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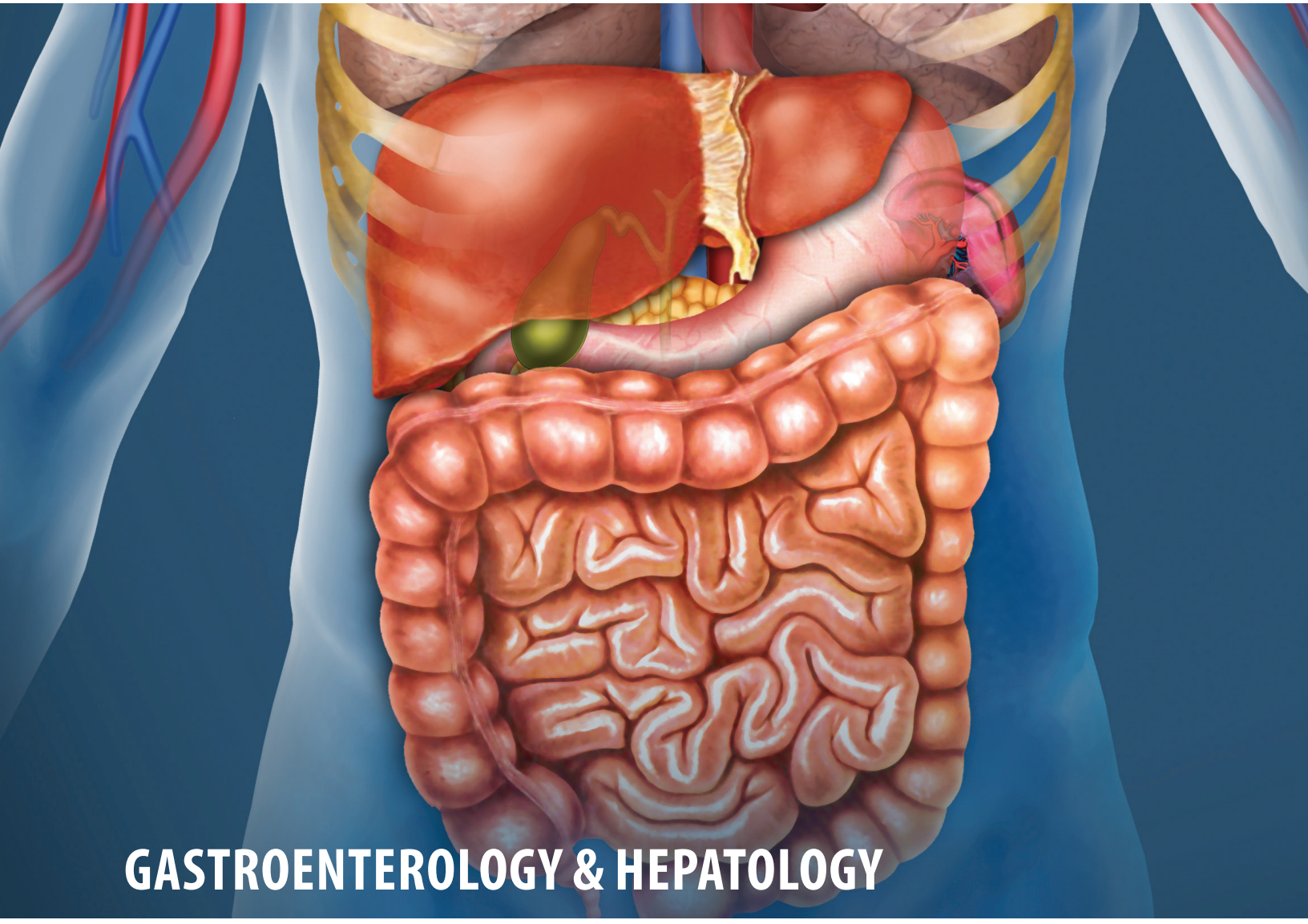

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Dyspepsia leads to significant impairment of HRQoL[*1]

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Rabeprazole 20 mg + Domperidone 30 mg SR Capsules

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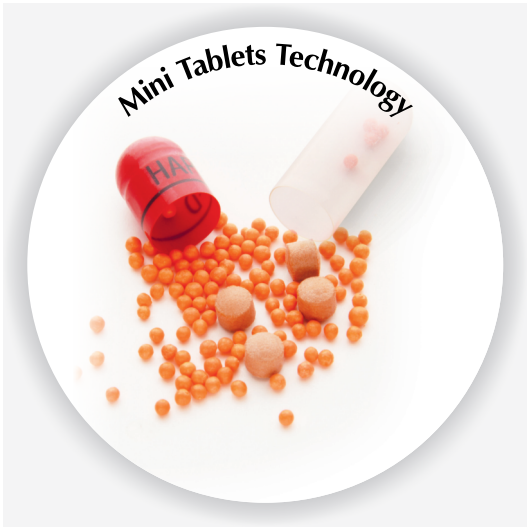

- Relieves heartburn[2]
- Alleviates nocturnal dyspeptic symptoms[3]
- Improves Quality of life[4]

Dyspepsia Gone
Happiness ON

*HRQoL - Health Related Quality of Life

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2. American J gastroenterol. 2000;95(9):2435
3.World J Gastroenterol. 2010;16(5):613-7
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EDITORIAL

Optimal PPI Dosing for Improving GERD Symptoms: Is Timing Everything?

David Y. Graham[1]

Published online: 20 September 2018

Background and Significance

There have been a large number of clinical studies published regarding the effect of proton pump inhibitors (PPIs) on acid secretion; it is generally accepted that gastroesophageal reflux disease (GERD) symptoms are most often related to esophageal acid exposure [1, 2]. Furthermore, for once-daily PPI administration, morning administration is superior to evening administration [3, 4]. GERD patients also differ in relation to acid sensitivity [2]. Importantly, PPIs also vary greatly in relative potency [5], expressed as differences in the percentage of time the intragastric is ≥ 4 throughout a 24-h day (pH > 4-time) [5]. One key variable is also the timing of a PPI dose relative to a meal, under the hypothesis that peak PPI serum concentrations should coincide with maximal postprandial proton pump activation [6].

In this issue of *Digestive Diseases and Sciences*, Waghray et al. [7] investigated the effect of changing the time of administration of PPIs on GERD symptoms. They defined taking a PPI 20–30 min before breakfast as "optimal" timing; taking it at some other interval was termed "suboptimal." The main outcome variable was improvement in gastroesophageal reflux disease symptom assessment scores (GSAS). Subjects were recruited from patients taking PPIs suboptimally with persistent GERD symptoms. Subjects continued to take 20 mg of omeprazole daily using the suboptimal pattern of administration; after a 2-week run-in period, symptoms were scored. Then, 64 subjects were randomized to take 20 mg of omeprazole 20–30 min before breakfast (24 subjects) or to continue the suboptimal pattern of administration. After 4 weeks, the GSAS was repeated. The study ended for those receiving optimal therapy and the 40 subjects receiving suboptimal therapy were re-randomized to either continue suboptimal therapy (23 subjects) or take 20 mg of omeprazole 20–30 min before breakfast (17 subjects). After an additional 4 weeks, the GSAS was again calculated. Overall, they report that GSAS improved for those receiving PPI therapy 20–30 min before breakfast compared to those taking it at other times. Assuming that these results were generalizable to all PPI users, they then used the results in a cost model for PPI use in the USA, concluding that if all US patients took their PPIs 20–30 min before breakfast, it would produce a more satisfied patient population and could save more than 4 billion USD annually [7].

Controversies

The Waghray et al. study was based on the belief that the timing of PPI administration in relation to the morning meal is an important variable in terms of PPI effectiveness and that their results were generalizable to all patients taking a variety of PPIs for GERD. Their hypothesis should be evaluated in terms of preexisting data; for example, the effect of PPI administration in relation to breakfast on intragastric pH was previously studied by Brummer et al. [8] who found that the potential benefits were limited to the first few days of therapy. Boltin et al. [9] also addressed the effect of timing of PPI use on GERD symptoms when they gave 40 mg of esomeprazole to GERD patients 30 min before or after breakfast, reporting no difference in symptom control. These studies suggest that the optimal administration timing hypothesis is neither an essential nor generalizable determinant of symptomatic response in GERD patients and that universal institution of optimal timing of PPI administration is unlikely to provide a substantial cost saving. How then can we put the Waghray et al. observations into perspective?

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Waghray et al. focused on a particular subgroup of subjects (i.e., those with GERD-like symptoms who achieved an incomplete clinical response to PPI therapy not taken 20–30 min before breakfast [7]). Their population was incompletely described; for example, they specifically excluded those with normal upper endoscopy within 1 year, Barrett's esophagus, or strictures, but did not specify whether all had endoscopy nor what proportion had erosive esophagitis, or whether they included patients with functional reflux. Their premise was that their intervention improved the effectiveness of pH control, which in turn improved the observed outcomes. Nevertheless, the authors did not provide objective evidence of a consistent effect on any physiologic measure such as cumulative esophageal acid exposure. Although some subjects received instructions in order to standardize patient instructions and expectations (e.g., you have symptoms because you were not taking the drug properly), the authors did not state whether a unified script was used. The study included randomization regarding the timing of PPI administration, but the design did not fully prevent bias: for example, to distinguish between improvement resulting because the physician "changed something" versus improvement related to a change in timing of PPI administration would require a different design such that each subject could receive a pill before and after breakfast consisting of the PPI and an identical placebo in order to prevent subjects being aware of when the PPI was given.

The Waghray et al. study specified a relatively low PPI dose (20 mg of presumably generic omeprazole). In contrast, the Boltin et al. study specified a high dose of 40 mg of esomeprazole which is equivalent to 64 mg of omeprazole with median intragastric pH > 4-times of ~ 45% and 60%, for these doses of omeprazole and esomeprazole, respectively) [5, 9].

It is unclear whether GERD patients with inadequate symptomatic response to low-dose PPI therapy fit a characteristic profile in terms of acid secretion, esophageal acid sensitivity, or esophageal acid exposure. While the group means of intragastric pH in response to PPI therapy are reproducible [10], there is considerable individual variation such that the mean or median pH > 4-times are only of limited usefulness when discussing an individual patient [11]. As shown in Fig. 1, the grouping of subjects with high or low pH > 4-times remained recognizable when tested (in this example) with a different PPI. This question can probably be answered from the data available within the large number of published studies addressing this issue.

Heterogeneity among GERD patients may also affect outcomes. For example, the Boltin et al. study [9] evaluated apparently average GERD patients, whereas Waghray et al. [7] studied patients with persistent heartburn while taking a PPI and with a defined pattern of timing of PPI ingestion termed suboptimal. There are numerous potential causes of an inadequate response to PPIs; to obtain generalizable results will likely require inclusion of patients characterized by parameters such as acid secretion measurements, pH > 4-times, esophageal acid exposure measurements, mucosal impedance, the presence or size of a hiatal hernia, enhanced esophageal acid sensitivity, or other reproducible anatomical characteristics and physiological measurements. For those with a high rate of gastric acid secretion, lengthy or very highly acidic esophageal pH exposures, and/or low pH > 4-times PPI effectiveness would likely be a critical variable, and we believe it is likely that improvement would relate to increase the omeprazole equivalents administered

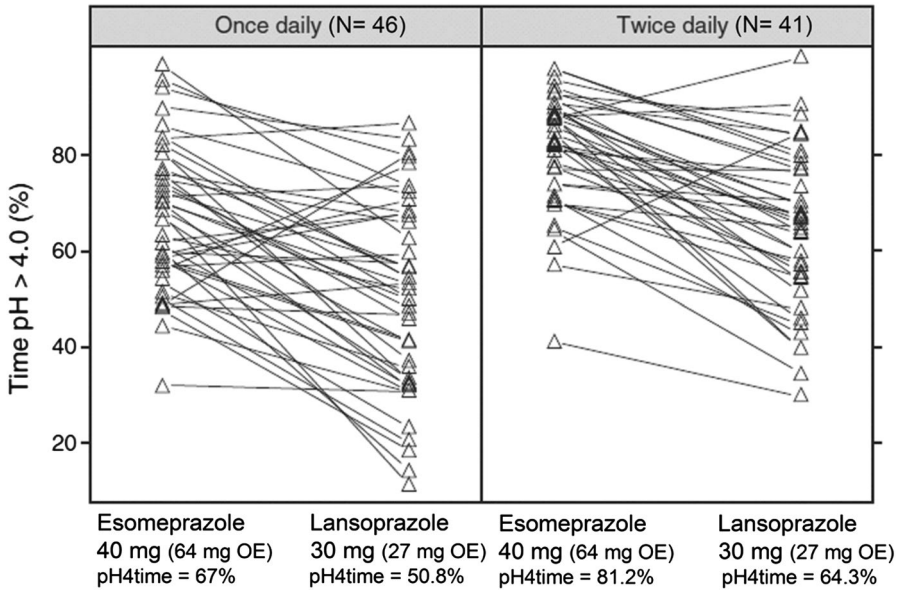

Fig. 1 Percentage of time during the 24-h monitoring period the intragastric pH < 4 stratified by treatment regimen. The omeprazole equivalents, OE, are shown for each PPI [5] as well as the mean pH 4-time. Adapted from Spechler et al. [11]

once or twice daily. This approach has been shown to increase pH > 4-time [5] and symptom response [12]. Further studies of large group of patients with what is considered to be inadequate PPI responses are needed to allow reliably identify subgroups for which specific therapy can be tailored to their primary abnormality, which in turn would enable the construction of reliable treatment algorithms.

Recommendations

One unproven assumption regarding persisting GERD symptoms while receiving PPI therapy is that the majority of sufferers have symptoms due to continuing esophageal acid exposure. Traditionally, the initial approach has consisted of physical maneuvers to reduce acid reflux such as elevation of the head of the bed, the elimination of late evening meals and smoking, a change in the timing of PPI administration, or in the recommended dose and type of PPI. Understanding relative PPI potency in terms of improving pH > 4-time increases PPI effectiveness by increasing the omeprazole equivalents administered, the frequency of PPI administration, or both. Omeprazole equivalents can be increased by increasing a PPI's dose or substitution of a more potent PPI [5]. The most marked increase in pH > 4-time is obtained by using twice-a-day dosing (i.e., approximately 10 mg of omeprazole twice a day is equivalent to 40 mg of esomeprazole or rabeprazole once a day.) [5]. Since PPIs also vary remarkably in cost to the patient, it should be possible to select a combination of PPI and once or twice-a-day dosing that is most cost-effective in any specific locality.

Summary

The Waghray et al. [7] study was a small study seeking a simple answer to a large and very complex question. The conclusion that in chronic usage, the importance of the timing of PPI administration in relation to breakfast (i.e., optimal administration) is the primary determinant of outcome appears either false or, at least, not generalizable. The notion that standardization of the timing of PPI administration will improve overall patient satisfaction and markedly reduce costs also seems unlikely. Nonetheless, this study brings attention to the important problem of failure to achieve symptom relief for some GERD patients and undoubtedly will stimulate many additional studies.

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Compliance with ethical standards

Conflict of interest Dr. Graham is a consultant for RedHill Biopharma regarding novel *H. pylori* therapies. He has also received research support for culture of *Helicobacter pylori* and is the PI of an international study of the use of antimycobacterial therapy for Crohn's disease. He is also a consultant for BioGaia in relation to probiotic therapy for *H. pylori* infection and for Takeda in relation to *H. pylori* therapies.

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Digestive Diseases and Sciences
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CASE REPORT

Necrotizing Pancreatitis: Common and Uncommon Sequelae and Solutions

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Keywords Ascites · Portal vein compression · Therapeutic endoscopy · Endoscopic stenting · Multimodal imaging

Introduction

Acute pancreatitis is the most common indication for hospitalization in the USA among all digestive diseases [1]. Cases of acute pancreatitis may be complicated by various local as well as systemic sequelae. Fluid accumulation in and/or around the pancreas represents a common complication and can lead to pseudocyst or walled-off pancreatic necrosis (WOPN) formation, which, in some instances, may cause mass effect on surrounding structures. Here, we present the first reported case of acute portal hypertension with new onset ascites formation due to compression of the main portal vein by a large WOPN collection. In addition, we describe the multimodal approach to addressing the patient's comorbidities, dual anti-platelet therapy need, and large-volume ascites (a relative contraindication to transluminal procedures) in the development of a comprehensive treatment plan for the WOPN and its associated complications.

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Case Presentation

A 69-year-old man with hypertension, dyslipidemia, asthma, and history of Takotsubo cardiomyopathy was transferred to our institution for management of acute pancreatitis. The patient initially presented to an outside hospital with progressive abdominal pain, distension, nausea, and jaundice and was found to have acute pancreatitis likely secondary to gallstones. His initial 3-week hospital course was notable for pneumonia, sepsis, and antero-septal myocardial infarction complicated by ventricular tachycardia necessitating automatic implantable cardioverter-defibrillator placement and initiation of dual anti-platelet therapy.

Physical examination revealed an ill-appearing, tachypneic, jaundiced, Latino male in acute distress. The abdomen was distended, dull to percussion, and tender in the epigastrium. Laboratory indices were significant for hemoglobin 9.0 g/dL, leukocytes 10.9×10^9/L, platelets 238×10^9/L, alanine aminotransferase 51 U/L, alkaline phosphatase 1648 U/L (normal 8–48 U/L), bilirubin 3.8 mg/dL (normal < 1.2 mg/dL), albumin 1.5 g/dL, creatinine 0.7 mg/dL, and international normalized ratio 1.2.

