum of 30 procedures must be carried out to significantly increase en bloc resection, and 90 procedures are needed to achieve a R0 resection rate >75%, with concomitant speed improvement. Indeed, we suggest that, ideally, only experienced endoscopists (preferably with >90 previous procedures) should carry out giant resections [11, 12].

In conclusion, ESD is an important novel organ-sparing therapeutic endoscopy for the treatment of early gastrointestinal neoplasia. Once the learning curve for ESD is overcome, previous studies have demonstrated that this technique is safe, effective, and worth pursuing.

Statement of Ethics

Ethical approval was not required for this study due to the retrospective design of the study, in accordance with local/national guidelines. Written informed consent to participate in the study was not required in accordance with local/national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

All authors contributed to the conception of the study, acquisition of data, its analysis and interpretation, revision, and final approval 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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Endoscopic Submucosal Dissection Is Safe and Effective for Lesions Located at the Anorectal Junction: Analysis from Two Referral European Centers

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Keywords
Endoscopic submucosal dissection · Anorectal lesions · Rectal lesions

Abstract

Introduction: Endoscopic submucosal dissection (ESD) is a well-established resection technique for colorectal superficial tumors, but its role in the treatment of anorectal junction (ARJ) lesions still remains to be determined. With this study, we aimed to evaluate the feasibility, safety, and efficacy of ESD for the resection of ARJ lesions, in comparison to more proximal rectal lesions. ***Methods:*** We performed a retrospective analysis of prospectively collected data concerning all consecutive rectal ESD procedures performed in two European centers, from 2015 to 2021. ***Results:*** A total of two hundred and fifty-two rectal lesions were included. Sixty (24%) were ARJ lesions, and the remaining 192 (76%) were located proximally. Technical success was achieved in 248 procedures (98%), and its rate was similar in both locations (p = 0.246). Most of the lesions presented high-grade dysplasia/Tis adenocarcinoma (54%); 36 (15%) had submucosal adenocarcinoma, including 20 superficial (sm1) and 16 deeply invasive (>SM1) T1 cancers. We found no differences between ARJ and rectal lesions in regard to *en bloc* resection rate (100% vs. 96%, p = 0.204), R0 resection rate (76% vs. 75%, p = 0.531), curative resection rate (70% vs. 70%, p = 0.920), procedures' median duration (120 min vs. 90 min, p = 0.072), ESD velocity (14 vs. 12 mm^2/min, p = 0.415), histopathology result (p = 0.053), and the need for surgery due to a non-curative ESD (5% vs. 3%, p = 0.739). Also, there was no statistically significant difference that concerns delayed bleeding (7% vs. 8%, p = 0.709), perforation (0% vs. 5%, p = 0.075), or the need for readmission (2% vs. 2%, p = 0.939). Nevertheless, anorectal stenosis (5% vs. 0%, p = 0.003) and anorectal pain (9% vs. 1%, p = 0.002) were significantly more frequent in ARJ lesions. ***Conclusion:*** ESD is a safe and efficient resection technique for the treatment of rectal lesions located in the ARJ.

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A dissecção endoscópica da submucosa é um tratamento seguro e eficaz para lesões da junção ano-rectal: a experiência de dois centros europeus de referência

Palavras Chave
Dissecção endoscópica da submucosa · Lesões ano-rectais · Lesões rectais

Resumo
Introdução: A dissecção endoscópica da submucosa (ESD) é uma técnica endoscópica com demonstrada eficácia nas lesões neoplásicas superficiais colorectais. No entanto, a evidência da sua eficácia nas lesões localizadas na junção ano-rectal é escassa. O nosso objectivo foi avaliar a segurança e eficácia da ESD nas lesões da junção ano-rectal (menos de 2 cm da linha pectínea), em comparação com as lesões mais proximais do recto. ***Métodos:*** Análise retrospectiva de registos colhidos prospectivamente de dois centros europeus de referência, entre 2015 e 2021. ***Resultados:*** Foram incluídas 252 lesões. Sessenta (24%) localizavam-se na junção ano-rectal, e as restantes 192 noutro local do recto. O sucesso técnico foi de 98% (n = 248) e foi semelhante nas 2 localizações (p = 0.246). A maioria das lesões eram displasias de alto grau/Tis (54%); 36 (15%) tinham adenocarcinoma submucoso, tendo 20 invasão submucosa superficial (sm1) e 16 invasão profunda (>SM1). Não foram encontradas diferenças entre as duas localizações relativamente às taxas de ressecção em bloco (100% vs. 96%, p = 0.204), R0 (76% vs. 75%, p = 0.531), ou curativa (70% vs. 70%, p = 0.920), duração da ESD (mediana 120 min vs. 90 min, p = 0.072), velocidade da ESD (14 vs. 12 mm^2/min, p = 0.415) ou resultado histológico (p = 0.053), assim como na necessidade de cirurgia por ESD não curativa (5% vs. 3%, p = 0.739). Além disso, as taxas de hemorragia tardia (7% vs. 8%, p = 0.709), perfuração (0% vs. 5%, p = 0.075) e necessidade de internamento por complicações (2% vs. 2%, p = 0.939) não revelaram diferenças estatisticamente significativas. A estenose ano-rectal (5% vs. 0%, p = 0.003) e a dor ano-rectal (9% vs. 1%, p = 0.002) foram mais frequentes nas lesões da junção ano-rectal. ***Conclusão:*** A ESD é uma técnica segura e eficaz no tratamento das lesões do recto localizadas na junção ano-rectal.

Introduction and Objectives

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are well-established resection techniques for colorectal superficial tumors, depending on their size, morphology, and localization [1–4]. For larger lesions (>40 mm diameter) and whenever superficial submucosal cancer is suspected or cannot be firmly excluded, ESD is the recommended approach, as it allows *en bloc* resection regardless of the lesion's size, leading to a minimized recurrence risk [5, 6].

In regard to low rectal lesions extending to the anorectal junction (ARJ) lesions, ESD could be more challenging. Indeed, in contrast to more proximal colorectal lesions, ARJ lesions could theoretically present a higher risk of bleeding (due to the presence of the rectal venous plexus) and post-procedural pain (given the presence of sensory nerves in the squamous epithelium of the anal canal). Moreover, local direct drainage into the systemic circulation could increase the risk of bacteremia. Additionally to these anatomical features, the narrow lumen and permanent contraction of the anal sphincter could also impair the endoscopic diagnostic accuracy and increase the resection technical difficulty due to poor maneuverability and reduced visualization of the lesion and resection field.

Randomized trials comparing different local resection techniques (EMR, ESD, and transanal surgery) are lacking, and the optimal management strategy in this context still remains to be determined. This multicenter cohort study aimed to evaluate the feasibility, safety, and efficacy of ESD for ARJ neoplastic lesions (<20 mm from the dentate line) in comparison to more proximal rectal lesions (>20 mm from the dentate line).

Material and Methods

Patient Selection and ESD Technique

We included all ESDs performed consecutively in two referral European centers (Gastroenterology Department of Centro Hospitalar Universitário S. João, Porto, Portugal, and Department of Gastroenterology, Hepatopancreatology, and Digestive Oncology, CUB Erasme Hospital, Université Libre de Bruxelles [ULB], Brussels, Belgium), from January 2015 to June 2021. Patients' data were prospectively recorded in an electronic database and retrospectively reviewed for this study. Written informed consent was obtained from every patient before ESD. The institutional Ethics Board of both centers approved the prospective collection and retrospective analysis of the included data.

Lesions selected for ESD resection included neoplastic epithelial rectal lesions (from the anal verge until 15 cm from this site) that had no endoscopic suspicion of deep submucosal invasion

and were unsuitable for *en bloc* EMR. For the purpose of the study, all the lesions totally or partially located within less than 2 cm from the dentate line were considered "ARJ lesions," as suggested by previous reports [7]. This is where the anal transition zone is most commonly found, with the mucosal folds (Morgagni columns) and the hemorrhoidal plexus usually unfolding distally from there. The remaining lesions were called "rectal lesions." The procedures were performed using the GIF-H190 gastroscope (Olympus®, Tokyo, Japan). High-definition endoscopy, dye chromoendoscopy, and/or narrow-band imaging were used for characterization of all the lesions. Dissection was performed using 1.5- or 2-mm dual knives (Olympus®, Tokyo, Japan) for mucosal incision. Dual knives, insulated tip-2, or insulated tip-nano knives (Olympus®, Tokyo, Japan) were used for submucosal dissection. Erbe ICC-200, ICC-300, VIO-300, or VIO-3 electrosurgical units (ERBE® Elektromedizin GmbH, Tubingen, Germany) were used, with ENDO CUT mode effect 2 or DRY CUT mode effect 2, 30 W for mucosal incision and forced or swift coagulation (effect 3 or 4, 30 W) for submucosal dissection. Hemostasis (soft coagulation effect 5, 50–80 W) was performed with a Coagrasper (Olympus®, Tokyo, Japan), whenever necessary and at the end of each procedure. There was no predefined ESD strategy, and each operator had the liberty to choose the best strategy and approach to each lesion, depending on his/her own experience and the lesion's presentation. Classic and tunnel strategies were mostly applied. All patients received antibiotic prophylaxis in case of anal canal involvement (either with amoxicillin-clavulanic acid [1,000 mg–62.5 mg] or with ceftriaxone [1 G] and metronidazole [500 mg]).

After ESD, all patients were followed in the outpatient clinic (with an appointment approximately 1 month after the procedure). Light analgesics (paracetamol) were prescribed at discharge, to be taken only in case of any pain or discomfort. Patients were also instructed to immediately call the department if any clinical abnormality appeared (including pain, bleeding, fever, or any other discomfort). Endoscopic follow-up was performed 3–6 months after ESD and posteriorly according to the current surveillance guidelines. Patients with malignant lesions were always discussed in a multidisciplinary dedicated board.

Histopathological Evaluation

ESD specimens were sent to pathology evaluation with pins on a cork plate, fixed in formalin. Sectioning at 2-mm intervals was performed to evaluate lateral and vertical margins.

Definitions and Outcomes

ESD failure was determined whenever the target lesion was not removed. *En bloc* resection required that the target lesion be retrieved in one single specimen, as opposed to a piecemeal resection (if the lesion was removed in more than one fragment). R0 resection was achieved when pathological evaluation showed free horizontal and vertical margins (even if there was <1 mm of normal tissue between the margins and the lesion) in an *en bloc* resected specimen. Specimens with thermal effects at the margins preventing the pathologist from definitely excluding the presence of abnormal cells were considered R1 resections. The area of the ESD specimen was calculated as the surface of an ellipse, multiplying half of the larger side with half of the smaller side with pi-value and expressed in mm^2. ESD velocity was calculated by dividing ESD area by the time of procedure in minutes (mm^2/min).

In regard to adverse events, perforation was defined as the visualization of the mesorectum or intra-abdominal cavity during the procedure. Every case of post-procedural bleeding (rectorrhagia) was registered, regardless of the severity. Procedure-related mortality was defined as any death resulting from the ESD procedure.

Statistical Analysis

Categorical variables were described as absolute (*n*) and relative frequencies (%). Mean and standard deviation or median and percentiles or range were used for continuous variables as appropriate. When testing a hypothesis about continuous variables, t-Student or Mann-Whitney tests were used as appropriate, considering normality assumptions and the number of groups compared. When testing a hypothesis about categorical variables, a χ^2 test and Fisher's exact test were used, as appropriate. The significance level used was 0.05. Statistical analysis was performed using Statistical Package for the Social Sciences v.25.

Results

Two hundred and fifty-two lesions were included in the study, with a mean age of 66 ± 11 years old and including 142 (57%) males. Sixty (24%) were located in the ARJ (Fig. 1), and the remaining 192 were located more proximally in the rectum. The mean lesion size was 48 ± 25 mm. Twenty-one (8%) lesions had already a previous resection attempt by EMR. In regard to morphology, the majority (43%) were Paris IIa + Is lesions, and only 10% were non-granular LSTs (Table 1). Technical success was achieved in 248 procedures (98%), 58 in the ARJ, and 190 in the rectum. En bloc resection was achieved in 97% of all cases and R0 resection in 75%. The median procedure time was 90 min (IQR 60–150 min). Hybrid ESD was required in 8 cases (3%), and the pocket-creation method was used in only 3 lesions (1%).

As opposed to the Belgian practice (where it's protocol for all patients to stay for overnight in-hospital observation), in the Portuguese center, rectal ESDs are routinely performed in an ambulatory setting, which is why 123 out of 161 (76%) patients were discharged after only 4–6 h observation. The remaining patients (*n* = 38) were admitted for longer observation due to extensive resection (*n* = 30), severe intraprocedural bleeding (*n* = 5), and intraprocedural perforation (*n* = 3). None of the patients were admitted due to post-procedural anal pain. Taking into consideration the patients from the two centers, most of those requiring hospital admissions (86%) were admitted for strict surveillance during 1 day only.