Computed tomography demonstrated an encapsulated, heterogeneous collection measuring $11 \times 21 \times 9$ cm with portal vein compression and large ascites in the setting of normal liver appearance (Fig. 1). Pre-procedural paracentesis was performed with removal of 8 L of fluid, with fluid analysis significant for SAAG > 1.1 (serum albumin 1.7 g/dL, ascitic fluid albumin 0.5 g/dL) and ascitic protein 2.2 g/

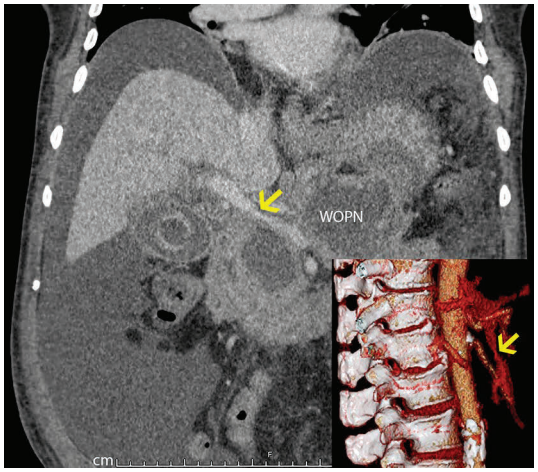

Fig. 1 Cross-sectional imaging demonstrating 11×21×9 cm walled-off pancreatic necrosis (WOPN) collection causing main portal vein compression. Note the liver contour and parenchyma appear relatively normal. Inset: Three-dimensional vascular reconstruction of computed tomography images reveals critical stenosis of portal vein related to compression from WOPN

dL consistent with hepatic ascites. Endoscopic ultrasound (EUS) revealed an echovariable collection posteroinferior to the stomach, with the shortest WOPN–gastric wall window measuring 1.5 cm (Fig. 2) despite large-volume paracentesis the day prior. A multi-disciplinary decision was made to pursue endoscopic ultrasound (EUS)-guided WOPN drainage as a minimally invasive therapeutic measure in lieu of surgical necrosectomy in light of the patient's comorbidities. In preparation for the procedure, clopidogrel was held for 3 days and large-volume paracentesis performed the evening prior. An Olympus curved linear array (GF-UCT180) echoendoscope was used to intubate the stomach; lumen-apposing stent (Hot AXIOS, Boston Scientific, Marlborough, MA, USA) placement was attempted but unsuccessful due to inadequate inter-flange length (Fig. 2 inset) relative to the combined thickness of the gastric wall, residual ascites fluid, and WOPN wall. Therefore, a 10×60 mm WallFlex (Boston Scientific) biliary fully covered self-expanding metallic stent (FCSEMS) was used to achieve endoscopic WOPN-gastrostomy, through which a 10 Fr×5 cm double-pigtail stent (Cook Medical, Winston Salem, NC, USA) was deployed for anchoring purposes (Figs. 3, 4). Within 2 days, the patient's abdominal pain began to improve, serum liver tests trended toward normal, ascites accumulation subsided, and clopidogrel was resumed. Two weeks later, the patient underwent single-session endoscopic necrosectomy through the FCSEMS, after which the FCSEMS was removed and a new double-pigtail stent placed through the existing transgastric track as a bridge to cholecystectomy. On 3-month follow-up, ascites had resolved, serum liver tests had normalized, and the patient had returned to his usual activities.

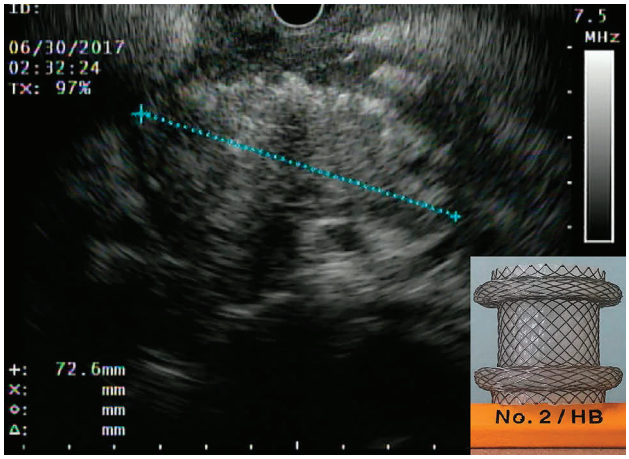

Fig. 2 Endoscopic ultrasound findings showing a 7.2-cm-diameter section of the WOPN. Despite this corresponding to the site where the shortest WOPN–gastric wall window was encountered, the window was still long at 1.5 cm. Inset: Image of AXIOS stent for size illustration purposes. The inter-flange length of the AXIOS stent measures 10 mm, and the diameter of the inter-flange segment (i.e., body) measures 10 mm as well (15 and 20 mm diameter models are also available, though they have the same inter-flange length of 10 mm)

Discussion

Fluid accumulation in and/or around the pancreas, such as pseudocysts or WOPN, is complication of acute pancreatitis for which specific terminology has been recently established

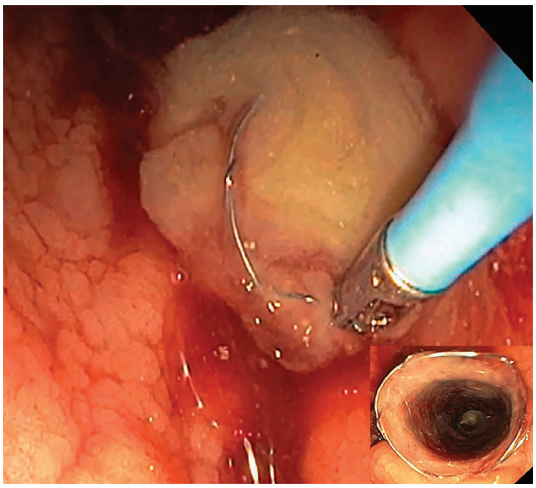

Fig. 3 Endoscopic image showing immediate drainage of turbid fluid from the WOPN collection into the gastric lumen upon placement of a 10×60 mm biliary fully covered self-expanding metallic stent (FCSEMS). Inset: Endoscopic view through transgastric FCSEMS after suctioning out liquid component of the WOPN

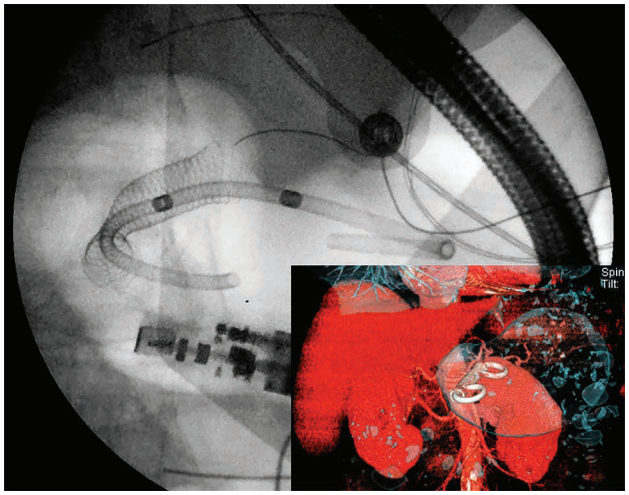

Fig. 4 Fluoroscopic image obtained after success transgastric placement of the 10×60 mm FCSEMS, through which a 10 Fr×5 cm double-pigtail stent was deployed for anchoring purposes. Inset: Three-dimensional reconstruction of computed tomography images demonstrating FCSEMS bridging the gastric lumen and WOPN lumen, anchored by the double-pigtail stent within it

to help ensure appropriate diagnosis and management [2]. Collections in the first 4 weeks following an episode of acute pancreatitis are referred to as "acute necrotic collections" or "acute peripancreatic fluid collections" depending on the presence or absence of necrosis, respectively. Collections which persist for approximately 4 weeks and become encapsulated are termed "pseudocysts" and "WOPN," respectively. WOPN can be distinguished based on clinical context and imaging features, as it is internally heterogeneous, generally not spheroid in shape (e.g., may be serpiginous in morphology), and may track or extend to nearly any portion of the abdomen. The pathogenesis of WOPN is thought to be related to disruption of the main pancreatic duct with leakage of pancreatic enzymes, causing auto-digestion of the pancreatic parenchyma and surrounding tissues (e.g., mesenteric adipose). The evoked inflammation can result in large epithelialized lesions that may cause symptoms through multiple mechanisms, as noted in the present case.

Large organized fluid collections (pseudocysts or WOPN) causing mass effect on adjacent structures have been previously described in the literature [3]. For example, gastric or duodenal outlet obstruction with recurrent nausea, vomiting, and weight loss can be seen in patients with large pseudocysts [3]. Other reports have described obstruction of the biliary system, urinary system, and inferior vena cava, with the former resulting in jaundice and hepatic dysfunction [4]. These complications may be managed by advanced endoscopic, interventional radiologic, or surgical techniques, depending on patient- and provider-level considerations. Multiple studies have compared endoscopic versus surgical cystogastrostomy and have shown that the endoscopic approach is less costly, with lower complications rates, and improvement in quality of life outcomes [5–7]. Although there remain a dearth of prospective randomized trials, endoscopic necrosectomy appears to be favored for a large proportion of collections related to acute pancreatitis; however, the endoscopic approach may require approximately 1–2 more necrosectomy sessions compared the (single-session) surgical approach.

The case presented herein is unique and clinically instructive, demonstrating that: (1) acute ascites can result from WOPN compressing the portal vein, (2) this and other sequelae (e.g., biliary obstruction) can be successfully resolved via endoscopic WOPN-gastrostomy, (3) while a distance ≥ 1 cm between the gastric wall and WOPN cavity can complicate endoscopic intervention and indeed preclude the existing lumen-apposing metallic stent (i.e., AXIOS) placement, (4) EUS-guided drainage with careful use of longer FCSEMSs can, in select cases, provide safe, effective, and minimally invasive management, and (5) although ascites has been considered a relative contraindication to endoscopic drainage, pre-procedural paracentesis and appropriate stent selection can help facilitate endoscopic drainage and avoid leakage.

Conclusion

Compression of the main portal vein by WOPN leading to acute development of ascites is a rare complication of acute pancreatitis. Successful endoscopic drainage of WOPN can lead to complete resolution of ascites. Although a distance ≥ 1 cm between the gastric and WOPN wall and the presence of ascites can complicate transluminal drainage and preclude the use of conventional endoscopic accessories, pre-procedure therapeutic paracentesis and selective use of longer stents can facilitate safe and effective EUS-guided drainage as a minimally invasive alternative to surgical intervention.

Author's contribution JHT, MD, and AY acquired data and images; AT and AK drafted the manuscript; JHT, JP, and MD provided critical revisions of the manuscript; all authors approved of the final manuscript.

Compliance with ethical standards

Conflict of interest None.

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SPECIAL SECTION: PANCREATITIS

Acute pancreatitis: an update on the revised Atlanta classification

Stephanie D. Colvin[1] · Elainea N. Smith[2] · Desiree E. Morgan[2] · Kristin K. Porter[2]

Abstract
Acute pancreatitis (AP) is the most common gastrointestinal disease resulting in hospitalization in the United States with reports of over 270,000 hospitalizations and costs up to 2.6 billion dollars per year. AP is highly variable in disease course and outcome. Established in 1992, the original Atlanta classification system aimed to categorize the wide spectrum of AP by creating consensus-based terminology for AP types, severity, and complications. Though the original system standardized terminology, certain terms and definitions (i.e. pancreatic abscess) were unclear and often misused. The 2012 revised Atlanta classification (RAC) system updated terms, clarified definitions, and incorporated the medical community's improved understanding of the physiology of AP. The resulting RAC effectively defined the morphologic types of pancreatitis, provided a more standardized system for disease severity grading, further classified the local retroperitoneal complications, and established objective measures to describe this highly variable but common disease. This review provides an update on the recent literature evaluating the RAC, discusses both the strengths and shortcomings of the RAC system (including problematic interobserver agreement), and considers improvements for future classification systems.

Keywords Acute pancreatitis · Revised Atlanta classification · Severity grading · Imaging appropriateness

Introduction

Acute pancreatitis (AP) is the most common gastrointestinal disease resulting in hospitalization in the United States with reports of over 270,000 hospitalizations and costs up to 2.6 billion dollars per year [1, 2]. AP is a highly variable disease, ranging from brief, self-resolving episodes to multimonth-long admissions complicated by multiorgan failure and widespread infection. Gallstones are the most common cause of AP in the United States, followed by alcohol [3]. The 1992 original Atlanta classification system for AP created consensus-based terminology for types, severity, and complications of AP. After 20 years of application, the revised Atlanta classification (RAC) was established to clarify terminology and more specifically categorize AP and its complications. In the time since the RAC was established, the literature has revealed its strengths primarily in its well-defined diagnostic criteria, outline of temporal relationships for local complications, and distinct three-tiered severity grading. Though the literature has edified the RAC's strengths, it has also uncovered apparent shortcomings including interobserver variability in interpreting local complications, limitations of a three-tiered severity grading system that does not incorporate infection, and a non-uniform system for determining organ failure and severity.

Purpose of the original Atlanta classification

Established in 1992, the original Atlanta classification system for AP created consensus-based terminology for types, severity, and complications of AP. These definitions were determined by 40 diverse pancreatitis professionals including gastroenterologists, radiologists, and surgeons, among others over the course of a 3-day meeting. The purpose was to create "a clinically-based classification system for AP" to be used not only by radiologists, but also by managing physicians and researchers alike [4].

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Why revision was necessary

After the original Atlanta classification, improved understanding of disease evolution and progression, advances in imaging, and misuse of terminology indicated to the pancreas community a need for revision. While advances in contrast-enhanced computed tomography (CECT) and magnetic resonance imaging (MRI) have improved radiologic identification and characterization of AP, better defined clinical parameters and acumen for diagnosing pancreatitis reduced the need for early imaging except in select cases [5, 6]. Additionally, persistently ambiguous terminology from the original classification and heterogenous use of terms became a means of controversy within the field [7]. In 2012, 20 years after the original classification was established, the revised Atlanta classification (RAC) was published [8]. The RAC updates terminology, definitions, and types of complications of AP (Table 1). With a similar purpose, the RAC aimed to clarify the previously established universal classification system while integrating updated terminology of local complications and severity grading.

Changes in revision from original

The RAC updates were created to improve the universal usability of the system. The RAC defines diagnostic criteria for AP, including establishing onset, distinguishes between morphologic types, divides the disease course into distinct phases, establishes specific severity categories, and clarifies the terminology for local retroperitoneal complications identified by imaging.

Diagnosis and types

The RAC establishes a clear definition of AP diagnostic criteria. AP is diagnosed by any two of the following criteria: (1) characteristic epigastric abdominal pain, (2) serum lipase and/or amylase greater than 3 times the upper limit of normal, and (3) evidence of AP on imaging [8]. Thus, the diagnosis of AP no longer warrants imaging confirmation if the first two clinical criteria are met.

The original Atlanta classification also failed to provide a distinction between types of AP, stating only that "pathologic changes in AP represent a continuum, with interstitial edema and minimal histologic evidence of necrosis at the minor end of the scale and confluent macroscopic necrosis

Table 1 Revised Atlanta classification (RAC) terminology and corresponding definitions

RAC terminology	
Term	Definition
Onset	Time of onset of *abdominal pain*
Early phase	< 1 week after onset
Late phase	> 1 week after onset
Acute complication	Occurs < 4 weeks after onset. Includes acute peripancreatic fluid collection and acute necrotic collection
Delayed complication	Occurs > 4 weeks after onset. Includes pancreatic pseudocyst and walled-off necrosis
Mild AP	No organ failure, usually short course and self-resolving
Moderately severe AP	Transient (< 48 h) organ failure and/or local complications
Severe AP	Persistent (> 48 h) organ failure, often includes local and systemic complications
Interstitial edematous AP	Type of AP characterized by diffuse inflammation and enlargement of the pancreas. CECT with *homogenous enhancement* of parenchyma often with peripancreatic fat stranding. Lower mortality, usually mild and self-limiting
Necrotizing AP	Type of AP characterized by necrosis of pancreatic parenchyma and peripancreatic tissues. CECT with *unenhanced/minimally enhanced* hypodense areas within the parenchyma, in peripancreatic tissues only, or both. Higher mortality and level of severity
Acute peripancreatic fluid collection	Acute complication of interstitial edematous AP characterized by a collection of homogenous fluid *without necrosis or a defined wall*
Acute necrotic collection	Acute complication of necrotizing AP characterized by a collection of *both fluid and necrosis without a defined wall*
Pancreatic pseudocyst	Delayed complication of interstitial edematous AP characterized by a *well-defined, encapsulated collection of homogenous fluid with little-to-no necrosis*
Walled-off necrosis	Delayed complication of necrotizing AP characterized by *well-defined encapsulated collection of fluid and necrosis of the pancreatic parenchyma, the peripancreatic retroperitoneal fat, or both*

AP acute pancreatitis, *CECT* contrast-enhanced computed tomography

at the other extreme" [4]. The RAC divides AP into two morphologic types: interstitial edematous AP and necrotizing AP (Fig. 1). It subsequently emphasizes differences in severity and outcomes by type. Interstitial edematous AP represents 85% of AP with a low mortality rate of only 3% [9]. It is characterized by diffuse inflammation and enlargement of the pancreas with homogenous pancreatic parenchymal enhancement on CECT, usually with stranding of peripancreatic fat [8, 10]. It is classically mild and self-limited, often resolving within 1 week without intervention [8]. Complications of interstitial edematous AP are usually local and include acute peripancreatic fluid collection (APFC) and sometimes subsequent pancreatic pseudocyst.