Regarding histopathology, most of the cases presented high-grade dysplasia/Tis adenocarcinoma (54%). Thirty-six (15%) had submucosal adenocarcinoma, including 20

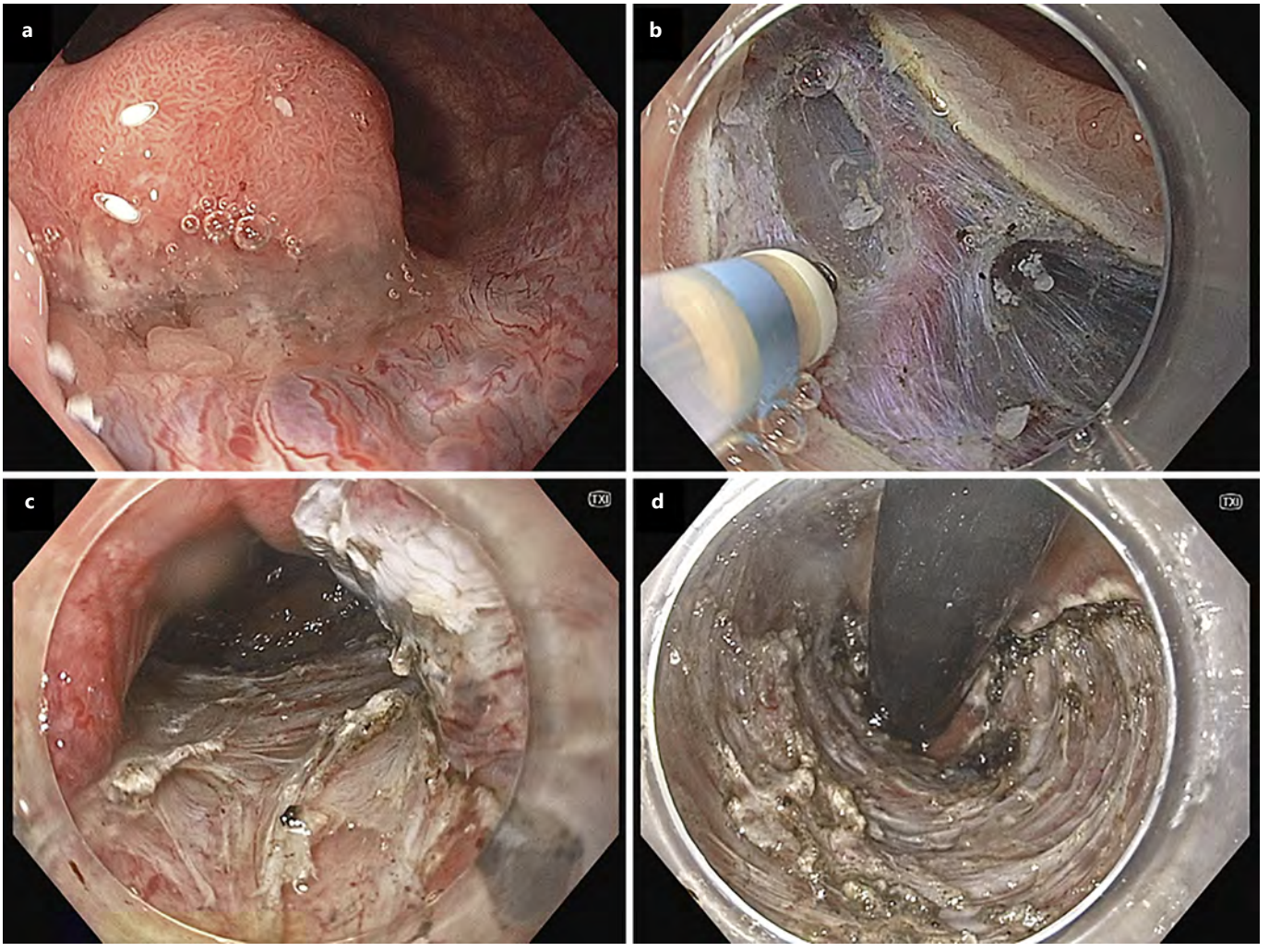

Fig. 1. A case of a granular mixed nodular lateral spreading tumor located at the ARJ. **a** Lesion extending to the dentate line. **b** Cut in the anal squamous mucosa. **c** Mucosal defect in the anal canal. **d** Final mucosal defect. Final histology shows SM1 submucosal adenocarcinoma.

superficial (sm1) and 16 deeply invasive (>SM1) T1 cancers. According to a multidisciplinary board decision, 13 patients were submitted to surgery due to a non-curative ESD, with 2 patients presenting lymph node metastasis but none with residual intramural dysplasia in the surgical specimen. From the remaining, 165 patients have already been submitted to follow-up endoscopies, with a median follow-up time of 12 months (IQR 6–18.5 months) and including 71% of the ARJ lesions and 64% of the rectal lesions group ($p = 0.321$). In total, only 2 patients presented residual lesions during follow-up.

Adverse Events

A total of 10 intraprocedural perforations (4%) were observed, all of them endoscopically resolved by the application of hemostatic clips. None of the patients required surgery due to an intraprocedural adverse event, and mortality was 0%.

Twenty patients (8%) developed post-procedural bleeding. Of them, only 3 patients needed endoscopic clipping; in the remaining cases, bleeding had stopped at the time of the rectoscopy and no treatment was required. Seven patients (3%) developed post-procedural anal pain, which resolved with systemic or topic analgesics, and 7

Table 1. Baseline characteristics of the two groups

	All lesions (*n* = 252)	ARJ lesions (*n* = 60)	Rectal lesions (*n* = 192)	*p* value
Patient characteristics				
Male sex, *n* (%)	142 (57)	26 (45)	116 (61)	0.029
Mean age (SD), years	66±11	64±14	67±10	0.224
Lesion characteristics				
Size, mm	48±25	57±31	46±22	0.020
Paris classification, *n* (%)				
0-IIa	50 (20)	14 (28)	36 (19)	0.085
0-Is	56 (23)	10 (17)	46 (24)	
0-IIa + Is	108 (43)	25 (43)	83 (44)	
Any 0-IIc component	17 (7)	1 (2)	16 (7)	
Other	17 (7)	8 (10)	9 (6)	
LST classification, *n* (%)				
G-H	28 (11)	11 (27)	17 (11)	0.013
G-MN	142 (57)	30 (73)	112 (75)	
NG-FE	8 (3)	0	8 (5)	
NG-PD	12 (5)	0	12 (8)	
Non-LST morphology	58 (24)	–	–	
Histology, *n* (%)				
Low-grade dysplasia	73 (29)	21 (36)	52 (28)	0.053
High-grade dysplasia/Tis	133 (54)	25 (43)	108 (57)	
Adenocarcinoma, T1SM1	20 (8)	4 (7)	16 (8)	
Adenocarcinoma, deeply invasive	16 (7)	4 (7)	12 (6)	
Others (4 serrated, 1 SCC, 1 hyperplastic)	6 (2)	4 (7)	2 (1)	

(3%) developed fever in the first day after the ESD that resolved with paracetamol.

Comparison between ARJ Lesions and Rectal Lesions

We found no differences between the location of the lesions regarding intraprocedural bleeding, *en bloc* resection, R0 resection, curative resection, duration of ESD, area of the lesions, ESD velocity, or histopathology result, as well as the need of surgery due to a non-curative ESD (Table 2). Also, there were no statistically significant differences regarding the hospitalization rate, delayed bleeding, perforation, fever, and the need of readmission due to adverse events.

Three patients from the ARJ lesions group developed post-procedural stenosis (5%), against none in the rectal lesions group (p = 0.003). Also, 5 patients with ARJ lesions (9%) reported anal pain, in opposition to only 2 (1%) from the rectal lesions group (p = 0.002).

From those followed up by endoscopy, 2 patients had residual lesion (1 in the first endoscopy following the ESD procedure at 15 months and 1 in the second follow-up at 17 months). They were both low-grade dysplastic adenomas and occurred in patients with ARJ lesions (p = 0.064) that had positive horizontal margins in the ESD. From those submitted to surgery (n = 13), the only 2 patients with lymph node metastasis belong to the rectal lesions group (p = 1.000). At ESD pathological evaluation, one had positive lateral and vertical margins and tumor budding, while the other had deep submucosal invasion and budding.

Discussion and Conclusions

In our study, we performed a comparative evaluation of 252 rectal lesions treated by ESD, including 60 ARJ lesions and 192 non-ARJ lesions. We found similar results in regard to *en bloc* resection, R0 resection, and curative resection rates in both groups, independent of the rectal location. Similarly, the rates of residual lesion and overall complication rates were comparable between the two groups, except for a higher rate of post-procedural stenosis (p = 0.003) and anal pain (p = 0.002) in the ARJ lesions group. As reported in the literature [8], most of the patients with ARJ lesions were female, contrary to those located elsewhere in the rectum.

Regarding efficacy, Imai et al. and Probst et al. [8, 9] had previously consistently described a lower rate of R0

Table 2. Comparison of the outcomes of ESD procedures between the two groups

	All lesions (*n* = 252)	ARJ lesions (*n* = 60)	Rectal lesions (*n* = 192)	*p* value
Duration (IQR), min	90 (60–150)	120 (70–160)	90 (60–130)	0.072
Velocity, mm^2/min	12 (7–19)	14 (7–22)	12 (7–19)	0.415
Technical success, *n* (%)	248 (98)	58 (97)	190 (99)	0.241
En bloc resection, *n* (%)	240 (97)	58 (100)	182 (96)	0.204
R0 resection, *n* (%)	187 (75)	44 (76)	143 (75)	0.531
Curative resection, *n* (%)	172 (70)	40 (70)	132 (70)	0.920
Delayed bleeding, *n* (%)	20 (8)	4 (7)	16 (8)	0.709
Perforation, *n* (%)	10 (4)	0	10 (5)	0.075
Pain, *n* (%)	7 (3)	5 (9)	2 (1)	0.002
Admission due to adverse events, *n* (%)	4 (2)	1 (2)	3 (2)	0.939

resections in ARJ lesions, probably due to thermal damage at the anal side of the resection specimen. In our cohort, we did not verify this, as R0 resection rate was similar in both groups of patients, possibly reflecting an increased operator experience and improvements in pathology evaluation.

Recently, EMR effectiveness for the treatment of ARJ lesions has been reported [7, 10]. Nevertheless, in ARJ location, ESD shows the same advantages over EMR that had already been established for other colorectal regions [11, 12]. Mainly, it allows for an en bloc resection regardless of the lesion's size, resulting in a more accurate staging for invasive lesions. This is especially important in ARJ lesions, given the increased difficulty in making an accurate and qualitative endoscopic diagnosis of the lesions in this area, as a consequence of the narrow and constrictive character of the anal canal. Also, complementary surgical procedures after a non-curative ESD could harbor much more morbidity in the case of ARJ lesions comparing to other locations in the rectum, which highlights the importance of a R0 resection. Furthermore, ESD implies a direct vision cut and thus enables for a precise dissection above the vascular plexus, besides allowing the rigorous definition of the resection line and preventing the resection of excessive surrounding healthy tissue, thus minimizing mucosal defects and potentially reducing the risk of post-procedural stricture.

The number of patients that have been submitted to complementary surgery or endoscopic follow-up and demonstrated residual lesions was very low, as previously reported [13]. The only 2 cases of residual lesion corresponded to ARJ benign lesions, but they were both non-curative resections from the start. Therefore, we did not find any difference between the two locations, as supported by previous studies [8].

The risk of procedure-associated complications like bleeding, infection, pain, and stenosis has been of major concern. In our series, patients with ARJ lesions showed a higher incidence of post-procedural pain ($p = 0.002$), which is explained by the presence of nociceptive receptors in squamous epithelium on the distal margin. Previous authors have proposed that the injection of lidocaine to the submucosal layer could reduce post-procedural pain, even though strong data supporting this strategy are still lacking [14, 15]. Stenosis incidence was also significantly higher in the ARJ group ($p = 0.003$), which could be associated to the significantly greater diameter of the lesions included in this group comparing to more proximal rectal lesions (57 ± 31 mm vs. 46 ± 22 mm, $p = 0.02$) and to the smaller size of the luminal circumference in the distal rectum and canal anal. In regard to post-procedural bleeding and infection, there were no significant differences between groups, emphasizing the safety of ESD for ARJ lesion.

Our study is currently the largest series addressing ESDs in the ARJ. However, it has some limitations, including the retrospective design, even if based upon prospectively collected data, and the short follow-up period, which could lead to delayed complications rate and recurrence underestimation. Also, all procedures were performed by experienced endoscopists only, not allowing extrapolation for less experienced operators.

In conclusion, ESD is a safe and efficient technique for the treatment of rectal lesions located in the ARJ, similarly to those located elsewhere in the rectum. Randomized controlled trials comparing ESD and EMR are warranted to address the best approach for these lesions.

Statement of Ethics

The Ethics Committee of the Centro Hospitalar São João (approval number 255/2020) and the Ethics Committee of the Erasme Hospital (approval number P2021/539) both approved the prospective collection and retrospective analysis of the included data. As this is an observational retrospective study, no specific signed consent was obtained for inclusion in this study. All authors had access to the gathered data and approved the final manuscript.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Mariana Figueiredo and João Santos-Antunes contributed to the design and implementation of the research, to the statistical analysis and interpretation of the results, and finally, to the writing and revision of the manuscript. Mariana Figueiredo, Rui Morais, and João Santos-Antunes also contributed to data collection. Margarida Marques, Arnaud Lemmers, and Guilherme Macedo provided clinical and technical data, discussed the results, and commented on the manuscript.

Data Availability Statement

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

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The Efficacy and Safety of Treatment Outcomes for Refractory Benign Esophageal Strictures Using a Novel Combination of Needle-Knife Stricturoplasty, Balloon Dilation, and Steroid Injection (with Video)

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Keywords
Benign strictures · Dysphagia · Esophageal stricture · Stricturoplasty

Abstract

Background and Aims: Benign esophageal strictures often present with dysphagia and can significantly impair a patient's quality of life, especially when refractory to standard endoscopic techniques. When repeat dilations fail to achieve an adequate luminal diameter or resolve dysphagia, further therapy with needle-knife or steroid injections is needed. However, patients can still clinically fail. To manage such strictures, we employed a novel combination of all three techniques. ***Methods:*** Single-center case series of adult patients with benign strictures that were refractory to conventional endoscopic therapy and removable self-expanding metal stenting. Primary clinical success was defined as complete resolution in dysphagia. Secondary outcomes included periodic dilation index (frequency of dilations over the follow-up time), esophageal diameter changes, technical success, and complications. ***Results:*** Four patients (median age 49.7 years old, interquartile range [IQR] 30–59) underwent endoscopic therapy for complex, benign strictures using our triple therapy technique. Etiologies of the strictures included peptic strictures ($n = 3$) and an anastomotic stricture ($n = 1$). There was 100% technical success rate with no associated adverse events. There was a 50% clinical success rate, with 1 additional patient having partial improvement in dysphagia. The median diameter of the esophagus before and after triple therapy was 3.2 mm (IQR 3.5–5.5) and 12.8 mm (IQR 11.7–14.2), respectively. The periodic dilation index was 6.3 before and 1.5 after triple therapy. The median length of follow-up was 362.5 days. ***Conclusion:*** Triple combination therapy may be useful in benign strictures that are refractory to standard techniques. Larger studies are needed to validate these findings.