Necrotizing AP represents 15% of AP with a much higher mortality rate of 17%, which rises to 30% if infected necrosis is present [9]. Necrotizing AP involves necrosis of pancreatic parenchyma and peripancreatic tissues with unenhanced or minimally enhanced hypodense areas within the parenchyma, in the peripancreatic tissues only, or most often both on CECT [10]. Clinical complications of necrotizing AP are many, including local complications such as acute necrotic collection (ANC) and subsequent walled-off necrosis (WON), and systemic complications including organ failure, pancreatic and/or extra-pancreatic infection, and exacerbation of pre-existing disease [11, 12].

Phases

The RAC additionally establishes two distinct phases of AP that have important management implications, an early phase and a late phase. The early phase is the first week following onset of clinical symptoms. The late phase is the time after the first week. Each phase is characterized by distinct clinical, radiologic, and pathologic features and challenges.

Early phase

The early phase is defined by a systemic inflammatory response to pancreatic injury and typically lasts 1 week. Early phase assessment includes recording the time of onset, evaluating if the patient meets diagnostic criteria, and, most importantly, determining the presence and duration of organ failure. Onset is defined as the initial onset of abdominal pain and serves as an important measure for duration of organ failure [8]. Organ failure is defined as cardiovascular, respiratory, and/or renal failure. The RAC recommends use of the modified Marshall scoring system over the Sequential Organ Failure Assessment (SOFA) score, which is applied only in critical care settings [8]. The modified Marshall score utilizes FiO_2 (respiratory), serum creatinine (renal) and systolic blood pressure (cardiovascular) to assign a score. A score greater than or equal to 2 qualifies as organ failure [8, 13]. A meta-analysis by Petrov et al. showed a mortality rate of 30% in patients with AP and organ failure [14]. Making a definitive diagnosis of acute pancreatitis and excluding other common pathologies with upper abdominal pain (cholecystitis, peptic ulcer disease, etc.) is important in order to begin treatment promptly [15]. Importantly, cross sectional imaging is less useful during the early phase, particularly within the first 72 h, as the extent of disease and local complications are evolving and may not be fully apparent (Fig. 2) [6, 16].

Late phase

The late phase involves continued monitoring for local complications and worsening systemic disease. Patients with moderately severe and severe pancreatitis tend to have more local and systemic complications, with organ failure most common in severe cases. Imaging, particularly CECT, has

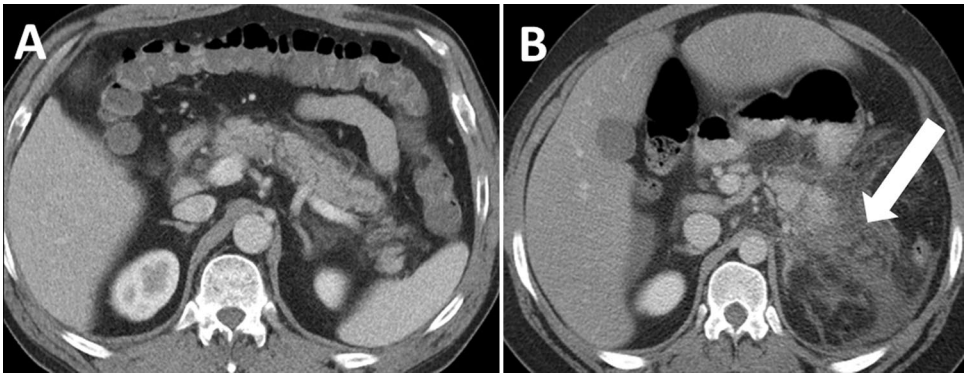

Fig. 1 Interstitial edematous AP compared to necrotizing AP. **a** Intravenous contrast-enhanced CT (CECT) axial image in a 49-year-old man with ethanol induced acute pancreatitis with onset 2 days prior shows a diffusely edematous pancreas with peripancreatic stranding, consistent with interstitial edematous AP. **b** CECT axial image in a 27-year-old man with 1 week history of abdominal pain demonstrates a diffusely edematous pancreas with peripancreatic stranding but also geographic, markedly diminished enhancement in the pancreatic tail (arrow), consistent with acute necrotizing pancreatitis

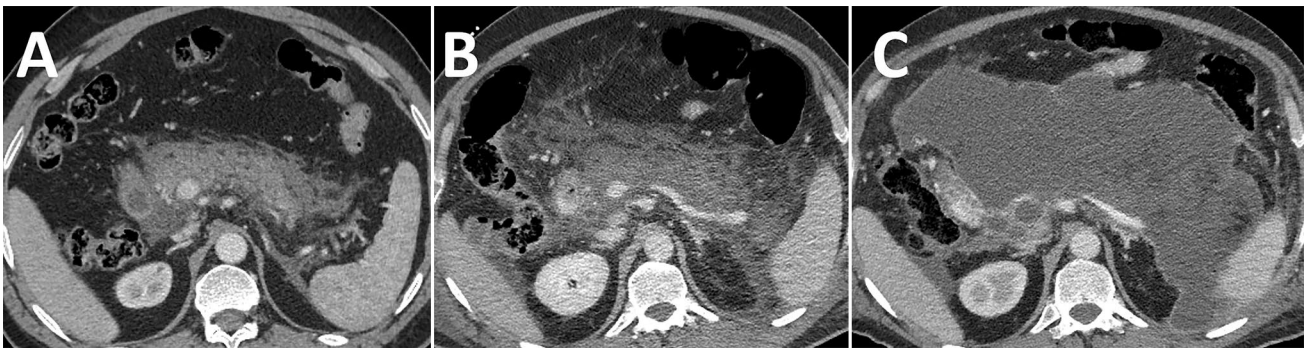

Fig. 2 Increased value of imaging over time. **a** CECT obtained 1 day after symptom onset in a 56-year-old man shows peripancreatic fat stranding and fluid most consistent with acute interstitial edematous pancreatitis. Areas of hypoenhancement or necrosis are not seen. **b** Six days after onset, the patient developed bilateral flank pain and Grey Turner sign. CECT now shows severe necrotizing pancreatitis with only a small amount of residual enhancing pancreatic parenchyma in the head/uncinate process. **c** Three weeks after onset, CT demonstrates ANCs. The largest collection extends into the left retroperitoneum and measures 28.9 × 12.2 cm. No residual enhancing pancreatic tissue is identified

value during the late phase as local complications become more evident with time. Persistent organ failure and systemic complications are continually managed while imaging aids medical decision-making. By defining specific phases and emphasizing the importance of diagnosis and severity grading, the RAC offers greater guidance for clinical and imaging decision-making and provides an objective framework for the management of a highly variable disease.

Severity grading

Arguably the most impactful change in the revised criteria, the RAC establishes a three-tiered severity grading system. The grading system is divided into mild, moderately severe, and severe AP based on the presence and duration of organ failure. Mild AP is defined by no organ failure and typically has a short, self-resolving course. Moderately severe AP is defined by transient organ failure (present for less than 48 h) and/or local complications. Severe AP is defined by persistent organ failure (present for greater than 48 h) often with local and systemic complications [8]. Persistent organ failure is associated with higher mortality and increased risk of local complications, thus requiring management that is more aggressive [12, 17].

Approximately, 15–20% of AP episodes will progress to severe AP [3]. The majority of severe AP have necrotizing AP, whereas only 1–3% of interstitial edematous AP progress to severe cases [18]. Severe AP has a mortality of 15–30% compared to mild AP which has a mortality of 0–1% [19]. In the setting of severe necrotizing AP, infected necrosis can further increase mortality twofold [14]. This updated severity grading and implementation of evidence-based organ failure scoring systems have created an objective and consistent stratification to guide disposition and management; in contrast the original classification described "mild AP" and "severe AP" based on the presence (severe) or absence (mild) of organ failure.

Local complications

The original Atlanta classification defined local complications such as "acute fluid collections", "acute pseudocyst" and "pancreatic abscess" [4]. While the establishment of universal terminology was valuable, misuse of these terms and poor interobserver agreement made a revision necessary [20–22]. Local complications are identified and monitored by imaging, particularly CECT. They can be divided into acute (< 4 weeks after onset) vs. delayed (> 4 weeks after onset) complications, and are typically dependent on whether interstitial edematous AP or necrotizing AP were present at the outset.

Acute

The original classification described "acute fluid collections" as an early complication of AP yet did not differentiate the contents of such fluid collections. As defined by the RAC, acute local complications occur within 4 weeks from onset and include APFC and ANC [8]. APFC occurs in interstitial edematous AP and is characterized by a collection of homogenous fluid without evidence of necrosis or a defined wall (Fig. 3). ANC occurs in necrotizing pancreatitis and is characterized by a collection of both fluid *and* necrosis without a defined wall (Fig. 4). When the necrosis involves the pancreatic parenchyma, distinguishing a collection as an ANC is easier than when the ANC is limited to the peripancreatic tissues alone (Fig. 3b).

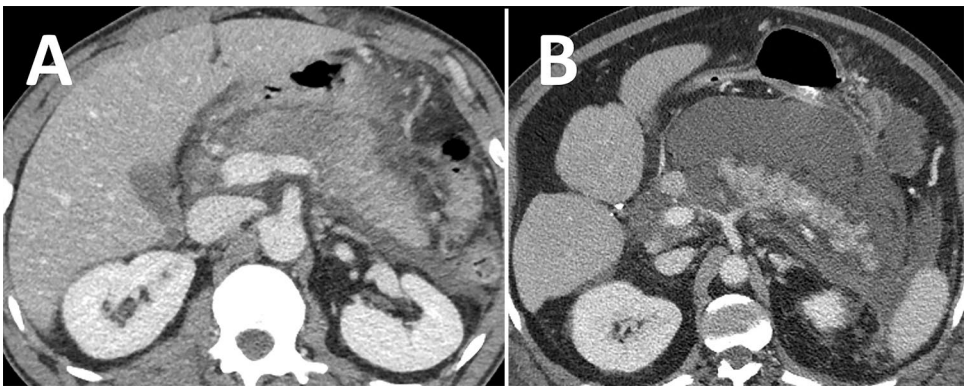

Fig. 3 Acute peripancreatic fluid collections (APFC). Two examples of patients with interstitial edematous AP with APFCs. **a** Axial CECT image in a 46-year-old man 1 day after symptom onset shows an APFC surrounding the pancreas and tracking into the left anterior pararenal space. **b** In a different patient, a 58-year-old man 5 days after symptom onset, an APFC is seen surrounding the pancreas and incorporating foci of retroperitoneal fat suggesting that extra-pancreatic necrosis is developing

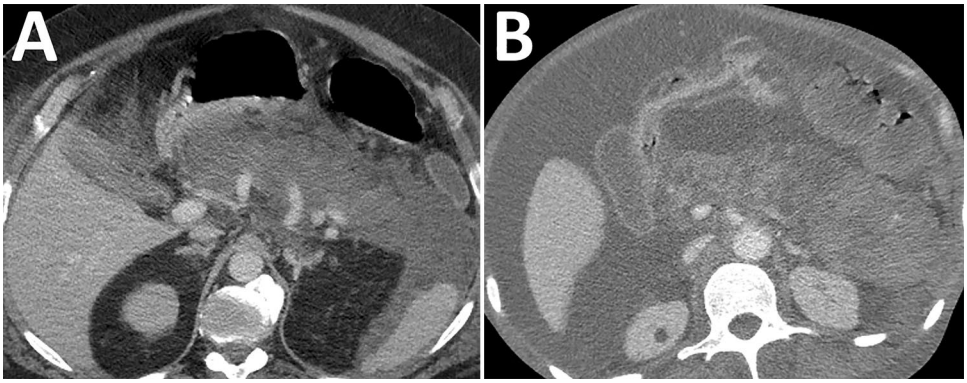

Fig. 4 Acute necrotic collections (ANC). Two examples of patients with necrotizing AP with ANC. **a** Axial CECT image in a 58-year-old man obtained 7 days after symptom onset demonstrates replacement of the entire pancreas with a non-enhancing, hypodense collection with poorly defined margins, consistent with an ANC. **b** Axial image CECT in a 28-year-old woman obtained 2 weeks after symptom onset demonstrates severe necrotizing AP with associated surrounding hemorrhage, hemoperitoneum, and a low attenuation collection anterior to the pancreatic head

Delayed

Late complications arise greater than 4 weeks after onset and include pancreatic pseudocyst and walled-off necrosis. A pancreatic pseudocyst occurs in interstitial edematous AP and is characterized by a well-defined, encapsulated collection of homogenous fluid with little-to-no necrosis (Fig. 5). Walled-off necrosis is present in necrotizing AP and is characterized by a well-defined encapsulated collection of fluid and necrosis of the pancreatic parenchyma, the peripancreatic retroperitoneal fat, or both (Fig. 6). The original Atlanta classification and the RAC describe the composition and timing of pseudocyst development (> 4 weeks after onset) similarly; however, use of the term "acute" in the original classification is not consistent with this longer course of development and was dropped. Possibly the most controversial term established in the original Atlanta classification, "pancreatic abscess" was previously described as a well-circumscribed non-necrotic collection of pus, typically developing greater than 4 weeks after onset [4]. This was a separate entity from infected necrosis in that it required positive bacterial or fungal cultures *in the absence of* a necrotic source. Often the term pancreatic abscess was inaccurately used to describe an infected necrotic collection In practice, a true pancreatic abscess is very rare [22]. Thus, the term pancreatic abscess has been abandoned in the RAC.

Application

Though not intended as a management guide, the RAC has affected practice by emphasizing: (1) diagnostic criteria, (2) severity grading, and (3) classification of local complications.

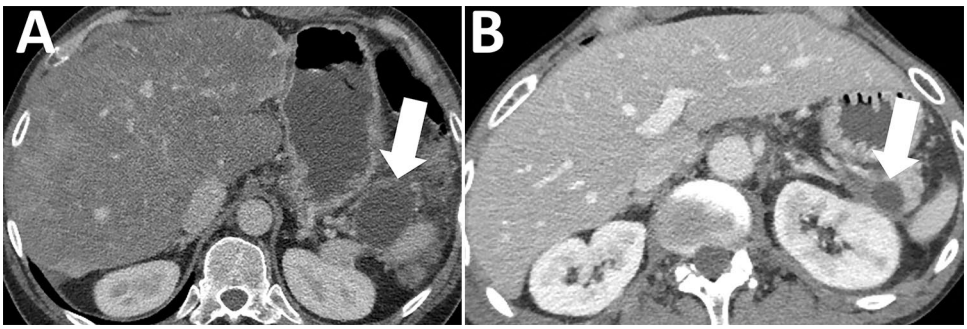

Fig. 5 Pancreatic pseudocyst. Two patients with interstitial edematous AP with development of pancreatic pseudocysts. **a** Axial CECT image obtained 1 month after symptom onset in a 49-year-old man shows a well-demarcated uniform low attenuating lesion in the pancreatic tail consistent with a pancreatic pseudocyst (arrow). **b** 52-year-old male with history of interstitial edematous AP onset 6 weeks earlier reveals a 1.7 cm pseudocyst (arrow) in the pancreatic tail

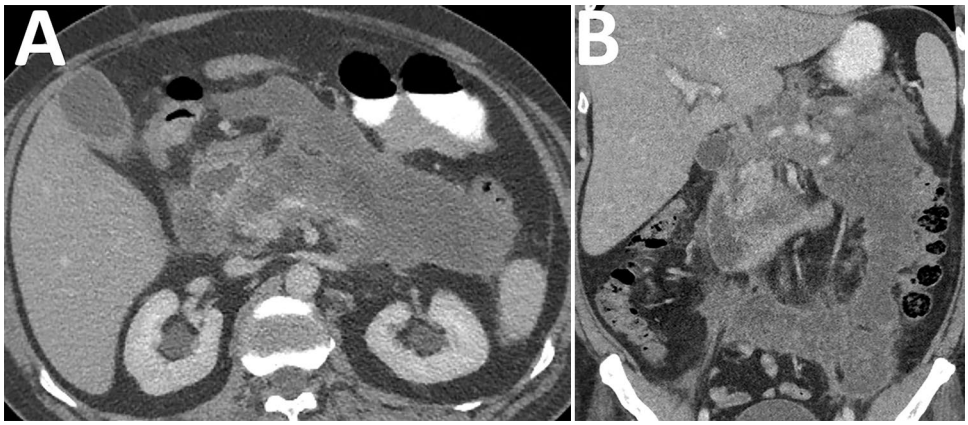

Fig. 6 Walled-off necrosis (WON). 52-year-old male 5 weeks after onset of necrotizing AP with WON involving the pancreatic body and tail that extends towards the splenic hilum laterally and along the left anterior pararenal space inferiorly seen on **a** axial CECT and **b** coronal reformatted image

Establishing a definitive diagnosis

The RAC's diagnostic criteria of AP provide an objective outline that physicians, radiologists, and researchers can apply easily. These criteria allow practitioners to diagnose AP without imaging, sparing the patient from unnecessary radiation exposure and reducing healthcare costs. Both the American College of Gastroenterology and the American College of Radiology Appropriateness Criteria recommend performing CECT and/or magnetic resonance imaging (MRI) only in patients with an unclear diagnosis or who do not improve within 48–72 h of admission [23, 24]. Additionally, studies show that early imaging rarely affects management in uncomplicated cases [6, 25]. In a study excluding patients with severe pancreatitis, Reynolds et al. showed that while 63.3% of patients with suspected pancreatitis were imaged, imaging affected management in only 1.2% of patients [16]. Despite these criteria set forth in the RAC, Shinagare et al. showed that over half of patients who met AP diagnostic criteria without imaging, underwent imaging regardless [5] and others stress that physicians need to actively apply specified diagnostic criteria in their medical decision-making [26].

Severity guides management

Given that the RAC severity grading system in the first week is primarily based on the presence or absence of organ failure, it is imperative to assess organ failure status at presentation. The RAC recommends use of the modified Marshall scoring system to determine organ failure. A variety of other scoring systems are often applied to predict severity and guide early management, including the Acute Physiology and Chronic Health Evaluation (APACHE) II, Ranson criteria, Computed Tomography Severity Index (CTSI), Bedside Index of Severity in AP (BISAP), and Systemic Inflammatory Response System (SIRS) criteria. Organ failure in AP is associated with higher mortality and can occur early or late in disease [14, 17, 27]; and different scoring systems may be used at different times in the patient's illness. Despite widespread use of prediction scores, there is no standardized severity prediction scoring system and the clinical utility of these systems is unclear [28]. However scored, all cases of

severe AP should be managed in an intensive care or high acuity unit with close monitoring [29, 30]. Contrast this to mild AP, which is typically managed with supportive care only.

Ignatavicius et al. showed that compared to the two-tiered original Atlanta classification, the RAC three-tiered system is more accurate and better at predicting complications, treatment needs, and outcomes in patients with AP [31]. Also established in 2012, the determinant based classification (DBC) of AP is based on local (necrosis, infection) and systemic (organ failure) determinants to divide severity into four groups: mild, moderate, severe, and critical [32]. This classification is based on similar principles to the RAC, and both have been shown to predict mortality and ICU admission better than the original Atlanta classification [33]. Despite similar results, the DBC is less frequently used as it is dependent on imaging, whereas the RAC suggested Marshall score is easily applied in the clinical setting alone [34].

Clarifying complications

The updates in classification and terminology of local complications have clarified confusing and misused terms from the original classification. Studies have shown interobserver agreement to be fair to moderate for classifying local complications [35–37]. This represents and improvement from the original Atlanta classification, which had poor interobserver agreement for identification of peripancreatic fluid collections [20]. The timing of imaging is also an important consideration. Sharma et al. showed that local complications are detected more frequently when CECT is performed greater than 5 days after onset and that performing earlier CECT does not affect overall surgical management or mortality [25]. In addition to CECT, MRI is an effective method for evaluating small collections, establishing relationship of collections to ductal anatomy, and most importantly for identification of pancreatic fat and debris within necrotic collections that appear uniformly low in attenuation on CT [38, 39]. Kamal et al. found that interobserver agreement for walled-off necrosis or pseudocyst was fair using CT but moderate using MRI [39]. Thus, MRI in addition to CECT can improve characterization of complicated pancreatic fluid collections and in particular help guide management (Fig. 7).

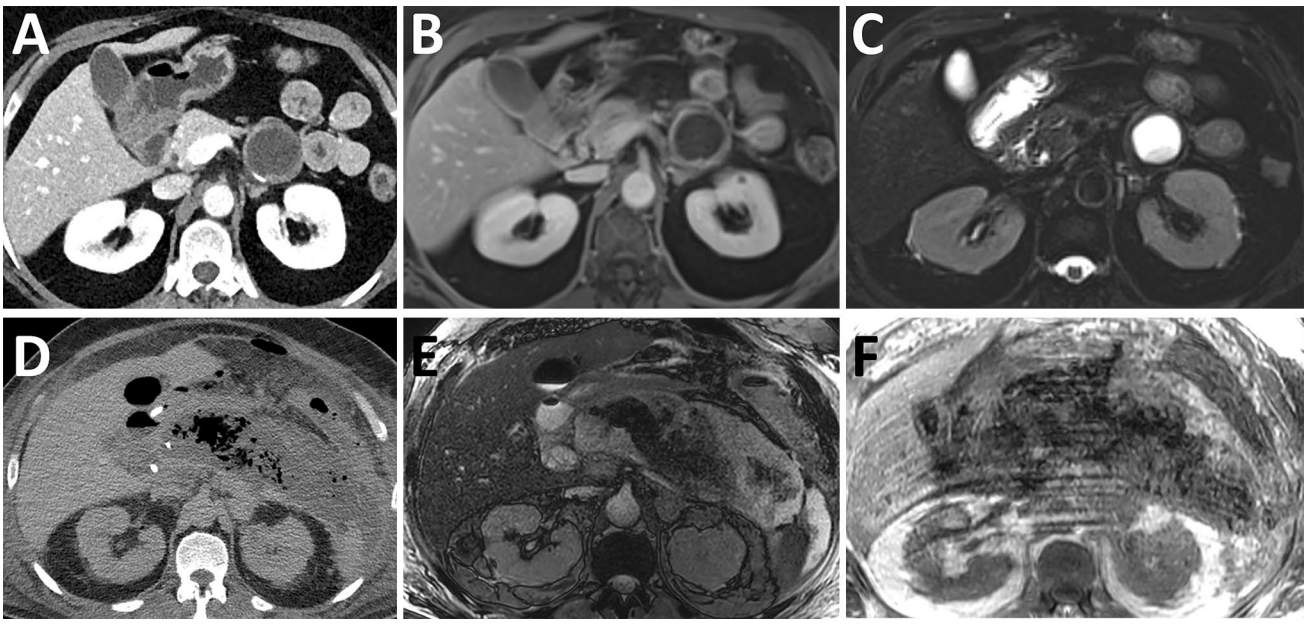

Fig. 7 MRI in addition to CECT can improve characterization of complicated pancreatic fluid collections. Top row, 60-year-old female with history of interstitial edematous AP. **a** Axial CECT 7 months after symptom onset shows a 3.8×3.8 cm cystic lesion in the tail of the pancreas with thin peripheral calcification posteriorly. **b** T1-weighted and **c** T2-weighted axial MR images of the abdomen with and without contrast, respectively, confirm that the lesion is a pancreatic pseudocyst. Axial T1 post gadolinium image reveals a well-defined wall and axial T2 weighted image demonstrates a fairly uniform hyperintense lesion within the pancreatic tail with minimal amount of dependent debris. Bottom row, 64-year-old man with acute necrotizing pancreatitis onset 6 weeks prior, now unable to receive iodinated IV contrast secondary to renal failure. **d** Axial unenhanced CT image shows a gas and fluid density collection replacing the pancreas, consistent with infected walled-off necrosis. **e** The extent of necrosis of the gland within the complex collection is more completely demarcated on the balanced turbo field echo axial image where the pancreatic sequestrum is seen amongst the fluid and retroperitoneal fat also incorporated into the collection; note that the gas is less well depicted on this series but easily detected on **f**, the unenhanced T1 mDIXON image

Shortcomings of the RAC

Though the RAC has made improvements in diagnosis, classification, and management of AP, further refinements may be made. While the RAC clarifies terminology of local complications, interobserver agreement has been less than optimal and variable among studies. Sternby showed only fair interobserver agreement for fluid collections [37], Badat et al. showed moderate interobserver agreement for detection of local complications within the first 4 weeks of disease, and Bouwense et al. reported good agreement [35, 36]. Further evaluation of interobserver agreement using larger sample sizes may shed light on the variations in results, as each of these studies evaluated a set of less than 400 CTs. Additionally, experts have better interobserver agreement than nonexpert radiologists and clinicians for determining local complications [36, 37]. However, since the purpose of the RAC was to establish a universal classification system, the usability of the system could be improved so that experts and nonexperts alike can utilize the terms accurately.

Severity grading affects management and risk stratification; however, severity prediction scoring systems are left to the discretion of the managing practitioner. This may create high variability in the initial (first 48 h) assessment and management decisions for patients. Multiple studies have shown APACHE II to be superior to others, with a higher predictive value and accuracy [40–42]. However, there is evidence that BISAP may be easier to apply in the emergency setting than APACHE II due to its simplicity [43]. Other studies have shown that APACHE II and BISAP perform similarly for predicting severity and mortality [44, 45]. Alternatively, the International Association of Pancreatology and the American Pancreatic Association recommend SIRS to predict severe AP on admission [30]. A systematic review by Di et al. evaluated 18 scoring systems, concluding that variations in sensitivity and specificity across studies make the utility of them uncertain [28]. In current practice, the decision regarding the severity prediction tool used is left to the discretion of the provider. Given the conflicting evidence, application of a universal prediction tool could be considered.

Suggestions have also been made to expand the severity grading system. Talukdar et al. showed that patients with early severe AP and patients with moderately severe AP with infected necrosis have disease that behaves more aggressively than the groups to which they were originally assigned [46]. Additionally, Choi et al. determined that mortality significantly increases in patients with severe AP plus infected necrosis vs. those without infected necrosis [47, 48]. Thus, the severity grading system may benefit from further stratification based on the presence of infected necrosis that develops over time.

Future directions

Future directions for the RAC include development of a standard severity prediction scoring system, an expanded severity grading system with assessment at other time points, and imaging techniques with better-defined descriptions of retroperitoneal collections that aid in consistent interpretations across all experience levels and medical disciplines. Larger studies and meta-analyses on severity prediction models could provide insight into the best model for guiding patient disposition. An expanded severity grading system including stratification for infected necrosis may improve our understanding and expectations regarding patient outcomes [47, 48]. Further, while the usability of the current system is far superior to the older Atlanta classification, there is variability among general and subspecialty radiologists and other clinicians in the interpretations of fluid collections and complications [36, 37]. Establishing widespread use of terminology and simplifying identification of such complications could improve medical communication and research goals.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to disclose.

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INFLAMMATORY BOWEL DISEASE (S HANAUER, SECTION EDITOR)

Maneuvering Clinical Pathways for Ulcerative Colitis

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Abstract

Purpose of Review Recent years have brought about several advances in the treatment of patients with ulcerative colitis (UC). Here, we discuss salient recommendations of recent treatment guidelines; review the efficacy, safety, and real-world data of vedolizumab and tofacitinib; appraise their place vis-à-vis established agents; and consider the newly proposed approaches of risk-stratified and treat-to-target therapy.

Recent Findings Once daily oral mesalamine dosing is equivalent to split dosing in mild–moderate UC. Real-world data are accumulating on the effectiveness and safety of vedolizumab for moderate to severe UC, while there are few such data on the most recently approved agent, tofacitinib. High-dose infliximab is being investigated for severe UC. New approaches are challenging the established paradigm of selecting therapy based on current disease activity. The risk-stratified approach incorporates long-term risk as well as the current burden of inflammation. The treat-to-target approach aims at improved long-term outcomes by adjusting therapy to resolve intestinal inflammation.

Summary The therapeutic options for UC are continually expanding. Risk-stratified therapy and the treat-to-target approach represent paradigm shifts in UC management. Optimal disease control requires an individualized approach that takes into consideration current inflammatory burden, long-term risk, patient preferences, and ongoing assessment of response to treatment.

Keywords Ulcerative colitis · Inflammatory bowel disease · Vedolizumab · Tofacitinib

Introduction

Until the late 1990s, the treatment arsenal of ulcerative colitis (UC) was restricted to mesalamine (5-ASA), corticosteroids, and thiopurines. The introduction of anti-tumor necrosis factor α (anti-TNF-α) agents represented a milestone in UC management [1]. Moreover, over the next few years, investigators recognized the importance of mucosal healing in improving long-term outcomes [2]. Although anti-TNF-α agents improve disease control, enhance quality of life, and prevent complications, primary non-response and loss of response (the latter, in large part, due to high rates of immunogenicity) remain significant challenges. Against this backdrop, the newly approved agents (vedolizumab and tofacitinib) hold the promise of producing significant therapeutic gains. The purpose of this article is to discuss salient recommendations of recently updated treatment guidelines; review the efficacy, safety, and real-world data on vedolizumab and tofacitinib; appraise their place vis-à-vis established agents; and discuss the newly proposed approaches of risk-stratified and treat-to-target therapy.

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Treatment Guidelines

Mild UC

The European Crohn's and Colitis Organization (ECCO) in 2017 [3] and the American College of Gastroenterology (ACG) [4••] in 2019 updated their guidelines for the management of mild, moderate, and severe UC. The American Gastroenterological Association (AGA) guidelines in 2019 addressed only induction of mild UC [5••]. Although UC severity has traditionally served as the basis for selecting therapy, there are no uniformly accepted definitions of disease severity. In the AGA technical review, mild-to-moderate UC

was defined as "<4–6 bowel movements (BM's) per day, mild–moderate rectal bleeding, absence of constitutional symptoms, and low inflammatory burden, based on biochemical and endoscopic assessment, and absence of features suggestive of high disease severity (e.g., absence of deep endoscopic ulcers, high inflammatory burden, repeated hospitalizations, and steroid-dependence)" [5••]. The ACG defined mild UC as < 4 BMs per day; intermittent rectal bleeding; mild, occasional urgency; normal hemoglobin; erythrocyte sedimentation rate (ESR) < 30 mm/h; elevated C-reactive protein (CRP); fecal calprotectin > 150–200 μg/g; Mayo endoscopic subscore of 1; and UC endoscopic index of severity (UCEIS) of 2–4 [4••]. Finally, ECCO defined mild UC as < 4 bloody BMs (per the Truelove and Witts classification) or ≤ 4 BMs daily, with or without blood (per the Montréal classification), with normal pulse, temperature, hemoglobin, ESR, and CRP [3].

For patients with extensive UC, all guidelines endorsed oral 5-ASA. Moreover, the guidelines suggested combined oral and rectal 5-ASA over oral 5-ASA alone. Whereas the AGA guidelines recommended standard 5-ASA dosing (2–3 g/day) or diazo-bonded 5-aminosalicylates (olsalazine and balsalazide) over sulfasalazine (strong recommendation, moderate-quality evidence) [5••], ACG and ECCO did not make any recommendations regarding the relative positioning of 5-ASA, diazo-bonded 5-aminosalicylates and sulfasalazine. The AGA technical review stated that oral 5-ASA doses of 2 g/day to 3 g/day (standard) or > 3 g/day (high) were more effective than doses of < 2 g/day (low) for the induction and maintenance of remission (moderate quality of evidence) [6]. The AGA guidelines [5••] recommended starting at the standard 5-ASA dose of 2–3 g/day (strong recommendation, moderate-quality evidence). In patients with a suboptimal response to standard dose 5-ASA, the AGA suggested high-dose 5-ASA (> 3 g/day) along with rectal 5-ASA (conditional recommendation, moderate-quality evidence for induction of remission; conditional recommendation, low-quality evidence for maintenance of remission). The ACG guidelines were slightly different in that they *suggested* low-dose 5-ASA (2–2.4 g/day) over high-dose 5-ASA (4.8 g/day) (conditional recommendation, very low quality of evidence). For patients with proctitis or left-sided disease, rectal 5-ASA is the treatment of choice and is preferred over rectal steroids. In these patients, oral 5-ASA can be used either as adjunctive therapy for patients with an incomplete response to rectal 5-ASA or as an alternative for patients who prefer the convenience of oral medications.

With regard to the frequency of oral 5-ASA dosing, the AGA suggested once-daily dosing rather than more frequent dosing (conditional recommendation, moderate quality of evidence) [5••]. The ACG recommended either once daily or more frequently dosing "based on patient preference to optimize adherence, as efficacy and safety are no different" (strong recommendation, moderate-quality evidence) [7]. The equivalence of these dosing strategies was reaffirmed in a recent, 48-week-long, non-inferiority trial [8] that randomized 602 subjects with UC in clinical remission to 2.4 g/day of pH-dependent–release mesalamine (Asacol®) given once daily or divided in three daily doses of 0.8 g. The non-inferiority margin was 10%. Non-recurrence rates were 88.4% and 89.6%, respectively, with a 95% confidence interval of − 6.2 to 3.7, i.e., within the non-inferiority margin. Compliance rates (97.7% and 98.1%, respectively) were comparable. Since frequent mesalamine dosing is associated with lower compliance rates in the real-world setting [9, 10], once daily dosing is the preferred strategy.

Besides 5-ASA, another option for mild–moderate UC is budesonide MMX. Budesonide has minimal systemic absorption due to extensive first-pass hepatic metabolism, while the MMX technology allows for drug release throughout the colon. In the registry trials (CORE-1 and CORE-2), budesonide MMX 9 mg daily (but not 6 mg daily) produced significantly higher rates of clinical remission and endoscopic improvement at 8 weeks compared with placebo [11, 12]. A more recent trial demonstrated the efficacy of budesonide MMX in patients with mild-to-moderate UC refractory to oral 5-ASA [13]. In this study, 510 patients with active disease while on 5-ASA ≥ 2.4 g/day were randomized to budesonide MMX 9 mg daily or placebo for 8 weeks. Baseline mesalamine was continued. In the modified intention-to-treat population, the rates of combined clinical and endoscopic remission at week 8 were 13.0% and 7.5% in the budesonide MMX and placebo arms, respectively ($P = 0.049$). The AGA guidelines suggested standard-dose oral 5-ASA (or diazo-bonded 5-ASA) over budesonide MMX for the induction of remission of mild–moderate UC (conditional recommendation; low-quality evidence) [5••]. Finally, the AGA *suggested* and the ACG *recommended* adding budesonide MMX or prednisone in patients with mild–moderate UC refractory to optimized oral and rectal 5-ASA.