Eficácia e segurança da combinação de estricturoplastia, dilatação com balão e injeção de corticóides no tratamento de estenoses esofágicas benignas refractárias (com vídeo)

Palavras Chave
Estenoses benignas · Disfagia · Estricturoplastia · Corticosteróides · Dilatação

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Resumo

Introdução e objectivos: As estenoses esofágicas benignas apresentam-se frequentemente com disfagia e podem prejudicar significativamente a qualidade de vida, especialmente quando refractárias às técnicas de dilatação endoscópicas padrão. Quando as dilatações não conseguem isoladamente atingir um diâmetro luminal adequado ou resolver a disfagia, são necessárias terapêuticas adicionais (incisão com faca ou injecções de esteróides), embora a taxa de falha clínica não seja desprezível. Para abordagem destas estenoses refratárias utilizámos uma nova combinação das três técnicas. ***Métodos:*** Série de casos incluindo doentes adultos com estenoses benignas refractárias à dilatação convencional e à colocação de prótese metálica auto-expansível removível. O endpoint primário foi definido como resolução completa da disfagia. Os endpoints secundários incluíram o índice de dilatação periódica (frequência de dilatações ao longo do tempo de seguimento), alterações do diâmetro esofágico, sucesso técnico e complicações. ***Resultados:*** Quatro doentes (idade média 49.7 anos, intervalo interquartil [IQR] 30–59) foram submetidos a terapia endoscópica para estenoses benignas complexas utilizando a técnica de terapêutica tripla. As etiologias das estenoses incluíam estenoses pépticas (n = 3) e estenose anastomótica (n = 1). A taxa de sucesso técnico foi de 100%, sem eventos adversos associados. A taxa de sucesso clínico foi 50%, com um doente adicional apresentando melhoria parcial da disfagia. O diâmetro médio do esófago antes e depois da terapêutica tripla foi de 3,2 mm (IQR 3.5–5.5) e 12.8 mm (IQR 11.7–14.2), respetivamente. O índice de dilatação periódica foi de 6.3 antes e 1.5 após a terapêutica tripla. A duração média do seguimento foi de 362.5 dias. ***Conclusão:*** A terapêutica tripla de combinação pode ser útil em estenoses benignas refractários às técnicas convencionais embora sejam necessários estudos adicionais de validação da técnica.

Introduction

Benign esophageal strictures are a common occurrence that present with dysphagia when the lumen diameter is ≤13 mm [1, 2]. Luminal narrowing can significantly worsen a patient's quality of life with complications associated with malnutrition, weight loss, and aspiration pneumonia [3, 4]. Historically, peptic strictures have accounted for up to 80% of benign strictures, though with the increased use of acid suppression therapy the incidence has somewhat decreased [2]. Other etiologies may occur following radiation, caustic ingestion, strictures following endoscopic submucosal dissection, or anastomotic strictures after esophagectomy [4]. These strictures are classified as simple or complex based on the diameter, length, and anatomic abnormalities [2, 4]. Complex stricture is generally longer (>2 cm), irregular, and angulated with severely compromised luminal diameters [5]. Endoscopic dilation is the mainstay of treatment. However, in up to 10% of cases these strictures are refractory to dilation and a luminal diameter >14 mm cannot be achieved [4, 6]. In this setting, the stricture is considered a benign recalcitrant stricture that requires alternative therapy to manage the underlying fibrostenotic disease.

To avoid feeding tube placement or surgery, adjunctive endoscopic therapies including corticosteroid injections or incisional therapy can be used in combination with standard dilation techniques [1]. Removable esophageal stents can also be used to induce stricture remodeling through expansion forces [7]. The use of four quadrant steroid injections (most commonly triamcinolone acetonide) into the stricture has been shown to inhibit matrix proteins that interfere with collagen synthesis and fibrosis [2, 4]. Incisional therapy, such as needle-knife, is a radial incision technique that delivers high-frequency energy to disrupt and remove the rim of stenosis [4]. While these modalities are readily available, the optimal technique remains uncertain, especially due to the heterogenous etiologies of these strictures. Adding needle-knife or steroid injection to standard dilation has produced mixed results [8–14]. No study has investigated a combination of all three modalities in benign refractory strictures. As such, the aim of our case series was to describe treatment outcomes using a novel combination of needle-knife, balloon dilation, and intralesional steroid injection.

Methods

This was a single-center clinical case study of consecutive adult patients (≥18 years old) diagnosed with benign esophageal strictures, refractory to standard dilation therapy, and esophageal stenting between November 2020 and March 2022. All procedures were conducted by a single advanced endoscopist. Baseline demographic and descriptive data were collected, as well as information regarding prior medical, endoscopic, and/or surgical therapies, procedure-related information, and length of follow-up. The stricture length and response to dilation were also recorded. The Institutional Review Board approved the study protocol (HP-00100530).

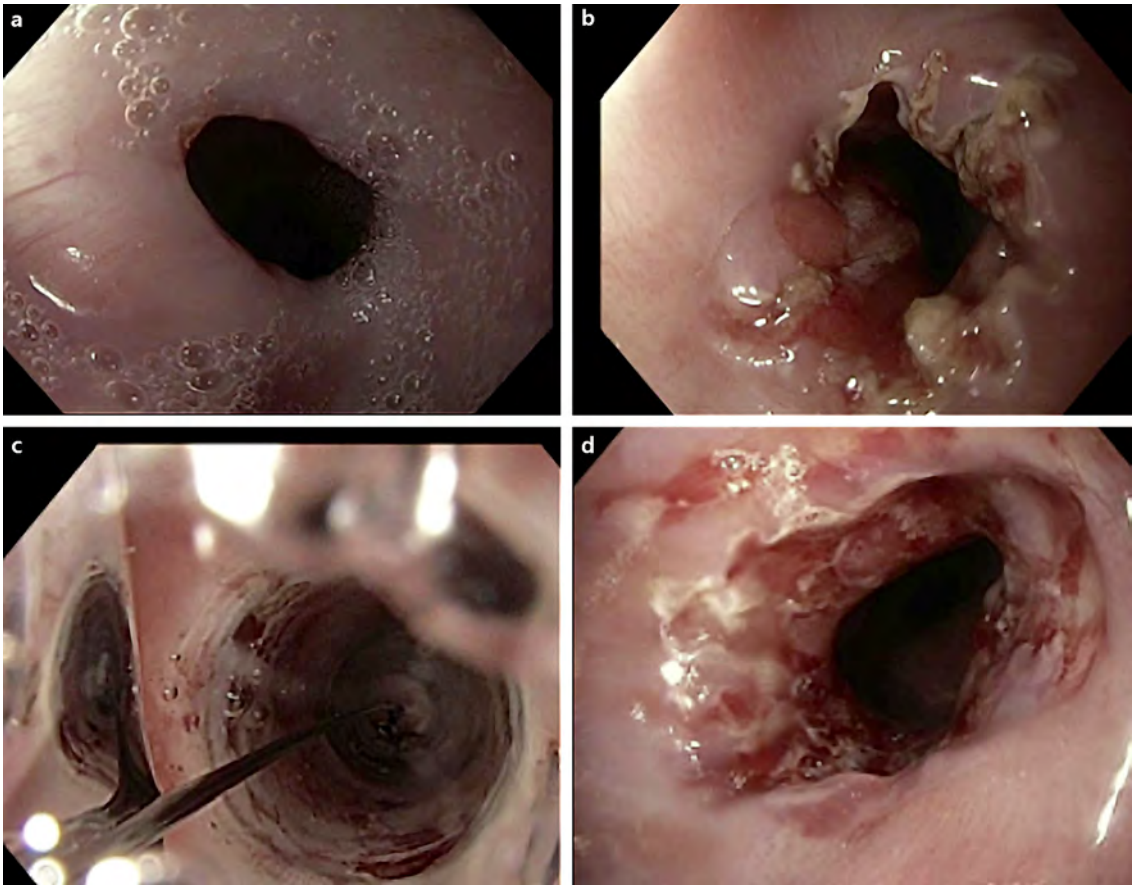

Fig. 1. Esophageal stricture (**a**) that was treated with needle-knife (**b**), balloon dilation (**c**), and then steroid injections (**d**).

The primary outcome was clinical success, defined as complete resolution dysphagia with an ability to tolerate a regular diet. Secondary outcomes included technical success, changes in the esophageal diameter, and a decrease in periodic dilation index needed. The periodic dilation index was defined by the frequency of dilations over the follow-up time in months. Procedure-related adverse events were defined by the American Society for Gastrointestinal Endoscopy lexicon severity scoring system [15].

Statistical Analysis

This was a descriptive study. Nonparametric data were presented as a median with an interquartile range (IQR). Due to a small size, logistic regression analysis was not incorporated.

Procedural Description

All patients underwent the same procedural technique (online suppl. Video 1; for all online suppl. material, see www.karger.com/doi/10.1159/000527770). First, longitudinal needle-knife XL (triple lumen needle-knife – 5.5 Fr Boston Scientific, Natick, MA, USA) incisions were performed at 3–4 mm in depth along the length of the stricture, circumferentially with at least four separate incisions. The incisions were made distal to proximal for optimal control. The needle-knife settings included ERBE Vio 3 with an endocut setting of 2 and forced coagulation setting of 1.5. Next, balloon dilation using a CRE balloon dilators (Boston Scientific) was done in a serial manner to allow the endoscope to pass. Finally, targeted four quadrant intralesional steroids (triamcinolone 40 mg/mL, 2 mL in total) were then injected (Fig. 1, 2).

Repeat endoscopy was done every 4–6 weeks until persistent esophageal dilation was obtained to pass the GIF H-160/H180 scope (~9.4 mm) through the stricture without intervention. From there, the procedures were repeated based upon symptoms and/or resolution of dysphagia.

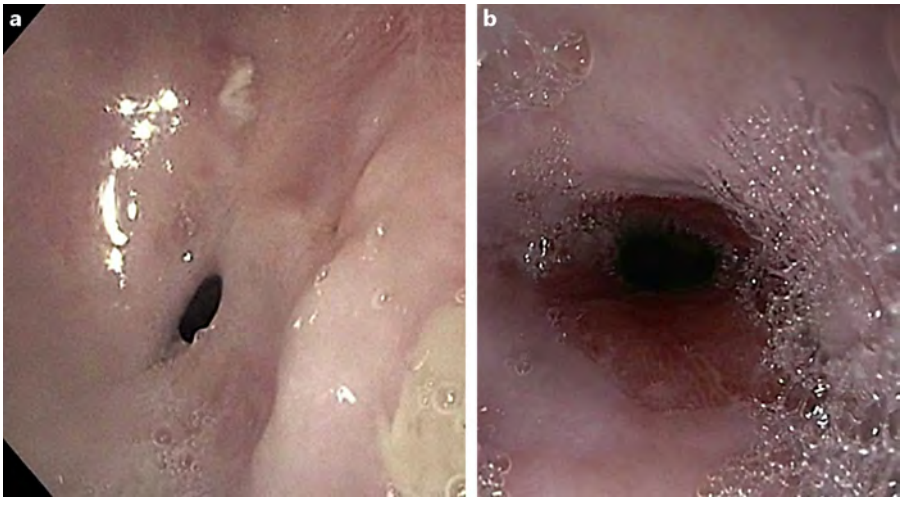

Fig. 2. Endoscopic evidence of a stricture treated before (**a**) and after (**b**) triple therapy 2 months apart.

Table 1. Patient characteristics

Patient	Age/sex	Body mass index, kg/m^2	Stricture etiology	Stricture distance from incisors	Total procedures before triple therapy	Total procedures after triple therapy	Length of follow-up, days
1	30/male	20.3	GERD	39 cm	15[b]	5	425
2	59/male	25.3	Anastomotic[a]	24 cm	8	0	421
3	57/male	19.6	GERD	35 cm	4[b]	0	304
4	53/male	26.1	GERD	30 cm	2[b]	1	116

GERD, gastroesophageal reflux disease. [a] Underwent esophagogastrectomy for gastric adenocarcinoma. [b] Required PEG tube at one point, that procedure is not counted here.

Table 2. Procedure outcomes and clinical success

Patient	Initial stricture diameter × length before triple therapy	Stricture diameter after triple therapy	Triple therapy procedures,[1] *n*	Symptom resolution
1	7 mm × 5 cm	13.5 mm	1	Partial
2	3 mm × 1 cm	15 mm	2	Yes
3	3 mm × 1 cm	11.5 mm	4	No
4	4 mm × 1 cm	12 mm	2	Yes

[1] Combination of needle-knife, balloon dilation, steroid injection.

Results

Four patients (median age 55 [IQR 30–59], 4 males, median body mass index 22.8 kg/m^2 [IQR 19.9–25.7], 2 Caucasians) underwent endoscopic therapy for a benign refractory stricture using our triple therapy technique for symptoms of dysphagia (Table 1). Etiologies of the strictures included peptic stricture ($n = 3$) and a post-surgical anastomotic stricture ($n = 1$). Prior to triple therapy, the patients underwent periodic dilation an average of 6.3 times, typically every month. All patients previously required esophageal stenting ranging from 1 to 3 times; 1 patient (# 4) was managed primarily with stenting and only underwent dilation once. Of note, the option for stent placement before incisional therapy was primarily because these patients were referred to our center with prior therapy. In cases of stent placement, we placed an 18-mm fully covered metallic stent (WallFlex; Boston Scientific).

Clinical success was achieved in 2 patients over a median length of follow-up of 362.5 days (IQR 210–423). One patient (#1) had a brief resolution in his solid food dysphagia; however, his symptoms returned 24 days later following triple therapy in which he reported occasional dysphagia to solids but was able to tolerate a soft diet. There was 100% technical success rate with no associated

adverse events. The median diameter of the esophagus before triple therapy was 3.2 mm (IQR 3.5–5.5) and improved to 12.8 mm (IQR 11.7–14.2) following triple therapy (Table 2). The periodic dilatation index decreased to 1.5 following triple therapy. The patients underwent a median of 2 (IQR 2–3) triple therapy procedures total.

Discussion

To our knowledge, this is the first case series to describe triple combination therapy in patients with benign refractory strictures. Clinically, 3 patients improved with no procedure-related complications. Furthermore, the median stricture diameter improved from 3.2 to 12.8 mm with a decrease in periodic dilations needed. The order of triple therapy chosen allowed for the balloon dilation to open the needle-knife tract so that targeted four quadrant steroid injections could provide optimal results.

These findings are important, especially since recurrent symptoms of dysphagia can be seen in up to 40% of patients undergoing dilation [16]. Typically, these patients undergo serial dilation to alleviate symptoms, though complex stricture can be refractory and persistent dysphagia often poses as a significant challenge for the endoscopist [4]. Recently, anastomotic strictures have emerged as common cause of complex strictures that are often difficult to treat with limited improvement following steroid use [17, 18].