With regard to maintenance therapy, the ACG recommended rectal 5-ASA for patients with proctitis and oral 5-ASA (≥ 2 g/day) for patients with left-sided or extensive UC [7]. Patients who require higher doses of oral 5-ASA to induce remission are typically treated with higher maintenance doses, but there is no robust evidence supporting this practice. In general, the ECCO recommendations for the induction and maintenance of mild–moderate UC were similar to those of the AGA and ACG. ECCO stated that rectal 5-ASA is an alternative to oral 5-ASA in left-sided UC (evidence level (EL) 1), and that combination oral and rectal 5-ASA may be used as second-line maintenance treatment (EL1) [14]. Notably, two RCTs found that combination of oral 5-ASA plus intermittent 5-ASA enemas was more effective than oral 5-ASA alone in maintaining remission [15, 16].

Moderate UC

The ACG guidelines, published in 2019 and incorporating tofacitinib, constitute the most up-to-date guidance for the treatment of moderate to severe UC [4••]. The ACG defined moderate to severe UC as > 6 BMs daily, frequent rectal bleeding and urgency, hemoglobin < 75% of normal, ESR > 30 mm/h, elevated CRP, fecal calprotectin > 150–200, Mayo endoscopic subscore of 2–3, and UCEIS of 5–8 [4••]. The ACG recommended systemic corticosteroids, anti-TNF-α agents (i.e., infliximab, adalimumab, golimumab), vedolizumab, or tofacitinib for the induction of remission [4••]. When infliximab is used as induction therapy for moderately to severely active UC, the ACG recommended combination therapy with a thiopurine (strong recommendation, moderate quality of evidence) [4••]. The thiopurines may be used as maintenance therapy in patients who achieve remission with corticosteroids (conditional recommendation, low quality of evidence), but these should not be used as monotherapy to achieve induction. The ACG recommended vedolizumab or tofacitinib after failure of anti-TNF-α therapy. Like the ACG, the ECCO recommended anti-TNF-α therapy, preferably combined with thiopurines, at least for infliximab, as one of several options for the treatment of steroid-dependent and steroid-refractory UC [3]. The ECCO guidelines differ from those of the ACG in that tacrolimus was offered as an option in patients with steroid-refractory UC [3].

Recent studies have examined the place of 5-ASA agents after escalation to biologic therapy. Ungaro et al. [17•] examined 3589 patients across two national databases (the USA and Denmark) and found that discontinuation of 5-ASA within 90 days of starting biologic therapy was not associated with adverse clinical outcomes, such as new steroid use, UC-related hospitalization, or surgery. Similar results were found in a pooled analysis of 2183 patients from the registry trials of infliximab and golimumab [18] and in 100 patients treated with vedolizumab [19]. The ACG suggested against using 5-ASA in patients with moderately to severely active UC who have failed 5-ASA therapy and are being induced with an anti-TNF-α agent (conditional recommendation, low quality of evidence) [4••].

Severe UC

The most recent guidelines for acute severe UC (ASUC) are those of ECCO (2017) [3] and ACG (2019) [4••]. Primary therapy consists of intravenous (IV) corticosteroids. When IV steroids fail, options include infliximab, IV cyclosporine, tacrolimus (in the ECCO guidelines), and proctocolectomy. Both guidelines emphasize the importance of excluding infection; endoscopic assessment of disease severity; treatment of anemia; correction of fluid and electrolyte disturbances; prophylaxis against thromboembolism; avoidance of NSAIDs, opioids, and anticholinergic agents; use of antibiotics and total parenteral nutrition only when indicated; and combined management by the gastroenterologist and the colorectal surgeon.

The increased inflammatory burden of ASUC may necessitate higher infliximab doses [20]. A recent meta-analysis found that the outcomes of dose-intensified induction were not significantly different compared to standard induction. However, these results were confounded by the greater inflammatory burden in patients who received intensified therapy [21]. In a retrospective series, 132 patients received standard infliximab therapy, while 81 received accelerated infliximab therapy (> 5 mg/kg at shorter intervals). There were no baseline differences between the groups, including levels of C-reactive protein or albumin. Rates of in-hospital colectomy were 8% and 9%, respectively (adjusted odds ratio, 1.35; 95% CI, 0.38–4.82). Similarly, there were no significant differences in the colectomy rates at 3 months, 6 months, 12 months, or 24 months. In the accelerated group, an initial dose of 10 mg/kg was associated with lower colectomy rates compared to an initial dose of 5 mg/kg followed by subsequent doses of ≥ 5 mg/kg [22]. Randomized trials are needed to assess high-dose infliximab in ASUC. The salient recommendations of recent guidelines are listed in Table 1.

Vedolizumab

Pharmacodynamics and Pharmacokinetics

Vedolizumab, approved for the treatment of UC in the USA in 2014, is a fully humanized, monoclonal IgG1 anti-α4β7 antibody. Vedolizumab blocks the binding of the α4β7 integrin expressed on circulating blood T cells to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) expressed on gut endothelial cells. In addition to gut-selective blockade of lymphocyte trafficking, other mechanisms of action may be at play [23]. This hypothesis is further supported by the observation that full α4β7 occupancy is evident at very low drug concentrations and is unrelated to response status [24]. The half-life of vedolizumab is 25.5 days [25]. Predictors of increased drug clearance include the presence of anti-drug antibodies, low albumin concentration (< 3.2 g/dl), high body weight (≥ 120 kg), and higher endoscopic score [25]. In contrast, concomitant immunomodulators, C-reactive protein, and fecal calprotectin levels do not predict drug clearance [25]. In the combined populations of the pivotal GEMINI 1 and GEMINI 2 trials ($n = 1434$), 4% of patients had anti-drug antibodies at any time during up to 52 weeks of treatment [24]. Although only 0.6% had persistent anti-drug antibodies, the rate of immunogenicity rose to 10% after patients stopped the drug. Compared to vedolizumab monotherapy, concomitant immunomodulators decreased the formation of anti-drug antibodies in patients who received interrupted vedolizumab

Table 1 Salient recommendations of the recent guidelines for the treatment of UC

Mild disease	1. Rectal 5-ASA is the first-line inductive therapy for proctitis or left-sided UC Comments: (a) Rectal 5-ASA is preferred over rectal steroids, and (b) oral 5-ASA can be used either as an adjunctive therapy for patients with incomplete response to rectal 5-ASA or as an alternative for patients who prefer the convenience of oral medications 2. Combination oral (2–3 g/day) and rectal 5-ASA is suggested over oral 5-ASA alone for the induction of remission in patients with extensive or left-sided UC 3. Once daily 5-ASA dosing is suggested over more frequent dosing 4. Standard dose 5-ASA (2–3 g/day) is recommended over budesonide MMX for induction in patients with extensive UC 5. Adding prednisone or budesonide MMX is recommended in patients who have mild UC (regardless of disease extent) and are failing optimized oral and rectal 5-ASA 6. Oral 5-ASA (≥ 2 g/day) is recommended for maintenance in patients with left-sided or extensive UC Comments: (a) Rectal 5-ASA is an alternative to oral 5-ASA in left-sided UC, (b) combined oral and rectal 5-ASA may be used for maintenance, and (c) patients who require higher doses of oral 5-ASA to induce remission are typically treated with higher maintenance doses, but there is no robust evidence supporting this practice. 7. Rectal 5-ASA is recommended for maintenance in patients with proctitis
Moderate disease	1. Systemic corticosteroids, anti-TNF-α agents (infliximab, adalimumab, golimumab), vedolizumab, and tofacitinib are recommended for the induction of remission 2. There are no recommendations regarding the relative positioning of these agents in inducing remission 3. When infliximab is used as an induction therapy for moderately to severely active UC, combination therapy with a thiopurine is recommended over infliximab monotherapy 4. After failure of anti-TNF-α therapy, options include vedolizumab or tofacitinib 5. The ACG suggested against using 5-ASA in patients with moderately to severely active UC who have failed 5-ASA therapy and are being induced with an anti-TNF-α agent
Severe disease	1. Primary therapy consists of intravenous corticosteroids 2. When intravenous steroids fail, options include infliximab, IV cyclosporine, tacrolimus (in the ECCO guidelines), and proctocolectomy

from 18 to 3% [24]. Among patients on continuous vedolizumab, anti-drug antibodies were observed in 4% of those on vedolizumab alone versus 3% among those on combination therapy [24]. In summary, vedolizumab immunogenicity rates are lower than those of the anti-TNF-α agents. Similar to the anti-TNF-α agents, interrupted vedolizumab therapy induces anti-drug antibodies. While concomitant immunomodulators reduce the immunogenicity of interrupted therapy, immunomodulators do not have any effect on the already low immunogenicity of scheduled therapy.

Efficacy

In the pivotal induction trial (GEMINI 1) [26], patients were randomized to intravenous vedolizumab (300 mg) or placebo at weeks 0 and 2 and were evaluated at week 6. Response rates at week 6 were 47.1% and 25.5% in the vedolizumab and placebo arms, respectively (difference with adjustment for stratification factors, 21.7%; 95% CI, 11.6–31.7%; $P < 0.001$). Similarly, vedolizumab was superior to placebo in the induction of remission (16.9% vs. 5.4%; $P = 0.001$) and mucosal healing (40.9% vs. 24.8%; $P = 0.001$) (PMID: 23964932). In the maintenance trial, vedolizumab responders from the induction trial or a separate open-label study were randomized vedolizumab every 8 weeks, vedolizumab every 4 weeks, or placebo for 52 weeks. At week 52, clinical remission rates were 41.8%, 44.8%, and 15.9%, respectively (adjusted difference, 26.1% for vedolizumab every 8 weeks vs. placebo [95% CI, 14.9–37.2; $P < 0.001$] and 29.1% for vedolizumab every 4 weeks vs. placebo [95% CI, 17.9 to 40.4; $P < 0.001$]). The frequency of adverse events was similar in the vedolizumab and placebo arms.

Safety

Colombel et al. [27•] analyzed the combined safety data ($n = 2932$; > 4000 patient-years of exposure) from two phase II and four phase III trials in IBD patients. The infection rate for vedolizumab was 63.5/100 patient-years (PY) compared with 82.9/100 PY for placebo. The rates of serious infection were 4.3/100 PY versus 3.8/100 PY for vedolizumab and placebo, respectively. Independent risk factors for serious infection in UC included prior failure of anti-TNF-α (HR, 1.99; 95% CIs, 1.16–3.42) and narcotic analgesic use (2.68; 1.57–4.58). Infusion-related reactions were reported in ≤ 5% of patients in each trial.

In the VICTORY consortium ($n = 1087$, CD = 650 and UC = 437) [28], serious infections occurred in 6.3% of patients (7.9/100 PY). Independent predictors of serious infection were active smoking (odds ratio (OR), 3.39) and the number of concomitant immunosuppressants (steroids or immunomodulators; OR, 1.72 per agent) [28]. Like other IgG1 monoclonal antibodies, vedolizumab crosses the placenta. Most, but not all, safety reports are reassuring in the setting of pregnancy [29–31]. The AGA IBD Parenthood Project Working Group recommended maintaining pre-pregnancy dosing, continuing dosing throughout all 3 trimesters, and resuming postpartum [32]. If possible, the working group

suggested planning the final pregnancy dose 6–10 weeks before the estimated date of confinement (or 4–5 weeks before the estimated date of confinement with every 4-week dosing).

Real-World Experience

Several studies from around the world have reported real-world experience with vedolizumab. In the VICTORY consortium ($n = 321$), 12-month cumulative rates of clinical and endoscopic remission were 51% and 41%, respectively [33•]. In the ENEIDA registry ($n = 244$), the rate of vedolizumab discontinuation was 27.6% per PY of follow-up [34]. A meta-analysis of real-world studies ($n = 9486$; $n = 4532$ CD; $n = 3216$ UC; $n = 1738$ IBD unspecified/indeterminate/other) found that vedolizumab was more effective in UC than CD [35]. Corticosteroid-free remission rates at 12 months were 42% and 31% for UC and CD, respectively. Another meta-analysis found that the pooled incidence rate of loss of response in UC was 39.8 per PY. Dose intensification restored response in 53.8% of secondary non-responders [36].

Predictors of Response

An important unmet need with inductive therapies concerns the prediction of late response and non-response. In multivariate analysis of the pivotal GEMINI 1 trial [26], predictors of response included higher drug levels and anti-TNF-α–naïve status [35, 37]. Multivariate analysis of the VICTORY consortium showed that prior anti-TNF-α exposure was associated with a lower probability of clinical (HR, 0.53; 95% CI, 0.38–0.75) and endoscopic remission (HR, 0.51; 95% CI, 0.29–0.88) [33•]. The overall colectomy rate at 12 months was 13%, 2% in the anti-TNF-α–naïve patients compared to 19% in the anti-TNF-α–experienced patients [33•].

Although vedolizumab improved rectal bleeding and diarrhea by 3 weeks of therapy in GEMINI 1, further gains were observed at weeks 4 and 6. However, these improvements were restricted to anti-TNF-α–naïve patients [38]. Dulai et al. [39] developed and validated a scoring tool for predicting treatment outcomes with vedolizumab in UC. Factors independently associated with steroid-free remission were the absence of previous anti-TNF-α exposure (+ 3 points), disease duration ≥ 2 years (+ 3 points), baseline endoscopic activity (moderate vs. severe) (+ 2 points), and baseline albumin concentration (+ 0.65 points per g/l). Patients were stratified into low (≤ 26 points), intermediate (> 26 to ≤ 32 points), or high (> 32 points) probability of response groups. The higher probability group more rapidly achieved symptom activity reductions and attained higher rates of steroid-free remission ($P < 0.001$). In the validation set, a 26-point cutoff value showed high sensitivity (93%) for identifying non-responders.

Data on the utility of therapeutic drug monitoring for vedolizumab are still being generated. To determine optimal trough concentrations associated with clinical remission, a propensity score–based case-matching analysis was performed using data from the GEMINI 1 trial [40]. The investigators adjusted for potential confounder that can affect vedolizumab clearance, including age, weight, anti-TNF-α exposure history, serum albumin, and fecal calprotectin levels. Optimal trough levels were 37.1 μg/ml, 18.4 μg/ml, and 12.7 μg/ml at 6 weeks, 14 weeks, and steady state, respectively.

Use in Specific Clinical Settings

Due to its slower onset of action compared with anti-TNF-α agents and steroids, vedolizumab cannot be recommended in patients with severe disease. Preliminary studies suggest that vedolizumab is less effective than anti-TNF-α agents in the treatment of extraintestinal manifestations of IBD [41] and no more effective than placebo in controlling UC-associated arthritis/arthralgias [42]. Perioperative vedolizumab use is not associated with increased infectious complications in UC patients who undergo colectomy [43–45]. In a recent multicenter study that compared the safety and efficacy of anti-TNF-α ($n = 131$) and vedolizumab ($n = 103$) in IBD patients who were 60 years or older (range 60–88 years), therapies were similarly safe and effective at 6 months and 12 months [46].

Tofacitinib

Pharmacodynamics and Pharmacokinetics

Tofacitinib inhibits the Janus kinase (JAK) intracellular enzymes [47]. Binding of cytokines and growth factors to their cognate receptors on the cell membrane leads to JAK phosphorylation and dimerization (JAK1/JAK3, JAK1/JAK2, JAK1/TyK2, JAK2/JAK2). In turn, activated JAKs phosphorylate and activate signal transducers and activators of transcription (STATs) proteins, which modulate genes regulating cellular hematopoiesis and immune cell function. In vitro, tofacitinib inhibits the activities of JAK1/JAK2, JAK1/JAK3, and JAK2/JAK2 with IC_{50} of 406 nM, 56 nM, and 1377 nM, respectively [48]. However, the contribution of the inhibition of each JAK dimer to the effectiveness of tofacitinib is unknown.

Tofacitinib bioavailability is 74%. Peak plasma concentration is reached within 0.5–1 h. The elimination half-life is ~ 3 h, and steady-state concentrations are achieved in 24–48 h [48]. There is no clinically meaningful effect of age, sex, body weight, or disease severity at baseline (i.e., baseline albumin

level and Mayo score) on oral clearance and thus on average plasma concentration [49••].

As the drug is cleared via the liver (70%) and kidneys (30%), it should be dosed at 5 mg twice daily (rather than at the standard dose of 10 mg twice daily) in patients with moderate hepatic impairment or moderate or severe renal insufficiency, and it should be avoided altogether in patients with severe hepatic impairment. Tofacitinib is metabolized primarily via cytochrome P450 3A4 (CYP3A4) and, to a lesser extent, via CYP2C19. The dose should be lowered to 5 mg daily in patients receiving potent inhibitors of CYP3A4 (e.g., ketoconazole) or medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole). Conversely, exposure is decreased when the drug is coadministered with potent CYP3A4 inducers (e.g., rifampin) [48].