Data regarding combination steroid use and dilation in these strictures are variable, especially since there is no standardized technique with volumes per injection of triamcinolone ranging from 0.5 mL to 2.8 mL [4]. One comparative study of 21 benign strictures of varying etiologies found that steroids plus boogie dilation decreased the number of periodic dilations while prolonging dysphagia-free periods [12]. Yet, another prospective randomized study looking at 14 patients with caustic stricture found no difference in such outcomes [13]. That being said, a more recent prospective study (also evaluating caustic-related strictures) reported an improvement in dysphagia scores and periodic dilation index over a 1-year follow-up period [14]. It is possible that injecting steroids following dilation can enhance clinical outcomes. In fact, two randomized controlled studies analyzing anastomotic strictures produced conflicting results when analyzing steroid injections before or after dilation [18, 19]. Similar to our findings, the study with steroid injection after dilation found significant symptomatic improvement to the point that the study was ended early [19]. All patients in our cohort received steroid injections after dilation since the incisions were easier to place once the lumen was more open and the steroid was used to prevent restenosis by softening the fibrotic tissue.

Needle-knife therapy with dilation can improve long-term outcomes, especially in shorter anastomotic strictures [20]. A few studies have demonstrated favorable results [9, 10, 20, 21]. In fact, one study comparing needle-knife to balloon dilation reported longer term luminal patency in 62% and 20% of patients, respectively, at 12-month follow-up [9]. Another comparative study of 50 patients with Schatzki rings found that electrosurgical incisions allowed for longer symptom-free periods (8 vs. 5.8 months) compared to boogie dilation [10]. It also appears that short anastomotic strictures are particularly responsive to needle-knife [20]. However, one randomized study of 62 patients with anastomotic strictures found no differences in clinical outcomes or number of dilations needed when comparing Savary-Gilliard dilation to electrocautery incision [11]. Longer strictures (>1.5 cm) usually require re-treatment and are more difficult to manage [22]. As such, caution is needed when directly comparing these study outcomes. However, in our study 4 incisions were typically performed for the short segment strictures with a moderate clinical success rate when steroid injections were added to the procedure protocol.

Due to the varying complexity and etiologies of strictures, it is still difficult to interpret the current literature. However, given the possible long-term benefits of our triple therapy technique we do recommend needle-knife before dilation as a means to enhance the efficacy of steroid injections. In our cohort, 3 out of 4 patients had initial stricture lengths of 1 cm, and these longer strictures may respond differently. Additionally, deciding when to employ this technique should be determined on a case-by-case basis. Given our positive outcomes with no associated complications, we believe that this method should be considered when strictures are refractory after 2–3 dilation sessions and/or stent therapy.

There are a few limitations to highlight in this study. As a retrospective case series, there are inherent biases that can occur. Our limited sample size may also confound our findings; yet, this study was done at a large tertiary center with patients who failed numerous endoscopic therapies leading up to our novel technique. The majority of these strictures were secondary to peptic strictures, and there may be different outcomes based on varying stricture etiologies. Yet, all procedures were performed by the same endoscopist with the same technique used with long-term follow-up.

In conclusion, utilizing triple therapy for refractory benign strictures can improve therapeutic outcomes while reducing the need for repeat dilations. Further larger studies are needed to validate these findings and determine the optimal technique.

Statement of Ethics

This study protocol was reviewed and approved by the University of Maryland Institutional Board Review, approval number HP-00100530. Informed consent was obtained from the patients.

Conflict of Interest Statement

Eric M. Goldberg is a consultant for Medtronic and Ambu. All other authors have no potential conflicts (financial, professional, or personal) that are relevant to the content presented in this manuscript.

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Author Contributions

Andrew Canakis performed research, collected and analyzed data, and wrote the paper. Varun Kesar, Benjamin Twery, Osman Ali, Justin Canakis, and Caleb Hudspath collected data and revised the paper. Eric Goldberg designed the study and revised the paper.

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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Embryonal Sarcoma of the Liver in the Adult: Challenges in the Diagnosis of a Rare Entity

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Keywords
Sarcoma · Embrionary · Liver · Adult

Abstract

Introduction: Embryonal sarcoma of the liver (ESL) is a rare neoplasm of the liver occurring mainly in paediatric ages. Making the correct diagnosis can be challenging as the laboratory and radiological findings that are often nonspecific, and the tumour immunophenotype is poorly defined and even somewhat variable. ***Case Presentation:*** A large epigastric mass was detected in a computerized tomography scan of a 43-year-old woman presenting with abdominal pain and bloating. The mass was biopsied and submitted to histopathological study. Microscopically the tumour had sarcomatoid features and showed multinucleated cells with periodic acid-Schiff (PAS)-positive globules. Immunostaining revealed positivity for vimentin, CD10, glypican-3, and α1-antitrypsin and negativity for keratins, muscle, adipocytic, and melanocytic differentiation markers. The patient was then submitted to a left hepatectomy with similar histological findings. ***Discussion:*** ESL in adults is a rarity and its diagnosis requires the exclusion of other entities. While some microscopic features are very common, they remain nonspecific. The main feature is the presence of multinucleated cells with PAS-positive hyaline globules. While ancillary testing is key, the immunophenotype also lacks specificity and ESL may have variable staining for glypican-3 and epithelial or muscle differentiation markers. Although it has been described for more than 3 decades, the prognosis and optimal treatment are still not well defined, but surgery has yielded favourable results.

Sarcoma embrionário do fígado no adulto – desafios no diagnóstico de uma entidade rara

Palavras Chave
Sarcoma · Embrionário · Fígado · Adulto

Resumo

Introdução: O sarcoma embrionário do fígado (SEF) é uma neoplasia rara do fígado que ocorre principalmente em idades pediátricas. Fazer o diagnóstico correto pode ser um desafio, uma vez que os achados laboratoriais e radiológicos são muitas vezes inespecíficos e o imunofenótipo desta entidade é mal definido e algo variável. ***Apresentação do caso:*** Foi detetada em tomografia computorizada (CT) abdominal uma massa epigástrica volu-

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mosa numa mulher de 43 anos apresentando dor abdominal e distensão abdominal. A massa foi biopsada e submetida a estudo histopatológico. Microscopicamente, o tumor tinha características sarcomatoides e apresentava células multinucleadas com glóbulos hialinos com positividade para ácido periódico Schiff (APS). O estudo imunohistoquímico revelou positividade para vimentina, CD10, glipicano-3 e α1-antitripsina e negatividade para queratinas e marcadores de diferenciação muscular, adipocítica e melanocítica. ***Discussão/Conclusão:*** O SEF no adulto é uma raridade e o seu diagnóstico requer a exclusão de outras entidades. Embora algumas características microscópicas sejam muito comuns, estas permanecem inespecíficas. A principal característica é a presença de células multinucleadas com glóbulos hialinos positivos para APS. Ainda que o estudo imunohistoquímico seja fundamental, o imunofenótipo também carece de especificidade e o SEF pode ter marcação variável para glipicano-3 e marcadores de diferenciação epitelial ou muscular. Apesar de ter sido descrito há mais de três décadas, o prognóstico e o tratamento ideal ainda não estão bem definidos, mas a cirurgia tem apresentado resultados favoráveis.

Introduction

Primary liver sarcoma is a rare diagnosis, accounting for less than 1% of primary malignancies of the liver [1]. According to some studies angiosarcoma, leiomyosarcoma, and epithelioid hemangioendothelioma are the most prevalent primary liver sarcomas [2]. While occurring predominantly in children from 6 to 10 years of age, ESL is a rarer entity that can also affect adults as some have reported [3]. ESL is a malignant neoplasm with an aggressive course, but its treatment and prognosis may be more optimistic than was previously thought. In this paper, we describe a case of a 43-year-old female with a diagnosis of ESL.

Case Report

A Portuguese woman of 43 years of age resident in Southeast Asia presented to her local hospital emergency room with complaints of asthenia, abdominal bloating, anorexia, and nocturnal sudoresis with 2 months evolution. A CT-scan showed a 19 × 14 cm mass ranging from the epigastrium to the left hypochondrial region with centripetal peripheral hypervascularization suggesting the presence of necrosis or a cystic component. The origin of the mass was not evident. It seemed to encompass part of the liver, and it was attached to the diaphragm and spleen. Back in Portugal, the clinical presentation was unaltered, and the physical examination identified diffuse abdominal pain during palpation with objectified hepatomegaly and a homogeneous epigastric mass. The bowel movements were maintained, the aspect of faeces and urine unchanged and there was no jaundice. The blood work-up showed upper borderline levels of alkaline phosphatase and gamma-glutamyl transferase (187 U/L and 54 U/L), a considerable rise of C-reactive protein (16.04 mg/dL) and a slight rise of prothrombin time (14.5 s) as the only abnormal values. Alpha-fetoprotein, CA 19.9, and carcinoembryonic antigen were within normal ranges.

The images were reviewed with identical findings and the radiological diagnostic hypothesis were of gastrointestinal stromal tumour (GIST), angiosarcoma, or a neurogenic lesion. An ultrasound-guided biopsy of the mass was then performed. Stained slides were observed in light microscope – Nikon Eclipse 50i, and images were obtained using a Nikon-Digital Sight DS-Fi1 camera.

The collected material consisted of two biopsy cylinders in total with 18 mm width, showing hepatic tissue with normal architecture and signs of compression in relation to the presence of an adjacent space-occupying lesion. The lesion was well demarked from the liver tissue by a fine connective tissue band and was composed by a highly variable cell population (shown in Fig. 1), exhibiting multinucleated giant cells with enlarged irregular hyperchromatic nuclei, eosinophilic clear cytoplasm with fading limits. There were PAS-positive hyaline globules (shown in Fig. 2, 3), and other smaller cells with epithelioid, stellated, or spindled configuration, supported by a myxoid richly vascularized stroma. No mitotic activity was detected.

Several immunochemical panels were sequentially performed. The tumour cells were positive for vimentin, CD10, glypican-3, and α1-antitrypsin, with the latter two especially positive in the giant cells. They showed no expression of MNF-116, EMA, HepPar1, LCA, CD31, CD34, ERG, HMB45, S100, SOX10, CD117, DOG1, smooth muscle actin, desmin, MDM2, CD23, and AFP.

The conjugation of H&E morphology and ancillary studies was consistent with the diagnosis of ESL. The case was discussed by a multidisciplinary team that attested to the conditions for the tumour resection. The patient underwent left hepatic lobectomy with splenectomy and partial resection of the diaphragm. Upon gross examination of the main specimen, there was a 22 × 17 × 8 cm bilobate mass with a solid component stemming from the left hepatic lobe and a cystic component adherent through a fibrous pseudocapsule to the spleen (shown in Fig. 4). The microscopic examination of the surgical specimen showed once again stellated and spindled cells amongst multinucleated giant cells with hyaline globules. The cells were positive for vimentin, CD10, glypican-3, and α1-antitrypsin and negative for desmin, EMA, HepPar1, CD34, CD117, and S100, overlapping with the biopsy findings. The diaphragm showed involvement by the neoplasia.

Fifteen days after the surgery, the patient presented to the emergency room with a fever. Analytic studies revealed leucocytosis, thrombocytosis, and a rise of C-reactive protein (12.2 mg/dL). Thoracic and abdominal ultrasound exhibited pleural effusion and a liquid anechoic collection with 12 cm between the liver and the stomach suggestive of biloma. The pleural effusion was drained and sent for cytological examination that showed no tumour cells. The patient was treated with ceftriaxone and discharged after 5 days.

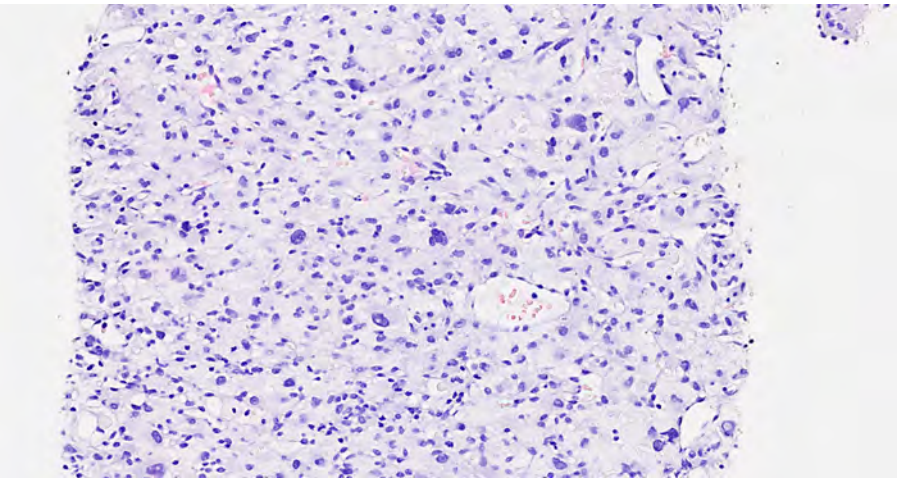

Fig. 1. Lesion with severely pleomorphic cell population (haematoxylin-eosin, original magnification, ×200).

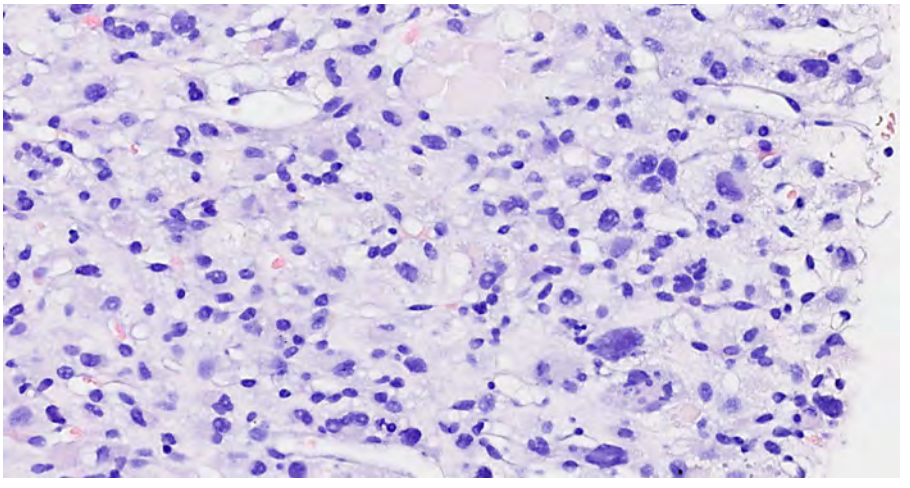

Fig. 2. Multinucleated giant cells with hyaline globules are a key feature of ESL (haematoxylin-eosin, original magnification, ×400).