Efficacy

The efficacy of tofacitinib was established in the pivotal induction (OCTAVE 1 and OCTAVE 2) and maintenance (OCTAVE Sustain) trials [49••]. In OCTAVE 1 ($n = 598$) and OCTAVE 2 ($n = 541$), patients with moderately to severely active UC despite previous conventional or anti-TNF-α therapy were randomized to tofacitinib (10 mg twice daily) or placebo for 8 weeks. Remission rates in the tofacitinib and placebo arms at week 8 were 18.5% versus 8.2% ($P = 0.007$), respectively, in OCTAVE 1, and 16.6% versus 3.6% ($P < 0.001$), respectively, in OCTAVE 2. Reductions in diarrhea and rectal bleeding were seen as early as 3 days of treatment [50]. In the OCTAVE Sustain trial, 593 responders to induction therapy were randomized tofacitinib (either 5 mg or 10 mg twice daily) or placebo for 52 weeks. Remission at 52 weeks occurred in 34.3% of the patients in the 5 mg tofacitinib group and 40.6% in the 10 mg tofacitinib group versus 11.1% in the placebo group ($P < 0.001$ for both comparisons with placebo) [49••]. Similar to clinical remission, tofacitinib treatment was associated with significantly higher rates of mucosal healing at week 8 (31.3% vs. 15.6% [$P < 0.001$] in OCTAVE 1 and 28.4% vs. 11.6% [$P < 0.001$] in OCTAVE 2) and week 52 (45.7% for tofacitinib 10 mg b.i.d., 37.4% for tofacitinib 5 mg b.i.d., and 13.1% for placebo [$P < 0.001$] for both tofacitinib and placebo comparisons) [49••].

Safety

In an analysis of the phase 2 and 3 trials ($n = 1157$; 1613 PY exposure) [51], there was a numerically higher incidence ratio (IR) of herpes zoster infection among patients who received tofacitinib 5 mg twice daily (2.1; 95% CI, 0.4–6.0) and a statistically higher IR among patients who received tofacitinib 10 mg twice daily (IR, 6.6; 95% CI, 3.2–12.2) versus placebo (IR, 1.0, 95% CI, 0.0–5.4). For the overall cohort (84% received average dose of tofacitinib 10 mg twice daily), IRs were as follows: death, 0.2 (95% CI, 0.1–0.6); serious infections, 2.0 (95% CI, 1.4–2.8); opportunistic infections, 1.3 (95% CI, 0.8–2.0); herpes zoster infection, 4.1 (95% CI, 3.1–5.2); malignancy (excluding non-melanoma skin cancer), 0.7 (95% CI, 0.3–1.2); non-melanoma skin cancer, 0.7 (95% CI, 0.3–1.2); major adverse cardiovascular events, 0.2 (95% CI, 0.1–0.6); and gastrointestinal perforations, 0.2 (95% CI, 0.0–0.5). The authors concluded that, except for a dose-dependent risk of herpes zoster infection on tofacitinib, the safety of tofacitinib and biologic agents in UC appeared similar. Most cases of herpes zoster infection are uncomplicated, mild to moderate in severity, and manageable without permanent discontinuation of treatment [52, 53]. Lymphoma and solid cancers were observed in patients with rheumatoid arthritis treated with tofacitinib in controlled trials and in long-term extension studies [48]. Epstein–Barr virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with tofacitinib and concomitant immunosuppressive medications [48].

In a meta-analysis of 5 five induction and maintenance UC trials (tofacitinib, $n = 938$; placebo, $n = 282$), greater increases in total cholesterol, high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c) were observed in subjects given tofacitinib compared with those given placebo [54]. The ratios of LDL-c to HDL-c and total cholesterol to HDL-c did not change significantly. Overall, the cholesterol changes were modest, reversible, and dose-dependent and were not associated with major adverse cardiovascular events.

Early, limited data suggest that prenatal exposure to tofacitinib is associated with pregnancy and newborn outcomes similar to those reported in the general population [55]. In the UC intervention studies, there were 11 cases of maternal exposure and 14 cases of paternal exposure before/at the time of conception or during pregnancy, resulting in 15 healthy newborns, 2 spontaneous abortions, and 2 medical terminations [55]. There were no fetal or neonatal deaths or congenital malformations. Given the limited data, the AGA IBD Parenthood Project Working Group recommended considering other options, particularly in the first trimester [32]. As data during lactation are limited, the working group advised against using tofacitinib in this setting [32].

There have been concerns that JAK inhibitors may increase the risk of thromboembolic events [56]. The A3921133 study is an ongoing, post-marketing study comparing the safety of two doses of tofacitinib (5 mg and 10 mg twice daily) and anti-TNF-α agents in patients with rheumatoid arthritis, aged 50 years or older, and at least on cardiovascular risk factor. Interim analysis showed that subjects treated with tofacitinib 10 mg twice daily had a statistically and clinically significant

increase in the rate of pulmonary embolism compared with patients treated with anti-TNF-α agents [57]. In addition, subjects in the high-dose tofacitinib arm had increased overall mortality compared to the low-dose and anti-TNF-α arms. In UC, a disorder already associated with an increased risk of thromboembolic events, maintenance doses exceeding 5 mg twice daily should be avoided.

Tofacitinib cannot be used in combination with other immunosuppressants [48]. Monitoring of blood counts, liver chemistries, and lipids is recommended. Patients starting therapy should be screened for latent tuberculosis and latent hepatitis B. Live vaccines should be avoided [48]. Colombel [52] recommended herpes zoster vaccination in all UC patients, regardless of age, before immunosuppressive therapy, including tofacitinib. In this regard, the Advisory Committee on Immunization Practice (ACIP) stated a preference for the recently approved recombinant, adjuvanted zoster vaccine (RZV; Shingrix®, GlaxoSmithKline Biologicals, Middlesex, UK) over the live virus vaccine [58]. RZV proved safe and effective in a randomized, placebo-controlled trial in renal transplant patients [59]. It should be noted that the ACIP has not made any recommendations regarding the use of RZV in immunosuppressed patients and that, presently, Shingrix has an indication only for immunocompetent individuals aged 50 years or older.

Real-World Experience

The real-world experience with tofacitinib in UC is limited. In a study from the University of Chicago, 58 patients, 93% of whom had failed anti-TNF-α therapy, completed at least 8 weeks of treatment [60]. At 8 weeks, 21 patients (36%) achieved a clinical response and 19 (33%) achieved clinical remission. Of the 26 patients followed for 12 months, 27% were in clinical, steroid-free remission. There were 12 systemic infections (mostly while on concomitant steroids) and one herpes zoster infection [60].

Predictors of Response

Predictors of response are beginning to be investigated. In the OCTAVE trials, response did not correlate with average drug concentration [49••]. Subgroup analysis showed that prior anti-TNF-α treatment or failure did not influence remission or mucosal healing at week 8 [49••]. A reduction in the baseline Mayo stool frequency subscore of ≥ 1 at days 3 and 7 predicted clinical response at week 8 with positive predictive values (PPVs) of 73.9% and 76.8%, respectively [50]. Similarly, reductions in the baseline Mayo rectal subscore of ≥ 1 at days 3 and 7 had a PPV of 65.0% and 69.9%, respectively, in predicting response at week 8 [50].

Use in Specific Clinical Settings

Due to its rapid onset of action, tofacitinib may be useful in hospitalized patients with ASUC. In a small case series, 4 patients with ASUC received tofacitinib 10 mg 3 times daily for a total of 9 doses [61]. Three of the patients also received IV methylprednisolone 60 mg daily, while the fourth received budesonide. All 4 patients had a rapid improvement in clinical symptoms and decline in CRP. Three patients achieved clinical remission. Of these 3 patients, one ultimately required elective colectomy 6 months after the hospitalization for multifocal dysplasia. The fourth patient was unable to achieve clinical remission. This patient had the highest CRP (242 mg/l) and colonic dilation despite previous treatment with IV corticosteroids for 1 week at an outside hospital. Despite these high-risk features, a rapid improvement in symptoms and CRP was observed until the dose was reduced 5 mg 2 times daily for maintenance on day 5. This dose adjustment was accompanied by a rapid rise in CRP and return of severe symptoms, necessitating urgent colectomy. No major adverse effects were observed during the induction phase of drug administration or up to 18 months of follow-up [61]. Case reports describe the successful treatment of uveitis/scleritis [62, 63] and pyoderma gangrenosum with tofacitinib [64].

Comparative Effectiveness

Studies of comparative effectiveness have used various methodologies. Propensity score–matched analysis by the VICTORY investigators showed that, compared to anti-TNF-α–treated patients, vedolizumab-treated patients had significantly higher 12-month rates of clinical remission (54% vs. 37%; HR, 1.54; 95% CI, 1.08–2.18) and endoscopic healing (50% vs. 42%; HR, 1.73; 95% CI, 1.10–2.73) [65]. Cumulative 12-month rates for steroid-free remission were numerically higher for vedolizumab-treated patients, but not statistically significant (49% vs. 38%; HR, 1.43; 95% CI, 0.79–2.60). The findings were consistent when stratified by disease extent and prior anti-TNF-α exposure. A network meta-analysis found that infliximab and vedolizumab were ranked highest as first-line agents for the induction of remission and mucosal healing of moderate–severe UC. Tofacitinib was ranked highest as a second-line agent [66].

The comparative safety of anti-TNF-α agents and vedolizumab was assessed using propensity score–matched analysis in the VICTORY cohort ($n = 872$ IBD, $n = 334$, $n = 436$ vedolizumab) [65]. Compared to anti-TNF-α–treated patients, vedolizumab-treated IBD patients had numerically lower rates of serious infections (6.9% vs. 10.1%; OR, 0.67; 95% CI, 0.41–1.07) and significantly lower rates of serious adverse events (7.1% vs. 13.1%; OR, 0.51; 95% CI, 0.32–0.81).

Among matched patients on biologic monotherapy ($n = 247$; $n = 142$ vedolizumab), vedolizumab-treated patients had numerically lower rates of serious infections (4.1% vs. 10.1%; OR, 0.37; 95% CI, 0.13–1.02) and significantly lower rates of serious adverse events (4.7% vs. 14.5%; OR, 0.29; 95% CI, 0.12–0.73). Finally, among matched patients on biologic therapy in combination with both steroids and an immunomodulator ($n = 137$; $n = 69$ vedolizumab), there were similar rates of serious infections (11.5% vs. 13.9%; OR, 0.81; 95% CI, 0.31–2.07) and serious adverse events (14% vs. 14%; OR, 0.66; 95% CI, 0.27–1.65).

The first randomized clinical trial comparing biologic agents in IBD was recently completed and is awaiting publication [67••]. VARSITY was a double-blind, double-dummy, randomized trial that compared standard doses of vedolizumab ($n = 383$) and adalimumab ($n = 386$) in patients with moderately active UC. The primary endpoint was clinical remission, defined as a complete Mayo score of ≤ 2 points and no individual subscore > 1 point, at week 52. Rates of clinical remission at week 52 were 31.3% and 22.5% for the vedolizumab and adalimumab arms, respectively (absolute difference = 8.8% [2.6%, 15.0%]; $P = 0.0061$). In subgroup analysis by TNF-α status, vedolizumab was superior to adalimumab among anti-TNF-α–naïve subjects (34.2% vs. 24.3%; absolute difference = 9.9% [2.8%, 17.1%]; $P = 0.0070$) but not anti-TNF-α–experienced subjects (20.3% vs. 16.0%; absolute difference = 4.3% [− 7.7%, 16.1%]; $P = 0.49$). Similar to the results on clinical remission, vedolizumab was associated with higher rates of mucosal healing at week 52 in the overall population (39.7% vs. 27.7%; absolute difference = 12.0% [5.3%, 18.6%]; $P = 0.0005$) and in anti-TNF-α–naïve subjects (43.1% vs. 29.5%; absolute difference $\Delta = 13.6\%$ [6.0%, 21.1%]; $P = 0.0005$), but not anti-TNF-α–experienced subjects (26.6% vs. 21.0%; absolute difference $\Delta = 5.6\%$ [− 7.6%, 18.8%]; $P = 0.41$). Rates of clinical response became significantly different after week 6 and remained so for the duration of the trial. A limitation of the trial concerns the lack of dose optimization. Studies have demonstrated rates of adalimumab dose escalation ranging from 20% to over 50% per year [68–72], indicating that standard dosing is insufficient in many patients. As a result, guidelines have endorsed dose optimization based on biomarkers of activity and drug trough levels [4••]. Forthcoming VARSITY data on trough levels and immunogenicity may, at least in part, explain the superiority of vedolizumab over adalimumab.

New Treatment Paradigms

Two new paradigms have emerged in the treatment of UC: risk-stratified therapy [4••] and treat-to-target therapy [73••]. The standard approach that bases drug selection on current clinical activity fails to consider long-term prognosis. As an example, a patient presenting with a mild flare may actually have a high CRP and endoscopic progression from distal disease to extensive colitis. Under the standard approach, this patient would be treated with higher mesalamine doses or budesonide MMX. In contrast, using the risk-stratified approach, the patient would be deemed high-risk based on the CRP elevation and extensive involvement and would therefore be treated with steroids plus a thiopurine, an anti-TNF agent, or vedolizumab [4••]. Other markers of increased colectomy risk include age at diagnosis less than 40, history of hospitalization, prior steroid therapy, history of *Clostridium difficile* colitis or cytomegalovirus colitis, and the presence of deep ulcers [4••]. In a step towards risk stratification, both the AGA and the ACG included endoscopic severity as well as standard clinical and biochemical parameters in defining overall disease severity [4••, 5••]. The ACG stated that "selection of induction and maintenance therapies for UC should be based on disease extent, severity, and *prognosis*" [4••]. In the future, markers of drug response (and loss of response) are expected to inform treatment decisions and may replace some, but not all, clinical markers.

Symptoms and endoscopic activity can be discrepant in many patients with UC [74, 75]. The treat-to-target approach posits that clinical remission is an insufficient treatment target in so far as persistent endoscopic and histologic activity is associated with a worse prognosis, even in patients who are in clinical remission. A large body of evidence has shown that endoscopic healing, typically defined as the absence of ulcerations and erosions, is associated with higher rates of long-term clinical remission and corticosteroid-free remission, decreased hospitalizations, a lower risk of colorectal neoplasia, and a lower risk of colectomy [2, 76–81]. Similarly, histologic activity predicts clinical relapse, corticosteroid use, hospitalization, and neoplasia [77, 81, 82]. Based on these data, the STRIDE group proposed that the treatment target in UC should be clinical/patient-reported outcome remission (defined as the resolution of rectal bleeding and diarrhea/altered bowel habits) *and* endoscopic remission (defined as a Mayo endoscopic subscore of 0–1). Histological remission was proposed as an adjunctive goal [73••]. Intrinsic to this approach are optimization of initial therapy and follow-up assessment to determine whether healing has occurred. Further therapeutic actions and assessments may be necessary until the goal of healing is achieved. In its recent guidelines, the ACG suggested mucosal healing (defined as the resolution of inflammatory changes [Mayo endoscopic subscore 0 or 1]) as a treatment goal (conditional recommendation, low quality of evidence) [4••]. Prospective studies are needed comparing treat-to-target with standard care. Patient acceptance in the community setting and cost-effectiveness will also need to be assessed.

Putting It All Together

The biggest knowledge gap concerns the relative positioning of the anti-TNF agents (vedolizumab and tofacitinib) in the treatment of moderately severe UC. Several considerations enter in the selection of therapy, including the properties of the agent (rates of induction and maintenance of remission, onset of action), the disease features in the individual patient, patient preferences, and, unavoidably, the costs to the patient and the health care system (see Table 2). We make the following general suggestions for the treatment of patients with moderately severe UC:

1. For most patients, we suggest vedolizumab over adalimumab. Forthcoming VARSITY data will allow a comparison of the efficacy and safety of the two agents at different trough concentrations. It should be noted that no randomized trials have compared infliximab and vedolizumab.
2. For patients with markers of more aggressive course (such as deep ulcers or systemic manifestations) or patients who need disease control within 2–4 weeks, we suggest anti-TNF-α therapy, preferably in combination with a thiopurine.
3. For patients with anti-TNF-α–sensitive extraintestinal manifestations (such as uveitis, arthritis, and pyoderma gangrenosum), we suggest anti-TNF-α therapy, preferably in combination with a thiopurine.
4. For patients at increased risk of infection, we suggest vedolizumab.
5. We do not use tofacitinib as a first-line therapy.

Table 2 Considerations when selecting UC therapy

Drug	Patient	Health care team
Clinical remission	Predictors of prognosis 1. Short-term (severity of inflammation) 2. Long-term	Experience of nursing staff and consultants
Rapid induction of remission	Prior response to therapy (steroids, anti-TNF-α, ≥ 1 biologics)	Health care system
Durability of remission	Extraintestinal manifestations	
Predictors of response (including therapeutic drug monitoring)	Age and comorbidities	
Mucosal healing	History of infections or malignancy	
Immunogenicity	Pregnancy	
Safety profile (including infection, malignancy, and perioperative risk)	Preferences Out-of-pocket costs	

There are limited data to inform treatment decisions in patients who have failed a biologic. Many scenarios can occur, including primary failure versus loss of response, the latter due to either escape of previously controlled disease or the development of anti-drug antibodies; failure of monotherapy versus combination therapy with an immunomodulator; failure of 1 versus ≥ 2 biologics; and steroid-responsive versus steroid-refractory disease. In the absence of robust evidence, clinical judgment remains paramount. Moreover, clinicians and patients should always consider investigational studies for such patients.