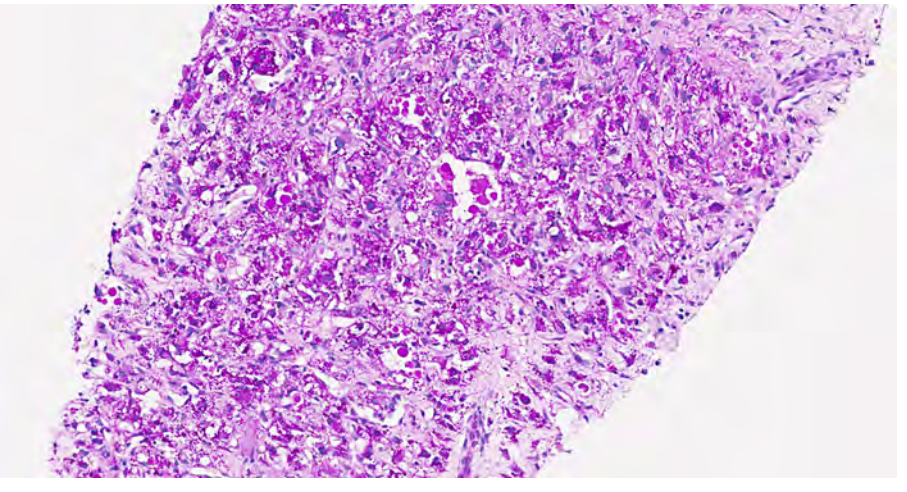

Fig. 3. Hyaline globules positive for PAS stain (original magnification, ×200).

Almost 4 months after the primary diagnosis and 2 months after the surgery, a CT-scan showed a 0.7 cm nodule in segment 7 of the liver. The lesion was hypervascular during the arterial phase and, subsequently isodense suggestive of metastasis. The patient underwent segmental hepatectomy during which a peritoneal perigastric nodule was found and submitted for intraoperative pathological examination that attested to its neoplastic nature. The post-surgery histological study confirmed the metastatic essence of the two nodules. The patient recovered from the surgery without further issues.

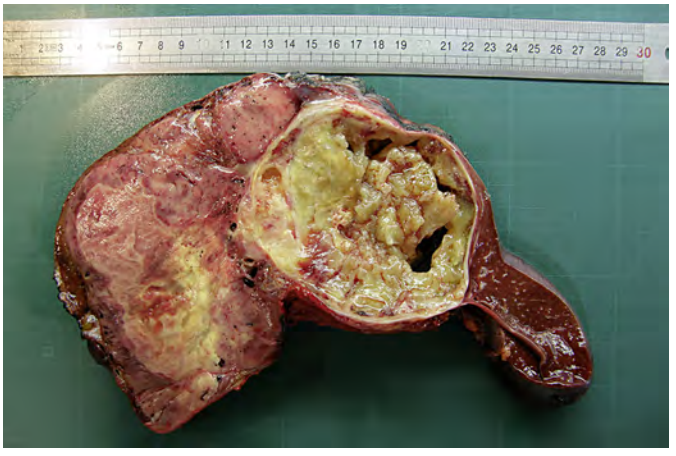

Fig. 4. Large hepatic mass with solid and cystic components adherent to the spleen.

Two months after the second surgery and 7 months after the primary diagnosis a follow-up, CT-scan detected a solid, vascularized nodule in the inferior lobe of the left lung. The patient is currently undergoing her second month of chemotherapy.

Discussion

ESL is a malignant mesenchymal tumour with predominance in children, with rare cases described in adults. This entity does not have a particular clinical or radiological presentation. Patients usually have no laboratory disturbances but may have leucocytosis or high serum alkaline phosphatase, while elevated tumour markers are rare. In this case, the patient had elevated alkaline phosphatase, gamma-glutamyl transferase and reactive C protein while the tumour markers are within normal ranges. The radiologic findings are nonspecific, showing most of the time a large and complex intraperitoneal mass usually with cystic degeneration. This cystic component is not uncommonly misdiagnosed as a benign lesion [4, 5]. In fact, the radiologic re-evaluation of our patient is reported as suggestive of a liver haemangioma. The gross presentation of this entity consists of a pseudocapsulated mass usually larger than 10 cm; it has severe heterogeneity on cut surface with solid and mucilaginous cystic components with haemorrhage and necrosis, being coincident with what we observed in the surgical specimen.

Histological analysis of ESL usually displays an array of pleomorphic cells supported by a myxoid stroma. While these cells include stellate and spindled shapes, multinucleated giant cells with cytoplasmic PAS-positive eosinophilic hyaline globules are the most distinctive histological feature of ESL. A very frequent facet that is not consonant with our analysis is the mitosis sum [3]. Although mitosis is frequently described in the medical literature, we only identified 1 mitosis/11.85 mm^2 and when using Ki67 stain less than 10% of the neoplastic cells were stained. Regarding the fact that the diagnosis was made in a biopsy sample, one might conjecture that there may be areas with different proliferation rates. On the other hand, as we obtained the same results in the surgical specimen, the existence of a subset of ESL with lower proliferation and therefore better prognosis can be hypothesized.

No specific immunophenotype of ESL is known but several reports denote positivity in most cases for vimentin, α1-antitrypsin, CD68, CD10 and, in a subset of tumours, glypican-3. Other stains that show variable results include desmin, keratins, and muscle specific-actin, and we should be on the lookout for pitfall diagnosis that this expression might suggest. Tumour cells are negative for EMA, HepPar1, AFP, myogenin, MYOD1, CD34, CD117, ALK-1, and S100 [3, 4]. Our immunochemistry results are concordant as neoplastic cells show positivity for vimentin, CD10, glypican-3, and α1-antitrypsin and are negative for EMA, HepPar1, AFP, CD34, CD117, and S100.

An extended immunochemistry study is designed to guide us regarding the differential diagnosis of ESL, which in adult patients include angiomyolipoma, epithelioid haemangioendothelioma, high-grade sarcomas, GIST, malignant melanoma, and HCC. Angiomyolipoma is predominant in female middle-aged adults, and its gross presentation is variable; histologic features include epithelioid cells, spindled cells in some cases, and pleomorphic cells are not uncommon [6]. Adipocytes and thick-walled vessels, other characteristic findings, were not found in our case. The hypothesis of epithelioid haemangioendothelioma is supported by the age and sex of our patient, as it is more common in middle-aged women and by the microscopic features as they have spindled, stellated and even giant multinucleated cells, with rare mitosis. Its macroscopic presentation of a firm and white mass on the cut surface, however, is not assonant with our observation [6]. In spite of our findings not being exceptionally consistent with high-grade sarcomas, such as angiosarcoma, leiomyosarcoma, and liposarcoma, these diagnoses are also taken into account as they present as a large mass, sometimes having cystic degeneration (leiomyosarcoma),

and histological elements include spindled and epithelioid cells with marked atypia [6–8]. Liposarcoma, especially, was considered as at the moment of the biopsy, since radiology cannot determine if the tumour had origin on the liver. GIST gross examination may present as a large mass with cystic degeneration and necrosis. Although it usually has little to no pleomorphism, epithelioid GISTs sometimes have a sarcomatous morphology [6]. Albeit extremely rare, malignant melanoma of the liver also presents as a large liver mass and microscopically reveals pleomorphic cells with spindled, round, and irregular morphology [9]. Malignant melanoma metastasis to the liver is a much more credible hypothesis but no history of cutaneous, ocular, or mucosal melanoma is present. HCC must simply be considered due to its prevalence, as it is by far the most frequent primary hepatic malignancy. In addition, its microscopic presentation encompasses a wide spectrum.

The tumour cells were negative for several markers, supporting the exclusion of differential diagnosis, namely CD117 and DOG1 (GIST), HMB45 and S100 protein (angiomyolipoma and melanoma), CD34 and CD31 (epithelioid haemangioendothelioma and angiosarcoma), MDM2 (liposarcoma), smooth muscle actin, and desmin (leiomyosarcoma). HepPar1 negativity is not enough to exclude hepatocellular carcinoma firstly because poorly differentiated HCC may lose HepPar1 expression and secondly because our case showed positivity for glypican-3. On the other hand, we have MNF-116 negativity and the histologic features are not concurring with that diagnosis.

There is not a well-defined treatment for ESL. However, hepatectomy seems to be a key part of it, as patients that do not undergo surgery – radical hepatectomy or hepatic lobectomy – have a significantly lower survival rate. Multimodal therapies such as neoadjuvant or postoperative chemotherapy or radiotherapy, paediatric age and negative surgical margins status have been reported to be favourable factors for both the survival rate and the disease-free survival of patients with ESL. While extrahepatic disease appears not to be a factor of major preponderance regarding prognosis, tumour size effect on survival is still uncertain. Wu and colleagues have reported a 65.8% 5-year survival rate for any treatment, featuring liver transplantation as the best therapeutic option [10, 11].

ESL is a rare sarcoma that while predominant in infancy ages must always be in the back of the pathologist's mind when thinking of differential diagnosis for large, heterogeneous masses of the liver. PAS-positive hyaline globules within giant multinucleated cells are a characteristic histopathological key finding. Although proper immunophenotyping of this entity is lacking, the majority show positivity for vimentin, α1-antitrypsin, CD68, CD10, and glypican-3. Even when a case is concordant to ESL, other diagnoses must be rejected first. Currently, there are no fitting guidelines for the management of ESL but the multimodal treatment seems to attain decent results. Further studies must take place to fill in the knowledge gaps for more efficient diagnosis and therapy.

Statement of Ethics

Ethical approval was not required for this study in accordance with local/national guidelines. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Guilherme Nogueira Fontinha: drafting the work and aiding in the macroscopic and microscopic study; João Martins Gama: aiding in drafting the work and in the microscopic study; Rui Caetano Oliveira: revising the paper and approving the final version for submission; Augusta Cipriano: main responsible for macroscopic and microscopic study, revising the paper, and approving the final version for submission.

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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Refractory Hidradenitis Suppurativa: A Diagnosis to Consider

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Keywords
Hidradenitis suppurativa · Lymphoma · Lymphoproliferative disorder · Methotrexate · Infliximab

Abstract
Hidradenitis suppurativa is a chronic inflammatory disease associated with multiple comorbidities, and its association with lymphoma has recently been a topic of debate. However, it is still controversial whether this risk can be attributed to the disease itself or whether it has any relationship with immunosuppressive treatment. Here, we describe the case of a patient with severe perianal hidradenitis suppurativa treated with methotrexate and infliximab, whose exacerbation with persistence of severe symptoms refractory to adequate treatment led to the diagnosis of diffuse large non-Hodgkin B-cell lymphoma. It was decided to perform a colostomy to improve perianal sepsis, and immunochemotherapy was proposed.

Hidradenita Supurativa Refractária – um diagnóstico a considerar

Palavras Chave
Hidradenite supurativa · Linfoma · Distúrbio linfoproliferativo · Metotrexato · Infliximab

Resumo
A hidradenite supurativa é uma doença inflamatória crónica associada a múltiplas comorbilidades e a sua associação com doenças linfoproliferativas tem sido, recentemente, um tema de debate. No entanto, é controverso se esse risco pode ser atribuído à própria doença ou se tem relação com o tratamento imunossupressor. Descrevemos o caso de um doente com hidradenite supurativa perianal grave tratada com metotrexato e infliximab, cuja exacerbação com persistência de sintomas graves refratários ao tratamento adequado levou ao diagnóstico de linfoma não-Hodgkin difuso de grandes células B. Optou-se pela realização de colostomia para melhoria da sépsis perianal e início de imunoquimioterapia.

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Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory condition that involves apocrine glands and hair follicles in intertriginous regions, such as inguinal, axillary, genital, perineal, and perianal areas [1]. The pathogenesis of HS remains incompletely understood, but three key processes have been implicated: follicular hyperkeratosis and dilatation, follicular rupture with subsequent inflammatory response, and chronic inflammation with architectural tissue changes [2]. Several inflammatory cytokines, such as tumor necrosis factor (TNF), interferon-γ, interleukin (IL)-10, IL-12, IL-17, IL-23, and IL-32, as well as antimicrobial peptides LL-37, psoriasin, and β-defensins 2 and 3, may have a role in the development of the disease [3]. The etiologic role of genetic, hormonal, and environmental factors is not completely established [2].

As a systemic inflammatory disease, HS is associated with multiple comorbidities including metabolic, cardiovascular, endocrine, gastrointestinal, rheumatic, and psychiatric disorders [1]. In this setting, the relationship with neoplastic disorders may be a new area of research, in which the chronic inflammatory state and the increased immune activation in HS can trigger the development of lymphoma [1].

Case Report

A 72-year-old male with a 30-year history of HS was referred to our center due to severe perianal involvement. Past medical and surgical history included multiple antibiotic courses, percutaneous drainage of abscesses, and three fistulotomies. After exclusion of inflammatory bowel disease, namely, Crohn's disease (normal findings in endoscopy, histology, and enterography), combination therapy with an anti-TNF was considered. At the time, although only a few cases of infliximab in HS were described, we decided to start it due to our center's vast experience with this drug in aggressive perianal Crohn's disease. Since the patient was a male above the age of 65 years, considering the risks of combining an anti-TNF with thiopurines in this subgroup, we opted for methotrexate to prevent immunogenicity and improve drug levels. Clinical remission was achieved.

Four years later, he presented with a 3-month course of intense proctalgia, purulent perianal exudation, and fever without a specific pattern, refractory to oral and intravenous antibiotics. Apart from a mild leukocytosis (13.960 G/L) and an increase in C-reactive protein (72.3 mg/L), other laboratory studies, such as complete blood count, erythrocyte sedimentation rate, renal and hepatic function tests, lactate dehydrogenase, and creatinine kinase, were unremarkable. Cytomegalovirus and Epstein-Barr virus (EBV) serologies were compatible with previous infection. Blood and stool cultures, stool ova and parasite test, and perianal exudate cultures were negative. Pelvic magnetic resonance imaging revealed diffuse thickening of the rectum, deep ulcerations in the lower rectum, intersphincteric fistulas (with one extending to the prostatic apex/base of the penis), and multifocal disruption of the sphincter planes (Fig. 1). He underwent proctological examination and colonoscopy, showing extensive circumferential ulceration involving the entire anal canal and the distal 3 cm of the rectum, with pseudopolypoid formations and several depressions, some with pus drainage, suggestive of fistula openings (Fig. 2). Histopathology demonstrated extensive ulceration of distal rectal and anal mucosa, along with infiltration by large and atypical lymphoid cells. The neoplastic cells were positive for CD20, BCL6, MUM-1, BCL2, and Epstein-Barr encoding region in situ hybridization and negative for CD3 and CD10. Ki-67 was estimated in 50%. These findings were consistent with EBV-positive diffuse large B-cell lymphoma (DLBCL) (Fig. 3). Additional investigation included a bone marrow biopsy and full-body computerized tomography scan, both without relevant findings. A diagnosis of stage IV non-Hodgkin DLBCL was made.

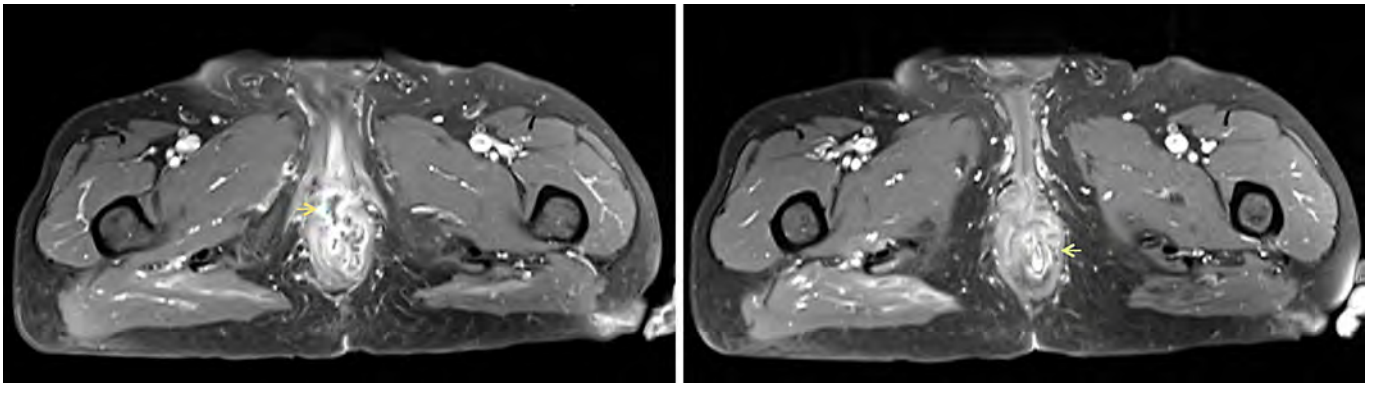

Fig. 1. Pelvic MRI (axial view, T1) revealing intersphincteric fistulas with one extending to the prostatic apex/base of the penis (orange arrow) and multifocal disruption of the sphincter planes (green arrow). MRI, magnetic resonance imaging.

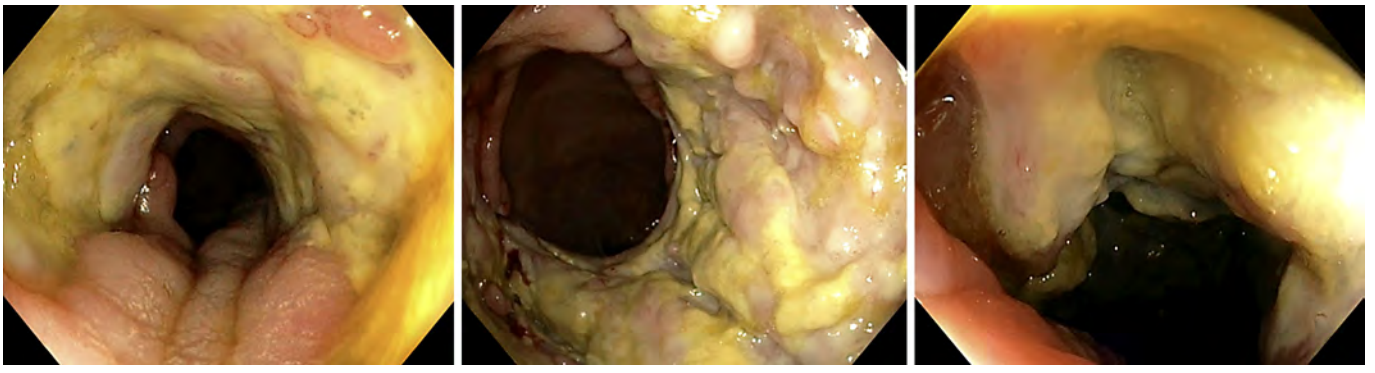

Fig. 2. Colonoscopy showing extensive circumferential ulceration involving the entire anal canal and the distal 3 cm of the rectum, with pseudopolypoid formations and several depressions, some with pus drainage, suggestive of fistula openings.

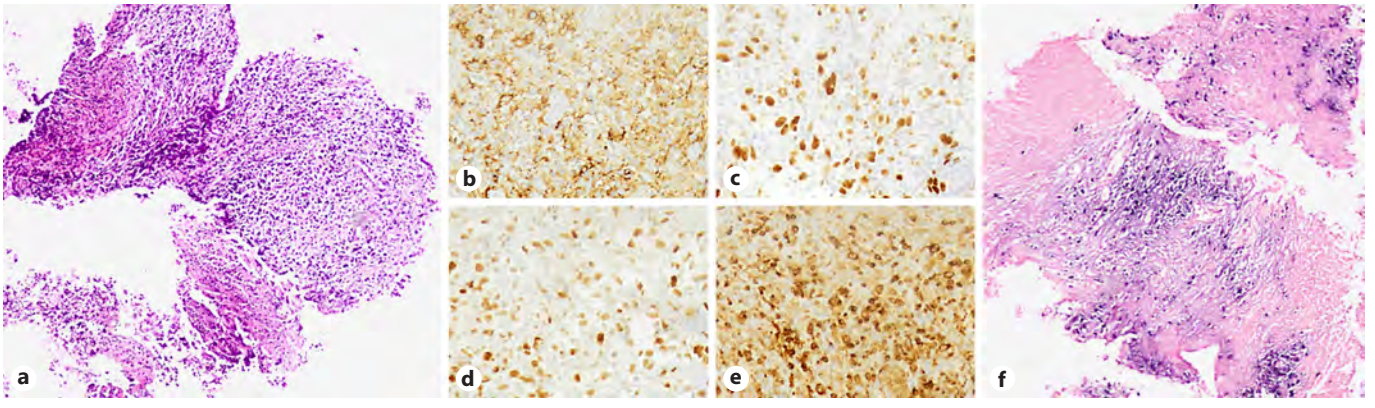

Fig. 3. Histopathology examination revealing rectal and anal mucosa with extensive ulceration and infiltration by large atypical lymphoid cells (hematoxylin-eosin [HE] ×100) (**a**). Neoplastic cells expressed CD20 (**b**), MUM-1 (**c**), BCL6 (**d**), and BCL2 (**e**) [×400]. EBER in situ hybridization revealed positive staining of the neoplastic cells (**f**) [×100]. EBER, Epstein-Barr encoding region.

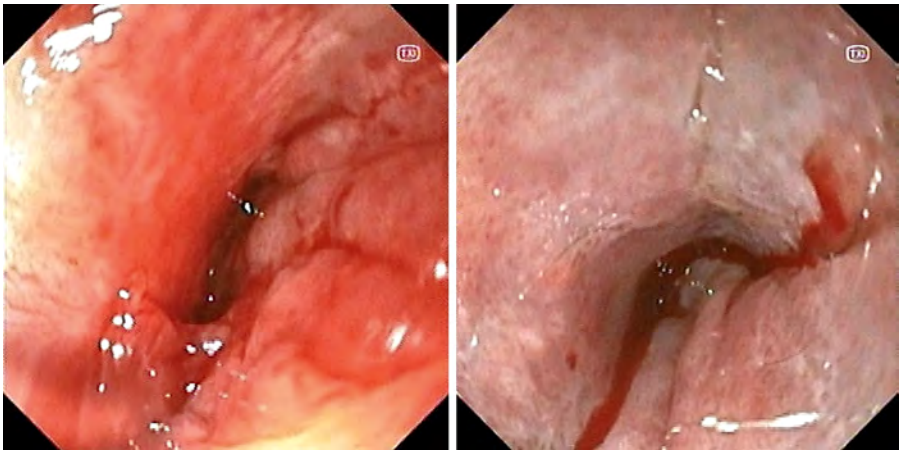

Fig. 4. Rectosigmoidoscopy showing stenosis of the proximal anal canal with friable scar-like mucosa.

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After an expert multidisciplinary discussion, we decided to stop immunosuppression (MTX and infliximab); perform a colostomy in order to improve perianal sepsis and reduce the risk of infectious complications; and afterwards initiate immunochemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone since he had no further comorbidities. Six cycles were performed with a complete response. Pelvic magnetic resonance imaging showed significant tumoral regression with some posttreatment inflammatory features and sustained anal canal and sphincter deformation. Reassessment rectosigmoidoscopy revealed a proximal anal canal stenosis with friable scar-like mucosa, which could not be overcome with the ultrathin endoscope (Fig. 4). Biopsies showed no evidence of lymphoma. Due to these findings, bowel transit reconstruction was not possible, and the patient remains with a colostomy.

Discussion/Conclusion

In the Western world, there has been an upward trend in the incidence of lymphoma in the past few decades, along with a parallel increase in the occurrence of inflammatory conditions treated with immunosuppressive agents [4]. Various studies have identified an increased risk of lymphoma among patients with several chronic inflammatory disorders [5, 6]. Persistent activation of the immune system may have a significant role in the genesis of lymphoproliferative disorders (LPD); chronic B-cell stimulation and proliferation, in particular, appear to have major roles [7]. With regard to HS, its association with lymphoma has recently been a topic of debate [2].

A case-control study showed a 2.03 greater odds of lymphoma in patients with HS relative to control individuals, although it was not statistically significant [8]. A recent cross-sectional study found that both males and females with HS were more likely to have LPD than the general population (odds ratio of 2.00 for non-Hodgkin and 2.26 for Hodgkin lymphoma), with male patients having a higher prevalence [9]. In another recent Korean nationwide population-based cohort study, patients with HS had an increased risk of Hodgkin's lymphoma. However, in subgroup analysis, only male patients with HS had an increased risk. In addition, the risk of Hodgkin's lymphoma was greater in patients with moderate to severe HS than those with mild disease, suggesting that the risk of LPD may be related with disease severity [3].

In fact, despite the remaining uncertainties regarding the potential independent role of the disease itself in the pathogenesis of these LPD, the contribution of immunosuppressive therapy has been widely assessed in other diseases, such as rheumatoid arthritis or inflammatory bowel disease [1, 3, 7, 9–20]. LPD induced by MTX (MTX-LPD) are categorized as other iatrogenic immunodeficiency-associated LPD in the most recent edition of the World Health Organization's classification of hematopoietic and lymphoid tissue tumors, being described predominantly in patients with rheumatoid arthritis [21]. MTX-LPD consists mainly of DLBCL (35–60% of cases), and approximately 40–50% cases occur in extranodal sites, such as the skin, salivary glands, lungs, digestive tract, liver, and spine [21, 22]. Although spontaneous remission of MTX-LPD after MTX removal occurs in approximately 50% of cases, chemotherapy may be necessary [22]. The frequency of EBV infection is highly variable in these cases. The degree and duration of immunosuppression, the degree of inflammation and/or chronic antigenic stimulation, as well as the patient's genetic background play an important role in the development of EBV-positive LPD [23].

The potential effects of anti-TNF on malignancy are difficult to accurately predict, given the pleotropic effects of these inhibitors and the complexity of the pathways involved in inflammation and tumor development [10]. Although some recent studies have associated the use of anti-TNFα with an increased risk of LPD [11, 12], others did not find this relation, and apart from the case of hepatosplenic T-cell lymphoma for which anti-TNFα seems to enhance the deleterious effect of thiopurines [13], there is not enough evidence to claim that these agents may contribute to an increased LPD incidence [14–20].

To date, no study has specifically examined the general additional risk of LPD in patients with HS exposed to MTX or anti-TNFα. This case reinforces the concept that chronic inflammation is a very important pathway that leads to the development of LPD. The key point is that in the presence of severe disease presentation refractory to adequate treatment, reconsidering the patient's initial diagnosis is mandatory. The possibility of LPD should be considered in these HS patients with long-standing active disease under immunosuppressive therapy. Further studies are necessary in order to assess the role of the disease itself and of immunosuppressive therapy in the development of LPD in patients with HS.

Statement of Ethics

Ethical approval was not required for this study in accordance with local/national guidelines. Informed consent was obtained from the patient for the publication of this article and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest.

Funding Sources

The authors have no funding sources to declare.

Author Contributions

All the authors contributed equally to the conception, analysis, and interpretation of data, as well as drafting and critical revision of the article for important intellectual content. All the authors approved the final version of the manuscript.

Data Availability Statement

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

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Endoscopic Snapshot

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Acute Pancreatitis and Cholangitis due to Biliary Parasites: A Snailing Endoscopic Retrograde Cholangiopancreatography

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Keywords
Endoscopic retrograde cholangiopancreatography · Biliary parasitosis · Acute cholangitis · Acute pancreatitis

Pancreatite e colangite aguda secundárias a parasitose biliar

Palavras Chave
Colangiopancreatografia retrógrada endoscópica · Parasitose biliar · Colangite aguda · Pancreatite aguda

The authors report 3 cases of different patients with biliary parasitosis, diagnosed, and treated by endoscopic retrograde cholangiopancreatography (ERCP) (online suppl. video). All patients denied relevant risk factors for parasitosis, namely environmental, hygiene, or dietary factors. The first 2 cases illustrate biliary colonization by *Fasciola hepatica*. One of these patients presented with obstructive jaundice and the other with recurrent pancreatitis (two previous acute pancreatitis with mild dilation of extrahepatic bile ducts with biliary sludge in the common bile duct, described on emergency ultrasound). In the first case, abdominal ultrasound was suggestive of biliary parasites. In both patients, cholangiography performed during ERCP revealed multiple small filling defects with elliptic and sigmoidal shapes in the main bile duct with common bile duct dilation. After clearance of the bile ducts using an extraction balloon, the diagnosis was confirmed to be biliary parasitosis due to *Fasciola hepatica*. In the second case, the parasite was retrieved alive (shown in Fig. 1). Each patient received complementary treatment with triclabendazole the day after the endoscopic procedure at a dose of 10 mg/kg orally twice daily for 2 days.