Summary

Recent years have brought about several advances in the treatment of patients with UC. Vedolizumab and tofacitinib are contesting anti-TNF-α agents as a first-line therapy for moderately severe UC. A recent trial showed that vedolizumab was superior to adalimumab in achieving steroid-free clinical remission and mucosal healing at 52 weeks. We need more data on the long-term effectiveness and safety of tofacitinib. More comparative trials are urgently needed. The paradigm of drug selection based on current inflammatory activity has been challenged by the risk-stratified approach, which incorporates long-term risk as well as current burden of inflammation. The treat-to-target approach aims at improved long-term outcomes by adjusting therapy to resolve intestinal inflammation.

Compliance with Ethical Standards

Conflict of Interest Christopher M. Johnson, Catherine D. Linzay, and Themistocles Dassopoulos declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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GASTROENTEROLOGY IN GERIATRIC PATIENTS (S CHOKHAVATIA, SECTION EDITOR)

Chronic Diarrhea Evaluation in the Elderly: IBS or Something Else?

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Abstract

Purpose of Review Chronic diarrhea is a common problem in all age groups but is a particularly challenging diagnostic problem in the elderly, since many different conditions need to be considered. The purpose of this review is to discuss the evaluation of chronic diarrhea in older individuals. It highlights those conditions that seem to occur with increased frequency in the elderly, discusses the diagnostic tests that are of greatest value in sorting out these problems, and presents an approach to evaluation that is both practical and affordable.

Recent Findings There appears to be little value in distinguishing irritable bowel syndrome with diarrhea (IBS-D) from functional diarrhea in most patients, including older individuals. Both conditions need a thoughtful analysis of potential causes that may lead to more focused treatment. Older individuals may be more at risk of having certain structural disorders, and these need to be considered when constructing a differential diagnosis. In addition, elderly patients may have atypical presentations of specific disorders that require an increased index of suspicion. Diagnostic tests generally seem to perform well in older patients but have not been validated in this cohort of patients. Although the pretest probabilities of certain diseases are different in the elderly, the conventional algorithm for assessment of chronic diarrhea should lead to a diagnosis in most cases.

Summary Better studies are needed to adequately quantitate the likelihood of different diagnoses and the operating characteristics of diagnostic tests in older patients with chronic diarrhea. Lacking that information, physicians can still do a good job of making a diagnosis in these patients by adopting a stepwise approach.

Keywords Chronic diarrhea · Elderly · Differential diagnosis · Epidemiology

Introduction

Chronic diarrhea—the habitual passage of unformed stools for > 4 weeks—is a common symptom in people of all ages, occurring in 6.6% of the population [1]. It has a broad differential diagnosis, encompassing many different structural problems, absorptive and biochemical anomalies, infections, and functional problems. Sorting out the different causes of chronic diarrhea can be difficult. The standard evaluation of patients with chronic diarrhea begins with a detailed history, complemented by a careful physical examination and basic diagnostic tests [2•, 3••]. Initially, thought needs to be given to several possibilities: (a) fecal incontinence masquerading as diarrhea, (b) iatrogenic diarrhea due to drugs, surgery, or therapeutic radiation, (c) chronic infections, and (d) irritable bowel syndrome with diarrhea (IBS-D) for those patients with abdominal pain related to changes in stool form or frequency who meet the published criteria. Most patients with IBS-D have underlying food intolerances, bile acid malabsorption, or small intestinal bacterial overgrowth which can be evaluated with therapeutic trials or further diagnostic testing. If a diagnosis has not been reached after this initial evaluation, most patients should then undergo an evaluation for structural problems with abdominal imaging (CT or MRI scan with enterography) and colonoscopy with mucosal biopsies. If diarrhea still evades diagnosis, comprehensive stool analysis can help to categorize the type of diarrhea and direct further evaluation [4].

The main question of this review is to what extent this diagnostic approach needs to be altered for older patients.

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The likelihood of having specific problems varies as patients go through life, but there is no sharp age cut-off for disease prevalence. Likewise, there is no precipitous change in gastrointestinal physiology as we age that makes one arbitrary age more relevant to this discussion than another. For purposes of this discussion though, I will define "older persons" as age 65 and above, roughly the last quarter of the average lifespan in economically advantaged countries.

Epidemiology of Chronic Diarrhea in the Elderly

Relatively few population-based epidemiologic studies of chronic diarrhea have been published from US data. Two patient-reported symptom surveys in the general population conducted 25 years apart suggest that diarrhea is common but is reported less often by older respondents than younger individuals [5, 6]. A survey in Olmsted County, MN, focused on elderly community residents aged 65–93 yielded an age- and sex-adjusted prevalence of chronic diarrhea of 14.2% (95% CI, 10.1–18.2%) [7]. A more recent national survey showed prevalences of 9.7% and 9.6% in respondents aged 60–69 and 70+ (95% CI, 6.2–13.2% and 6.3–12.9%, respectively) [1]. These studies suggest that chronic diarrhea may be somewhat more common in the elderly than in the general population. No information is available from these studies about the causes of diarrhea. Despite the widespread use of electronic health records in the USA, there is no good picture of the frequency of specific diagnoses in either younger or older patients with chronic diarrhea. Most information about disease frequency in the USA comes from tertiary centers and is subject to referral bias. Epidemiologic studies from Europe are more inclusive of data from broader populations but are still subject to variations in diagnosis coding.

Incidence and prevalence data also are complicated by the fact that older individuals tend to have more coexisting illnesses and take more medications than younger individuals. For example, the prevalence of diabetes increases in the elderly. Diabetes has been associated with an increased prevalence of diarrhea (11.2% vs. 6.0% in non-diabetics, $p < 0.0001$) [8]. In any given individual, it may be difficult to attribute diarrhea to diabetes or one of its complications, such as small intestinal bacterial overgrowth, pancreatic exocrine insufficiency, celiac disease, and autonomic neuropathy. Just by being older, elderly individuals will have had more time to develop chronic diseases and may be taking medications which may be associated with diarrhea. In addition, different diagnoses may become more common as patients age, making the prior probabilities of specific diagnoses different than in younger individuals.

All of this makes it difficult to assign accurate pretest probabilities for various problems that might be causing diarrhea in older patients. Currently, clinicians rely on their "gut feelings" about the likelihood of specific problems and use this to inform their selection of diagnostic tests in individual patients. In the future, computer-assisted algorithms will depend on more accurate assessments of prior probabilities and the operating characteristics of diagnostic tests. This information will have to come from population-based sources, such as interoperable electronic health records.

Conditions which Seem to Be More Likely Causes of Diarrhea in Older Patients

Table 1 lists the different categories of diarrhea by stool characteristics and highlights those conditions under each category which seem to be more common in older individuals. For the reasons stated above, precise prevalence data are unavailable for most of these. This list also does not take into account coexisting conditions which may make diarrhea more or less likely to occur.

Osmotic Diarrhea Patients with watery diarrhea due to ingestion of poorly absorbed substances are said to have osmotic diarrhea [4]. While ingestion of these materials in sufficient amounts will cause diarrhea at any age, some poorly absorbed substances are more likely to be ingested by older individuals.

Table 1 Causes of diarrhea that may be more common in older individuals by type of diarrhea

Watery, osmotic diarrhea
Ingestion of magnesium supplements
Sorbitol ingestion in elixirs, medications
Lactose intolerance (developing late in patients with fading lactase persistence)
Enteral nutrition
Watery, secretory diarrhea
Medications
Microscopic colitis
Inflammatory diarrhea
Malignancy
Radiation enteritis
Recurrent *Clostridioides difficile* colitis
Fatty diarrhea
Enteropathy (autoimmune, drug-induced, e.g., olmesartan)
Whipple's disease
Chronic mesenteric ischemia
Small intestinal bacterial overgrowth (SIBO)
Post-operative diarrhea
Chronic pancreatitis

For example, many older adults are advised to take calcium and magnesium supplements to try to prevent osteopenia. There may be sufficient magnesium in the dose ingested to cause diarrhea. Similarly, many older individuals take liquid medications to avoid swallowing a pill. Many of these liquid medications include sorbitol as a sweetener; this too can induce diarrhea if taken in large enough quantities.

Dietary components also may contribute to osmotic diarrhea. The best example of this is lactose intolerance in patients with lactase deficiency. Juvenile mammals depend on mucosal lactase activity to digest and absorb lactose in milk. Most mammals decrease lactase activity after weaning when it is no longer needed. Humans tend to have down-regulation of lactase activity toward the end of adolescence except for those who have inherited a mutation for lactase persistence [9, 10]. These individuals can continue to consume lactose into adult life. Even in this group, however, lactase activity may decrease in time, and previously tolerated amounts of lactose may now produce excess flatus and osmotic diarrhea. Older individuals are more likely than younger individuals to have this age-related reduction in lactase activity. Enteral feeding is another way in which poorly absorbed substances may enter the alimentary tract; it to may be associated with diarrhea in some patients [11].

Secretory Diarrhea Secretory diarrhea has a broad differential diagnosis, but relatively few of these conditions are particularly likely to happen in older individuals. Medications are a frequent cause of secretory diarrhea, and it is important to assess each patient's exposure to potential drug-induced diarrhea by reviewing the medication list [12, 13]. Because of the increasing likelihood of concurrent diseases as patients age, the number of medications consumed may go up with time making this a more likely possibility.

Despite its name (which might suggest an inflammatory type of diarrhea), microscopic colitis usually presents with a watery, secretory diarrhea. Microscopic colitis has been attributed to various medications and immune phenomena but frequently occurs without a remediable cause [14•, 15]. Epidemiologic studies from Sweden and Olmsted County show a marked increase in the incidence and prevalence of microscopic colitis in the seventh and eighth decades of life [16, 17]. Anecdotal experience in referral centers suggests that microscopic colitis is among the most common causes of secretory diarrhea in the elderly. The frequency with which it is found in older individuals makes it important to obtain colonoscopic biopsies in elderly patients being evaluated for chronic diarrhea.

Fatty Diarrhea Several conditions causing malabsorption may occur more frequently in the elderly [18, 19]. The most common presentation of Whipple's disease, infection of the gut with *Tropheryma whipplei*, is in older patients with weight loss, fatty stools, and systemic manifestations (e.g., arthritis, heart disease, neuropathy) [20]. Two other rare syndromes producing malabsorption in older patients are autoimmune enteropathy and drug-induced enteropathy (typically due to ingestion of angiotensin II receptor blockers, such as olmesartan) [21, 22]. Celiac disease does not appear to be more common in older individuals but can present for the first time at an advanced age and needs to be considered [23]. Another condition typically affecting older patients and sometimes producing fatty diarrhea is chronic mesenteric ischemia, although the weight loss in this condition may be more due to food avoidance than to malabsorption [24]. These conditions typically produce histologic changes in the small bowel mucosa and point out the need for obtaining small intestinal biopsies in older patients presenting with fatty diarrhea.

Not all conditions producing steatorrhea are associated with mucosal changes, however. In the absence of underlying diseases, aging does not produce enough reduction in exocrine pancreatic secretion to produce steatorrhea [25]. It is conceivable that aging-associated problems like diabetes may produce exocrine pancreatic insufficiency and thus the prevalence of pancreatic insufficiency may be higher in older patients than in younger patients. The course of chronic pancreatitis may differ from that in younger patients with more pseudocysts, more pancreatic exocrine insufficiency, and less abdominal pain [26]. Pancreatic insufficiency should be part of the differential diagnosis of steatorrhea, and imaging of the pancreas, functional testing, or a therapeutic trial of pancreatic enzyme replacement therapy may be part of the diagnostic evaluation.

One condition causing steatorrhea that probably is more common in older individuals is small intestinal bacterial overgrowth (SIBO) [27, 28•]. This may occur as a result of drugs inhibiting gastric acid secretion (e.g., proton pump inhibitors), structural abnormalities (e.g., jejunal diverticulosis or previous gastric surgery), or motility disorders of the upper gastrointestinal tract which may inhibit clearance of luminal bacteria (e.g., scleroderma). Since many of these underlying causes are more likely to occur in the elderly, SIBO should be a consideration in older patients presenting with steatorrhea. Frail elders may be at special risk [29]. Quantitative culture of small bowel contents or breath testing (typically with glucose) can be used to confirm or lend credence to this diagnosis [28•].

Inflammatory Diarrhea Although there may be a second peak in incidence of inflammatory bowel disease (IBD) in older patients, most patients with ulcerative colitis or Crohn's disease present at a younger age. Unfortunately, when IBD does occur in older individuals, it often has a severe course. Anyone with chronic diarrhea who has blood and/or pus in stool should be evaluated for IBD with colonoscopy regardless of age [30–32]. In addition to IBD, colonoscopy in patients with inflammatory diarrhea may reveal other problems that occur in older

patients with increased prevalence, such as malignancy or radiation enteritis.

Invasive infections can cause inflammatory diarrhea, but most of these present as acute illnesses in young and old alike [33, 34]. One exception is recurrent *Clostridioides difficile* infection, which seems to occur predominantly in older individuals who may have senescent immune systems [35, 36]. This infection occurs both in institutional and free-living settings and is an important consideration in elderly patients in whom the risk of mortality is higher than in younger patients. Initial diagnosis of *C. difficile* typically involves a screening test, such as a glutamate dehydrogenase assay (GDH) or nucleic acid amplification test (NAAT), with positive results evaluated with a second stage test (sensitive enzyme immunoassay for *C. difficile* toxin A/B or toxigenic culture). Other potential causes for loose stools, such as medications or laxative use, should be excluded by history before ordering testing for *C. difficile*, and only liquid stools should be sent for assay. Diagnosis of recurrence is tricky; organisms and spores may be excreted for weeks after the infection has subsided. Very sensitive tests, such as multiplex PCR testing, may remain positive for weeks. Confirmation of recurrence should involve toxin testing or toxigenic culture. Several recent guidelines address the management of recurrent *C. difficile* infection [37••, 38].

IBS-D and Functional Diarrhea in the Elderly

Older patients with chronic diarrhea may meet Rome IV criteria for IBS-D or functional diarrhea [39••]. Epidemiologic studies suggest that the incidence (new cases) of these diagnoses is lower in older individuals than in younger patients [40]. Moreover, plausible alternative diagnoses may be more common than in younger individuals. In my opinion, this alters the equipoise of the standard advice to make a diagnosis of IBS-D based on history alone and proceed with treatment with minimal or no evaluation. To my knowledge, this has not been studied scientifically as yet in older subjects; it should be. Clinicians should keep an open mind toward the further evaluation of chronic diarrhea in older patients and not settle on IBS-D as a default diagnosis.

Scheme for Evaluating Chronic Diarrhea in the Elderly

Although the pretest probabilities of specific diagnoses may be different in the elderly than in younger adults, I think that the same diagnostic approach previously advocated for adults with chronic diarrhea will lead to an expeditious diagnosis and specific treatment for most elderly patients [3••].

It starts with a comprehensive history, thoughtful physical examination including digital rectal examination, and simple laboratory evaluation (complete blood count, comprehensive metabolic profile, C-reactive protein level, fecal occult blood test, fecal lactoferrin (or calprotectin or smear for white blood cells), and microbiology studies). The clinician then should consider one of five different possibilities: (a) fecal incontinence, (b) iatrogenic diarrhea, (c) chronic infections, (d) IBS-D, or (e) everyone else with chronic diarrhea, including those in the other categories who have not improved with empiric therapy.

Fecal incontinence is a prevalent problem in older individuals. It comes up in this context because most patients consider incontinence to be a manifestation of severe diarrhea and use the term "diarrhea" when describing fecal incontinence. In point of fact, incontinence usually is related to malfunctions of the nerves and muscles that mediate continence and is present in approximately 5% of elderly subjects [41]. Being clear about what the patient means when they complain of diarrhea, asking specifically about the accidental passage of stool, and assessing continence dynamics with a digital rectal examination are the most straightforward ways to assess this possibility. One important problem to recognize in institutionalized elders is overflow incontinence related to fecal impaction; digital rectal examination can detect impaction if present [42]. If fecal incontinence seems likely, assessment of anorectal dynamics with anorectal manometry may be helpful, and biofeedback training may mitigate the problem.

Iatrogenic diarrhea due to drug therapy, previous surgery, and radiation therapy also may be more common in the elderly, but its exact prevalence is not known. Older people accrete more chronic illnesses over time that may be treated with drugs. Obviously, a careful history including a review of the medication list can be an important clue. A surprisingly large number of drugs have been associated with diarrhea as a side effect [12, 13]. The only way to confirm drug therapy as a cause for diarrhea is to discontinue the medication and see if diarrhea goes away. Rechallenge with the potentially offending agent can strengthen the association. If the drug is essential and cannot be stopped, reducing the dosage or adding a nonspecific antidiarrheal drug may improve symptoms.

Gastrointestinal surgeries, including bariatric surgery, bowel resection, and cholecystectomy, have been associated with diarrhea in some patients [43]. Again, older individuals are more likely than younger patients to have had surgeries because of their longer lifespans. Several different mechanisms may cause diarrhea postoperatively, including reduced fluid and electrolyte absorptive capacity, bile acid malabsorption, SIBO, and altered motility. Defining the mechanism for postsurgical diarrhea may help with treatment. Therapy with opioid antidiarrheal agents may optimize absorption by allowing more time for absorption to take place by slowing motility

[44]. Bile acid binders may help some patients with relatively small ileal resections by reducing intracolonic bile acid concentrations below the cathartic threshold, and antibiotics may suppress SIBO [28•, 45]. The extent to which diagnostic tests for these mechanisms are needed versus therapeutic trials depends on the utility of the diagnostic specific tests available to the clinician. Radiation therapy may produce ideal dysfunction or frank radiation enterocolitis which often is treated empirically with bile acid binders or opioid antidiarrheal drugs [46].