The third case corresponds to a patient that presented with acute cholangitis. During ERCP, cholangiography revealed many elongated irregular filling defects and dilation of the common bile duct without intrahepatic duct dilation. After performing sphincterotomy, the bile duct was cleared using a Dormia basket and a balloon extractor, allowing the removal of *Ascaris lumbricoides* already without motility (shown in Fig. 2). Endoscopic treatment was also supplemented with albendazole 400 mg orally as a single dose the day after the procedure. All patients had significant clinical improvement shortly after ERCP and have been discharged asymptomatic after 3 days.

In Portugal, as in other developed countries, biliary parasitosis are rare diseases. However, the incidence of these infestations appears to be increasing in line with the increase in tourism and immigration. Diagnosis is usually supported by ultrasound, computed tomography, magnetic resonance imaging (MRI), or endoscopic ultrasound

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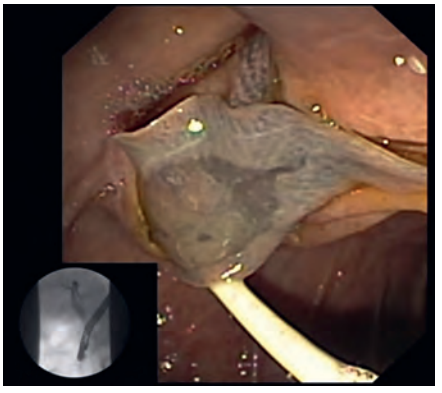

Fig. 1. ERCP revealing removal of *Fasciola hepatica* through the papilla.

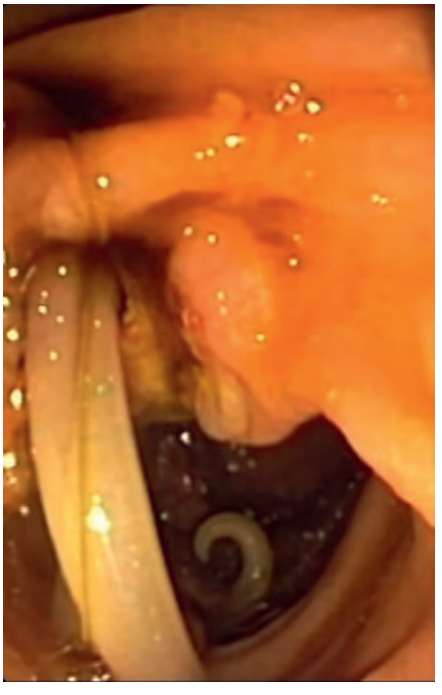

Fig. 2. ERCP revealing removal of *Ascaris lumbricoides* through the papilla.

[1]. Although ERCP is mainly used for therapeutic aspects, in rare cases ERCP is the key to the diagnosis [2]. We intend to illustrate the typical findings of parasitosis in cholangiography and duodenoscopy and demonstrate the usefulness of ERCP in the diagnosis and treatment of biliary obstructions due to biliary parasitosis.

Statement of Ethics

The study has been granted an exemption from requiring ethics approval in July 2022 (ULSAM Ethics Committee). Subjects have given their written informed consent to participate and publish their case and any accompanying images. Subjects have given their written informed consent to publish their 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 sources to declare.

Author Contributions

Ana Catarina Carvalho: drafted the manuscript and performed video edition. Marta Moreira: acquired data and performed image edition. Luís Lopes: was responsible for conception and performance of the endoscopic procedure and critically revised the report. All 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. Further inquiries can be directed to the corresponding author.

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Endoscopic Snapshot

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Endoscopic Submucosal Dissection of a Large Gastric Lesion Using a Novel Adjustable Traction Device: A-TRACT 4

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Keywords
Endoscopic submucosal dissection · Early gastric cancer · Traction device

Disseção endoscópica da submucosa de uma lesão gástrica usando um novo dispositivo de tração ajustável: A-TRACT 4

Palavras Chave
Disseção endoscópica da submucosa · Cancro gástrico precoce · Dispositivo de tração

Gastric cancer constitutes an important health problem. Despite a gradual decline of incidence and mortality in recent decades, and despite improvements in prevention, diagnosis, and therapeutic option, the burden remains high. In the particular case of Portugal, an intermediate to high incidence of gastric cancer is reported [1]. Earlier detection is therefore crucial since most patients with early gastric cancer (EGC) can be cured by endoscopic resection.

Endoscopic submucosal dissection (ESD) is currently recommended as the first-line therapy for EGC [2]. Nevertheless, a major barrier to the expansion of ESD in the West is the technical difficulty and risk of complications associated with the procedure. Several traction devices and techniques have been described to increase the ease, speed, and safety of this technique [3] but with many limitations that can preclude its use, especially the fixed amount of traction [4]. We describe the use of a new adjustable traction device (A-TRACT 4) in the endoscopic management of a gastric lesion (Fig. 1, 2).

An 87-year-old male was referred due to a large gastric lesion (Paris IIa+Is with 10 cm), located in the anterior, superior, and posterior face of the antrum (previous biopsies with high-grade dysplasia) (Fig. 3). After multidisciplinary discussion, endoscopic resection was attempted (online suppl. Video; for all online suppl. material, see https://doi.org/10.1159/000530828). Circumferential incision was performed using Dual-Knife® (Olympus, Tokyo) after submucosal injection with glycerol. ESD was started, but due to difficulties in accessing the submucosa, A-TRACT was used. Initially, fixation of the loops of the device in 4 cardinal points using clips was performed. Subsequently, another clip was used to attach the rubber band to the opposite wall, and ESD was continued. In the central part of the lesion, the device was tightened using grasping forceps in order to bring all the anchoring points of the device closer to the traction point between themselves and to the rubber band, which allowed a reestablishment of optimal traction. The procedure was completed in 120 min with complete en bloc resection of the

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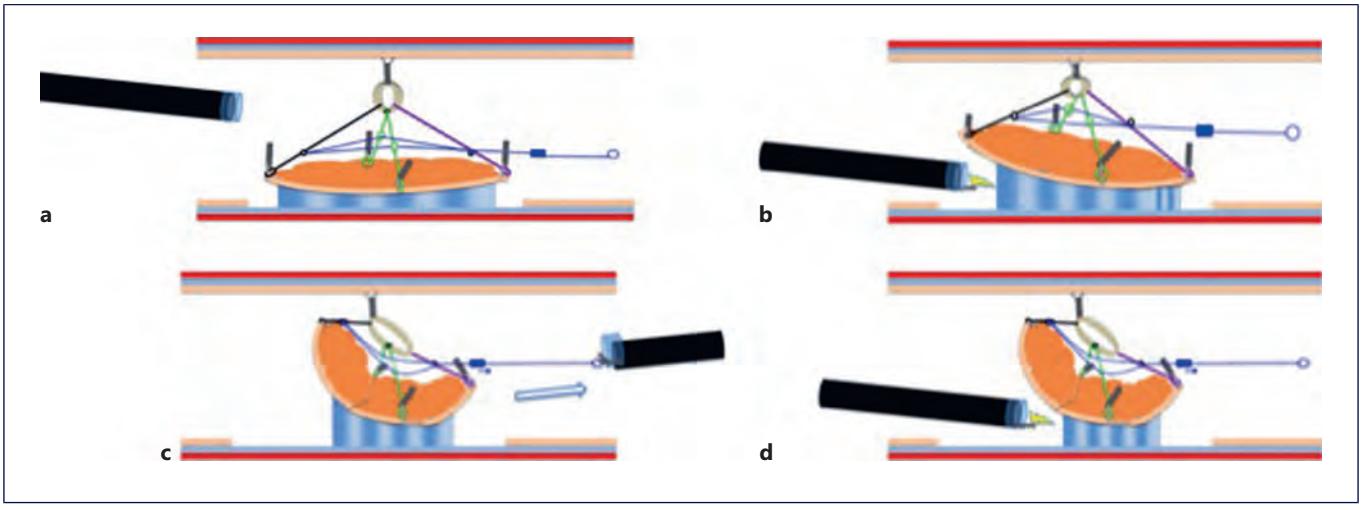

Fig. 1. Schematic representation of the A-TRACT 4 device. **a** After complete circumferential incision and trimming, fixation of the loops of the device in 4 cardinal points using clips is performed. **b** Dissection is started. **c** After around one-third of the lesion is dissected, traction begins to decline, and we tighten the device by pulling out the loop into the operating channel with a rat tooth forceps. **d** Increased traction allows faster and safer finishing of the dissection.

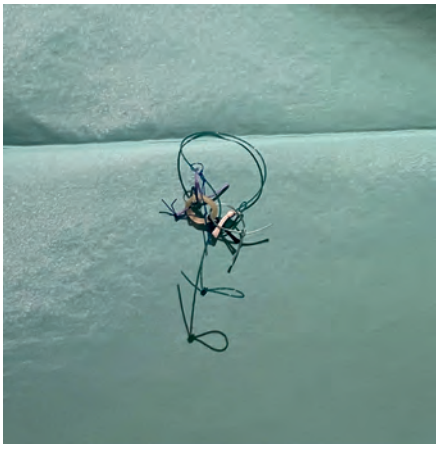

Fig. 2. A-TRACT 4 device.

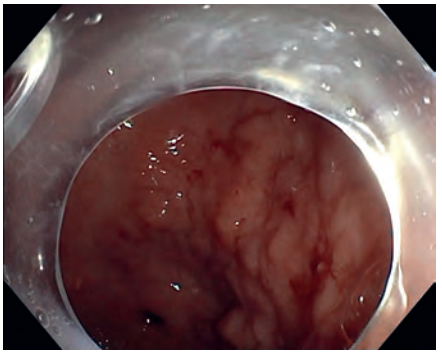

Fig. 3. Lesion located in the gastric antrum.

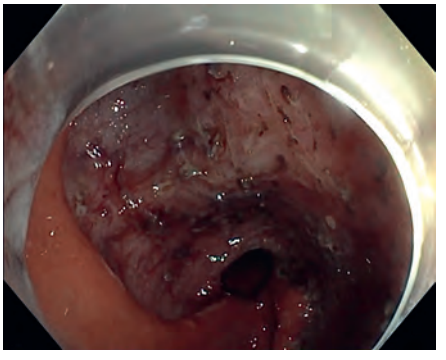

Fig. 4. Resection bed after ESD.

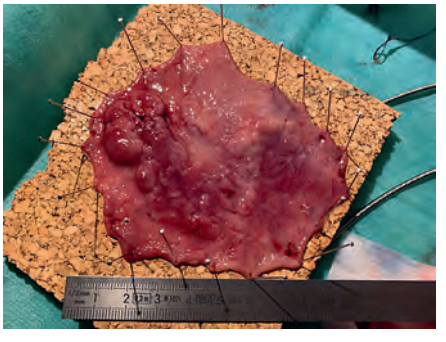

Fig. 5. Lesion after resection.

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lesion, without complications (Fig. 4, 5). At the end of the procedure, the device was removed together with the lesion using a snare. Histopathology revealed an adenocarcinoma pT1a R0 (very low-risk resection). The patient remains under endoscopic surveillance, without evidence of recurrence in the follow-up.

ESD remains a challenging technique, in spite of the positive and growing impact of training and experience dissemination [5]. In this regard, we report the use of a new device that can be helpful to increase the speed and safety of the procedure, allowing an easier access and visualization of the submucosa. Previously, other traction techniques such as clip and line, clip and snare, and S-O clip have been described to overcome the difficulties of gastric ESD [3]. Compared to these techniques, the use of adjustable traction overcomes a main limitation of previous traction devices that was loss or incorrect positioning of traction during the procedure. Moreover, the traction can be dynamically and more than once adjusted throughout the procedure, without need to remove the scope or reposition the traction device. Nevertheless, it is important to state that this device needs a precise sequence of instructions to install it properly, as was previously reported [6].

Although the A-TRACT was previously described in colonic lesions [7, 8], to our knowledge, this is the first case report of the use of an adjustable traction device for ESD of a gastric lesion. This technique is a promising and innovative addition to the therapeutic armamentarium for the treatment of EGC.

Statement of Ethics

Informed consent was obtained from the patient for the procedure and publishing of the case.

Conflicts of Interest Statement

Louis-Jean Masgnaux and Mathieu Pioche founded the company A-TRACT device & Co to develop the device they created.

Funding Sources

There are no funding sources to report.

Author Contributions

Rui Morais wrote the manuscript and performed literature review. Mathieu Pioche performed the procedure and did a critical review of the manuscript. Mariana Figueiredo and Louis-Jean Masganaux performed literature review and did a review of the manuscript.

Data Availability Statement

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

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Images in Gastroenterology and Hepatology

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Multiple Liver Nodules in Fontan-Associated Liver Disease

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Keywords
Fontan-associated liver disease · Liver nodules · Hepatocellular carcinoma · Multiple focal nodular hyperplasia

Nódulos hepáticos múltiplos associados a cirurgia de Fontan

Palavras chave
Doença hepática associada à cirurgia de Fontan · Nódulos hepáticos · Carcinoma hepatocelular · Hiperplasia nodular focal múltipla

A 22-year-old female, who had underwent Fontan procedure in childhood, presented with mild elevation of liver enzymes (AST 35 U/L, ALT 50 U/L, ALP 62 U/L, GGT 61 U/L). She had no liver dysfunction (total bilirubin 1.3 mg/dL, INR 1.1, albumin 3.7 g/dL), signs of cirrhosis or portal hypertension (platelets 177 × 10^9), encephalopathy or ascites.

Viral, autoimmune, metabolic, and toxic etiologies were excluded. Abdominal ultrasound showed a diffusely heterogeneous and micronodular liver parenchyma, compatible with Fontan-associated liver disease (FALD) in this context. Moreover, multiple de novo hyperechogenic nodules were found, imposing investigation.

MRI reported >12 nodules, maximum diameter of 27 mm, isointense in T1-weighted sequences, hypointense in T2, with no restricted diffusion (shown in Fig. 1). Some were halo-surrounded, while others displayed a central scar. Most displayed hyper-enhancement in the hepatic arterial phase (shown in Fig. 2), becoming isointense in the portal phase and hypointense in the delayed one, a worrisome feature known as washout (shown in Fig. 3). Using hepatobiliary contrast, all nodules showed hyperintensity (shown in Fig. 4). Bloodwork revealed normal alpha-fetoprotein (AFP). Therefore, the final diagnosis of multiple focal nodular hyperplasia (FNH)-like in a FALD background was made, and the patient kept under surveillance.

The Fontan procedure is a palliative surgery for patients with an anatomic or functional single-ventricular congenital heart disease, consisting of a total extracardiac cavopulmonary connection created by anastomosing the superior vena cava to the right pulmonary artery (PA) and insertion of an extracardiac conduit between the inferior vena cava and the PA [1, 2]. The

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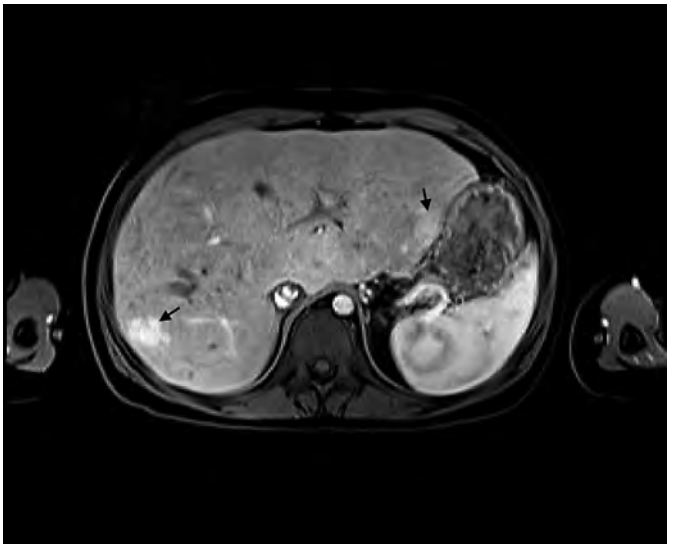

Fig. 1. Multiple de novo liver nodules are seen (arrows).

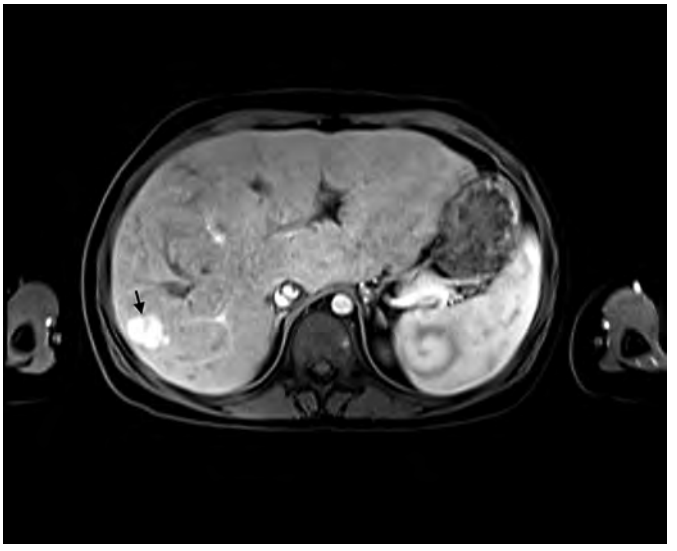

Fig. 2. Hepatic arterial phase shows enhancement of nodule in segment V (arrow).

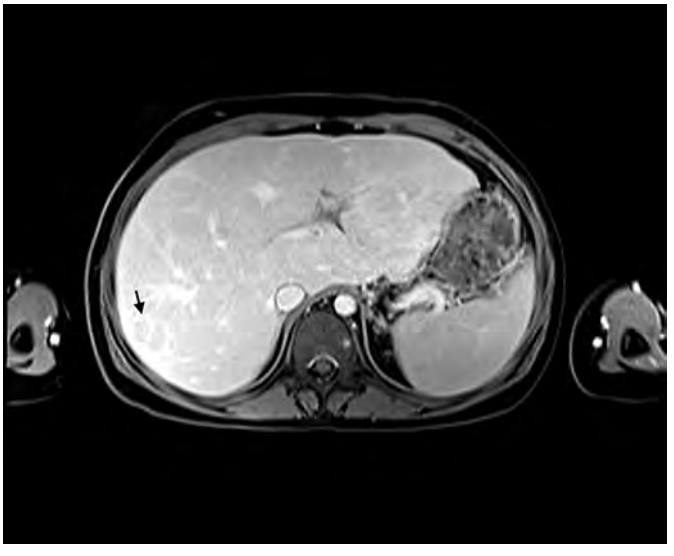

Fig. 3. Late phase shows washout in the same nodule (arrow).

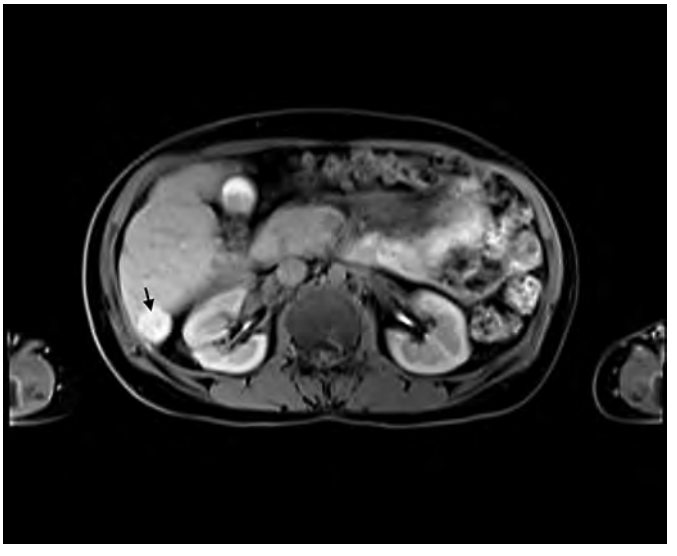

Fig. 4. Hepatobiliary phase shows hyperintensity of nodule in segment VI (arrow).

consequent chronic liver congestion and ischemia result in FALD, leading to cirrhosis in 1–5% of patients per year and hepatocellular carcinoma (HCC) in 1.3% [1–3]. Indeed, annual and early liver surveillance is mandatory [1].

Multiple FNH is a rare entity which has been associated with some vascular diseases and treatments [4, 5]. This clinical case highlights an association between multiple FNH and FALD. Given the inherent risk of HCC in FALD and similar MRI findings between FNH and HCC in this background, their differential diagnosis becomes challenging [1, 2]. In this context, AFP and MRI hepatobiliary contrast are key [2, 3]. Nonetheless, biopsy should be considered in dubious and atypical nodules [1].

Statement of Ethics

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

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

All authors participated in the design, construction, and revision of the paper.

Data Availability Statement

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

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Gastritis Cystica Profunda Presenting as an Ulcerated Subepithelial Lesion

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Keywords
Gastritis cystica profunda · Subepithelial lesion

Gastrite cística profunda manifestada como lesão subepitelial ulcerada

Palavras Chave
Gastrite cística profunda · Lesão subepitelial

A 59-year-old man with unremarkable medical history underwent upper endoscopy evaluation due to dyspeptic symptoms. A 20 mm ulcerated subepithelial lesion was found in the greater curvature of the gastric body (Fig. 1). Biopsies showed only chronic active gastritis, without specific changes. After therapy with proton pump inhibitors, a subsequent endoscopy showed complete resolution of the superficial ulceration and an endoscopic ultrasound (Fig. 2) showed a well-defined heterogeneous, hypoechoic mass originating in the second layer of the gastric wall, with small anechoic areas. Ultrasound-guided fine needle aspiration (22 G FNA needle) and bite-on-bite biopsies were again unremarkable. The patient opted for addition follow-up and further attempts at tissue acquisition as he did not intend surgery with an uncertain diagnosis. The lesion was followed up by endoscopic ultrasound (at 3 and 6 months) and endoscopy (a year after the last endoscopic ultrasound), remaining stable for 3 years, with unremarkable histology (two instances of fine needle aspiration and one instance of bite-on-bite endoscopic biopsies). Due to an absence of diagnosis, the patient finally opted for surgical removal (opting against endoscopic removal). The surgical specimen showed overlying eroded mucosa, subepithelial glandular proliferation, cystically dilated, without cytologic atypia (Fig. 3). Overall, these findings were suggestive of gastritis cystica profunda. Epstein-Barr virus serologies were obtained and were not consistent with current infection.

Gastritis cystica profunda is a rare form of subepithelial gastric lesion, typically found in post-gastrectomy patients, with around 65 cases described in the literature [1, 2]. In postsurgical patients, it is thought to arise from subepithelial migration of epithelial cells after surgical mucosal disruption. In patients without surgery, other factors such as EBV infection, ischemia, and chronic inflammation have been proposed but the underlying mechanism is unknown [3]. Animal studies show that GCP has malignant potential but the data on humans are still scarce [4]. The most frequent endoscopic ultrasound features are anechoic cysts in the submucosal layer and GCP should be suspected in this setting [2]. Although the sparse evidence available demonstrates a subpar diagnostic yield for endoscopic ultrasound fine needle aspiration, tissue sampling is still useful to exclude differential diagnosis such as gastrointestinal stromal tumors [2].

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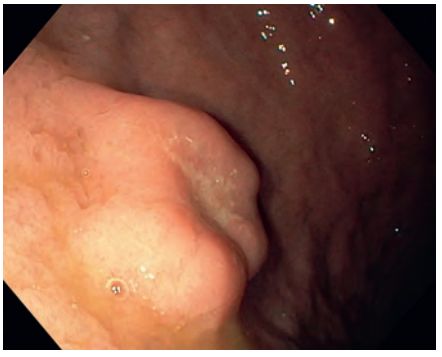

Fig. 1. Upper digestive endoscopy showing an ulcerated subepithelial lesion in the gastric body.

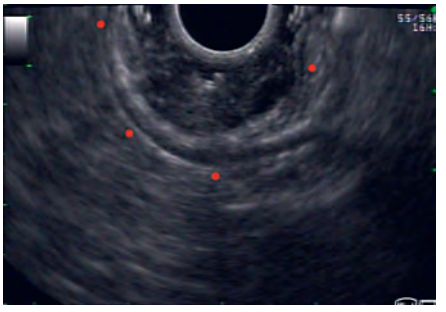

Fig. 2. Endoscopic ultrasound demonstrated a well-defined heterogeneous lesion originating in the second layer of the gastric wall. Small anechoic cysts can be seen inside the lesion.

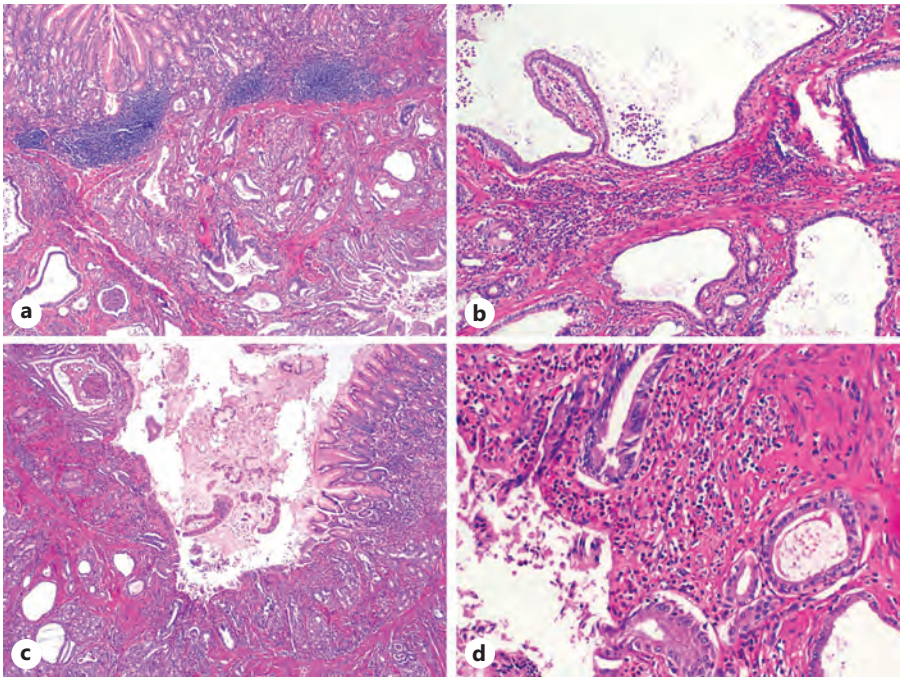

Fig. 3. On hematoxylin and eosin staining (H&E), a glandular proliferation was found within the submucosa of the gastric body (H&E, ×20) (**a**). Some of these glands were cystically dilated, lined by foveolar epithelium and without significant cytologic atypia (H&E, ×40) (**b**). The overlying gastric mucosa displayed foci of erosion and ulceration (H&E, ×20) (**c**), in association with a mixed inflammatory infiltrate and hemosiderin-laden macrophages (H&E, ×100) (**d**). These features are suggestive of gastritis cystica profunda.

It could be argued that by utilizing larger caliber or FNB-type needles we could increase the diagnostic yield but there is no published evidence to support these claims. The diagnosis is nevertheless difficult as there are no defined diagnosis criteria; clinical, radiological and imaging results have to be integrated; nevertheless most patients are only diagnosed after surgery. In our case, this was further complicated as the patient had no history of gastric surgery, the only proven risk factor. Additionally, we found no evidence of further gastric disease, systemic disorders, or medication known to impact gastric mucosa.

Statement of Ethics

Informed consent for publication of this case and associated iconography was obtained from the patient.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

Edgar Afecto: article inception, patient interview, and original draft. David João: pathology report and images. Sónia Fernandes: critical review of the article and patient interview.

Data Availability Statement

Clinical data are unavailable for open source consultation but further inquiries can be forwarded 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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