Infections usually cause acute diarrhea which subsides within a few days or weeks. Some agents can produce chronic diarrhea and should be considered in any patient presenting with diarrhea. Traditional culture and microscopy techniques can be applied, but newly developed multiplex PCR testing can identify most enteric pathogens within a few hours with a single test. As mentioned before, results of PCR testing need to be interpreted with care, however, because the tests are so sensitive [47]. PCR evidence of pathogens in the stool may reflect only transient carriage and may persist for weeks after clinical evidence of infection has subsided. When the infection is the cause of chronic diarrhea, antibiotic therapy usually is needed.

The fourth possibility to consider after the initial assessment is IBS-D or functional diarrhea. It is important that patients meet the published criteria for IBS-D before assigning this diagnosis [39••]. New onset IBS-D may be less common in the elderly than in younger patients, but it does occur. The diagnostic thought process should not stop with a diagnosis of IBS-D. Most individuals with IBS-D have one of three underlying diagnoses: food intolerances, bile acid malabsorption, or SIBO (usually without steatorrhea) [3••]. The relative frequencies of these disorders may be different in older patients with IBS-D, but this has not been studied. A food and symptom diary can help identify potential food intolerances and direct elimination diets; alternatively, a therapeutic trial of a low FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet may be tried [48•]. Diagnostic testing for bile acid malabsorption with a SeHCAT retention test (where available) or serum C4 level may be helpful in identifying bile acid malabsorption as a mechanism for IBS-D, but a therapeutic trial of a bile acid binder may be a more direct strategy in most settings [45, 49•]. SIBO can be assessed with the quantitative culture of small bowel contents or breath hydrogen testing with a variety of substrates [28•]. Alternatively, patients can receive a therapeutic trial of antibiotics targeted at SIBO. Antibiotic therapy can mitigate diarrhea due to SIBO but does nothing to address the underlying cause of SIBO, and so recurrence is likely.

Patients not falling into any of the four categories and those that do not respond to treatment for the suspected cause need further evaluation. This stage begins with additional laboratory tests (if not previously done), including testing for celiac disease (IgA anti-tissue transglutaminase and total IgA level) and a qualitative or quantitative fecal fat test. The next step is to examine the structure of the gastrointestinal tract with CT or

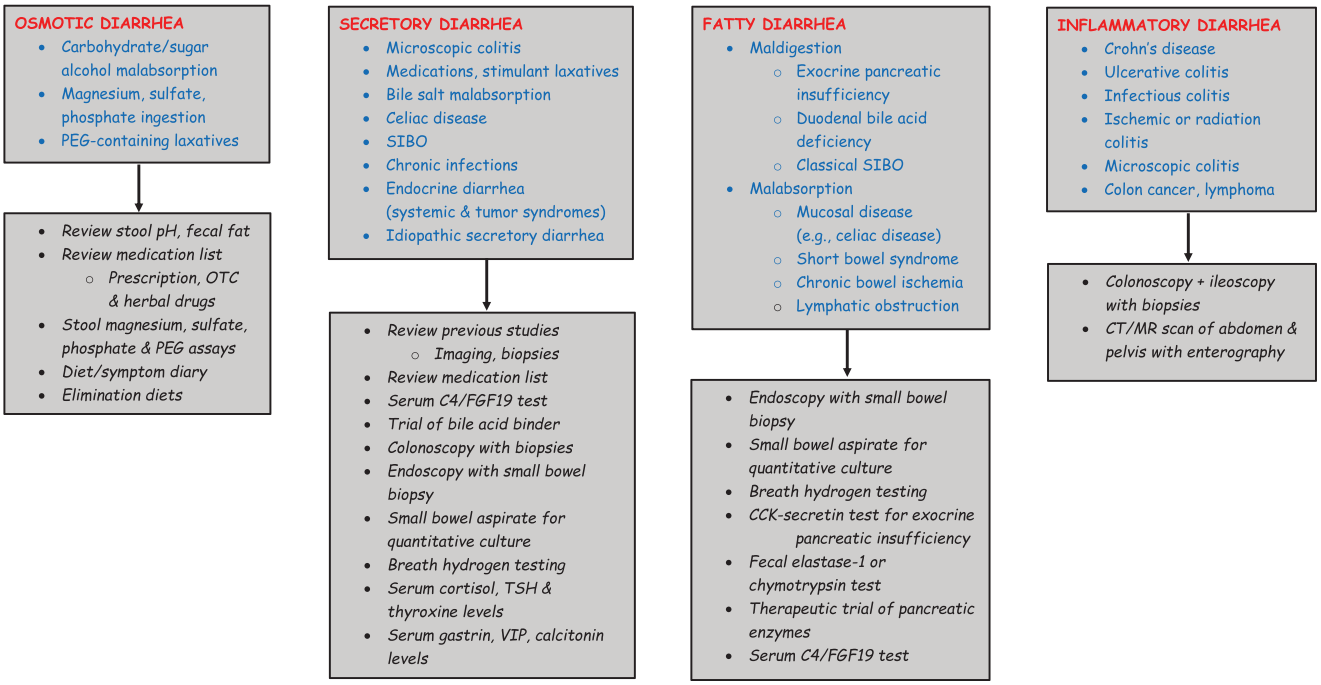

Fig. 1 Chronic diarrhea workup by type. Classification by stool characteristics limits differential diagnosis and directs further diagnostic testing. In most cases, this allows the establishment of a likely diagnosis and initiation of effective therapy (from: Schiller LR. Chronic diarrhea in the older adult. In: Geriatric Gastroenterology, 2nd ed., C. S. Pitchumoni and T. S. Dharmarajan, eds. Springer-Verlag, New York, in press)

MRI imaging with enterography and colonoscopy with biopsies. Upper gastrointestinal tract endoscopy with small bowel biopsy also should be done, if steatorrhea is present. These studies will identify many potential causes of diarrhea, including inflammatory bowel disease, microscopic colitis, malignancies, fistulas, mucosal diseases, and pancreatic disease.

If no structural problems are identified, more clues need to be assembled. This can be done by quantitative chemical analysis of stool (stool electrolytes, pH, osmolality, fat excretion) [4]. Along with testing for fecal leukocytes and red blood cells, these tests can be used to categorize diarrhea into one of three types: watery (with subtypes of osmotic and secretory diarrhea), inflammatory, and fatty. Each category has a more restricted differential diagnosis than the whole and a suite of tests that can lead to a diagnosis (Fig. 1).

Conclusions

Chronic diarrhea in the elderly presents a challenging differential diagnosis which may differ some from that in younger individuals, particularly in the pretest probabilities of specific diagnoses. Epidemiological studies should be conducted to better define the prevalence and pretest probabilities of conditions causing chronic diarrhea in older patients. The evaluation of older patients with chronic diarrhea can follow the same staged diagnostic approach advocated for other adults with a good likelihood that a diagnosis can be reached. IBS-D may be less common in older patients than in younger individuals. The canny clinician should look beyond a diagnosis of IBS-D in older patients with chronic diarrhea; often the diagnosis will prove to be something else.

Compliance with Ethical Standards

Conflict of Interest Lawrence Schiller reports personal fees from Allergan, Ardelyx, Ironwood, Salix/Bausch, Shire, Commonwealth Laboratories, Prometheus Laboratories, Abbvie and Romark, outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

The course of elderly patients with persistent hepatitis C virus infection without hepatocellular carcinoma

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Abstract

Background Little is known about the course of elderly patients with persistent hepatitis C virus (HCV) infection. We investigated the course of HCV infection in this patient population.

Methods Among 9,126 HCV antibody-positive patients who visited our hospital between 1995 and 2015, there were 453 patients with continuous follow-up who survived to age 80. They were included in the study following the inclusion criteria: confirmed persistent detection of HCV RNA, no HCV eradication if anti-HCV therapy occurred before enrollment, and no development of hepatocellular carcinoma (HCC) before enrollment. For all study patients, baseline was defined as the date when they turned 80. Mortality rates after the age of 80 years and cause of death were analyzed.

Results During the study period, 155 patients (34.2%) died. Median survival time (MST) after age 80 was 8.8 years, which was comparable to that of the general population (10.1 years). Among 155 deceased patients, the majority (115 patients, 74.2%) died due to non-liver-related disease, followed by HCC (28 patients, 18.1%) and liver-related disease other than HCC (12 patients, 7.7%). Patients with advanced liver fibrosis (FIB-4 index $> 3.25, n = 245$) had shorter MST than patients with mild liver fibrosis (FIB-4 index $\leq 3.25, n = 208$) (7.1 vs. 10.2 years; $p = 0.020$) due to a higher mortality rate from liver-related complications, including HCC.

Conclusion Most elderly HCV patients die from non-liver-related disease, especially those with less advanced liver fibrosis.

Keywords Hepatitis C · Hepatocellular carcinoma · Fibrosis · Elderly · Motility disorders

Abbreviations

ALBI	Albumin-bilirubin
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
CI	Confidence intervals
DAAs	Direct-acting antiviral agents
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HRs	Hazard ratios
IFN	Interferon
IQR	Interquartile range
MST	Median survival time
SVR	Sustained virologic response

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Introduction

Chronic hepatitis C virus (HCV) infection is a major cause of hepatocellular carcinoma (HCC) [1–3], and liver failure. The prevention of these complications is a major

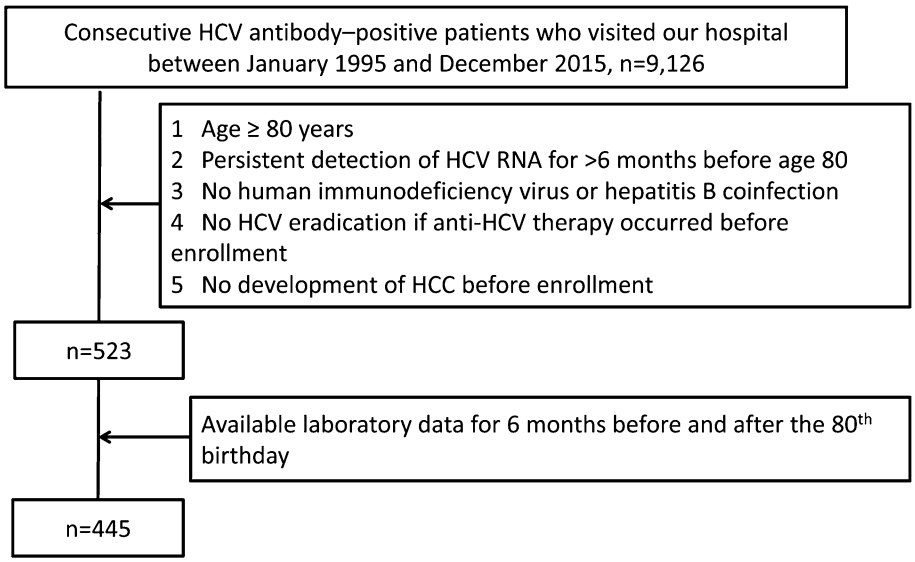

Fig. 1 Study flowchart. *HCV* hepatitis C virus, *HCC* hepatocellular carcinoma

goal of antiviral therapy in patients with chronic hepatitis C. Many studies on interferon (IFN)-based antiviral therapy suggest that sustained virologic response (SVR) is associated with resolution of liver fibrosis [4–6] and a reduced risk of HCC [7–11]. However, IFN-based antiviral therapy does not result in a high SVR rate and might not be indicated in patients with severe fibrosis or elderly patients due to its adverse effects.

In recent years, IFN-free therapies with direct-acting antiviral agents (DAAs), which have high rates of SVR, have become the standard of care for chronic HCV infection. Recent studies have reported that IFN-free therapy with DAAs might be indicated even in elderly patients [12–16]. Patients over 70 or even 80 years can undergo anti-HCV therapy with high tolerability and SVR rates, similar to younger patients [12–16]. However, it remains unclear whether the eradication of HCV in elderly patients provides survival benefit and whether they should undergo anti-HCV therapy [17]. This is partly due to the lack of information on the course of elderly patients with persistent HCV infection, especially those aged more than 80 years.

In this study, we investigated the course of elderly patients with persistent HCV infection without HCC. We evaluated overall survival and causes of death among patients with HCV infection aged 80 years or more.

Methods

Patients

Between January 1995 and December 2015, there were 9,126 consecutive HCV antibody-positive patients who visited our institution. Of these, 445 patients were included in this study based on the following inclusion criteria: (1) over 80 years of age with continuous, regular follow-up visits; (2) persistent HCV RNA detection at least twice over an interval of > 6 months before age 80; (3) absence of human immunodeficiency virus or hepatitis B coinfection; (4) no eradication of HCV if anti-HCV therapy occurred previously; (5) no development of HCC prior to this study; and (6) platelet count and other laboratory data available from within 6 months of turning 80, including serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and albumin (Fig. 1).

The study protocol was approved by the hospital's institutional review board. The study conducted in compliance with the Helsinki Declaration.

Baseline clinical data

Laboratory data collected within 6 months of turning 80 were used as baseline clinical data. To confirm the presence of persistent HCV infection, HCV RNA levels were determined using PCR-based detection methods, which consisted of COBAS AMPLICOR HCV version 2.0 (Roche Diagnostics, Tokyo, Japan) before January 2008 and COBAS TaqMan HCV (Roche Diagnostics) thereafter.

Cause of death determination

In this study, causes of death were divided into HCC, liver-related disease other than HCC, and non-liver-related disease. Data on cause of death were retrospectively collected by reviewing medical records if a patient died at our institution. In patients who died elsewhere, for example, in other hospitals, hospices, or their own home, information

regarding cause of death was obtained from the attending physician or the family physician.

Assessment of liver fibrosis severity

The FIB-4 index was used to assess severity of liver fibrosis [18]. The FIB-4 index was calculated based on baseline laboratory data using the following formula:

$$\text{Age (years)} \times \text{AST (IU/l)}/\text{platelet count } \left(\times 10^9/\text{l}\right) \times \text{ALT}^{1/2}(\text{IU/l}).$$

Age was set at 80 years for all study patients, because the laboratory data used to calculate the FIB-4 index were from samples at age 80 for all patients. HCV patients with FIB-4 index ≤ 3.25 were considered to have mild liver fibrosis (F0–F2 according to the METAVIR score) [19]. Patients with FIB-4 index > 3.25 were considered to have advanced liver fibrosis [20].

Liver function assessment

We used the recently reported albumin-bilirubin (ALBI) score to assess liver function [21]. The ALBI score was calculated based on laboratory data using the following formula:

$$(\log_{10}\text{bilirubin}[\mu\text{mol/L}] \times 0.66) + (\text{albumin}[\text{g/L}] \times -0.085).$$

Patients were assigned to one of the three groups based on their ALBI score: ALBI grade 1 (ALBI score ≤ -2.60), grade 2 ($-2.60 <$ ALBI score ≤ -1.39), and grade 3 (ALBI score > -1.39). Lower grades correspond to better liver function [21].

Statistical analysis

Characteristics of study patients were presented as medians (interquartile range [IQR]) for continuous variables and as numbers (percentages) for categorical data.

For the analysis of mortality, the 80th birthday was defined as the start of follow-up for all patients. The end of follow-up was defined as the date of death for patients who died during follow-up; these patients were not censored. Patients who survived during follow-up were censored, with the date of the final visit defined as the end of follow-up. If patients received anti-HCV therapy after age 80, they were censored on the date that anti-HCV therapy began. The Kaplan–Meier method was used to calculate mortality curves and the log-rank test was used to compare crude cumulative mortality rates. Actuarial analysis of cumulative mortality from each cause of death category (HCC, liver-related disease other than HCC, and non-liver-related disease) was performed using cumulative incidence with the competing risks method; differences across groups were tested using the Gray test. For multivariate analysis, Fine and Gray proportional hazards models with backward elimination [22] were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for disease-related mortality.

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics. Statistical significance was defined as $p < 0.05$.

Results

Patient characteristics and causes of death

Table 1 shows the characteristics of study patients at baseline, i.e., at 80 years of age, and causes of death for patients who died. The median follow-up after age 80 was

Table 1 Baseline characteristics of study patients at the age of 80

Factor	$n = 445$
Gender (female/male)	232 (52.1%)/213 (47.9%)
AST (IU/L)[a]	35.0 [26.0–49.0]
ALT (IU/L)[a]	25.0 [17.0–37.0]
Total bilirubin (mg/dL)[a]	0.60 [0.50–0.80]
Albumin (mg/dL)[a]	4.00 [3.70–4.20]
Platelets ($\times 10^3/\text{mm}^3$)[a]	165 [124–209]
FIB-4 index[a]	3.37 [2.46–4.87]
FIB-4 index ($> 3.25/\leq 3.25$)	237 (53.3%)/208 (46.7%)
ALBI grade (1/2/3)	290 (65.2%)/ 151 (33.9%) / 4 (0.9%)
HCV genotype (1/2/unknown)	232 (52.1%)/121 (27.2%) / 92 (20.7%)
Follow-up duration (years)	4.16 [2.31–6.93]
Anti-HCV therapy after enrollment	76 (17.1%)
Death	164 (36.9%)
Cause of death	
HCC	39 (23.8%)
Liver-related disease other than HCC	13 (7.9%)
Non-liver-related disease	112 (68.3%)

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *HCC* hepatocellular carcinoma, *ALBI* albumin-bilirubin, *HCV* hepatitis C virus

[a]Median, interquartile range

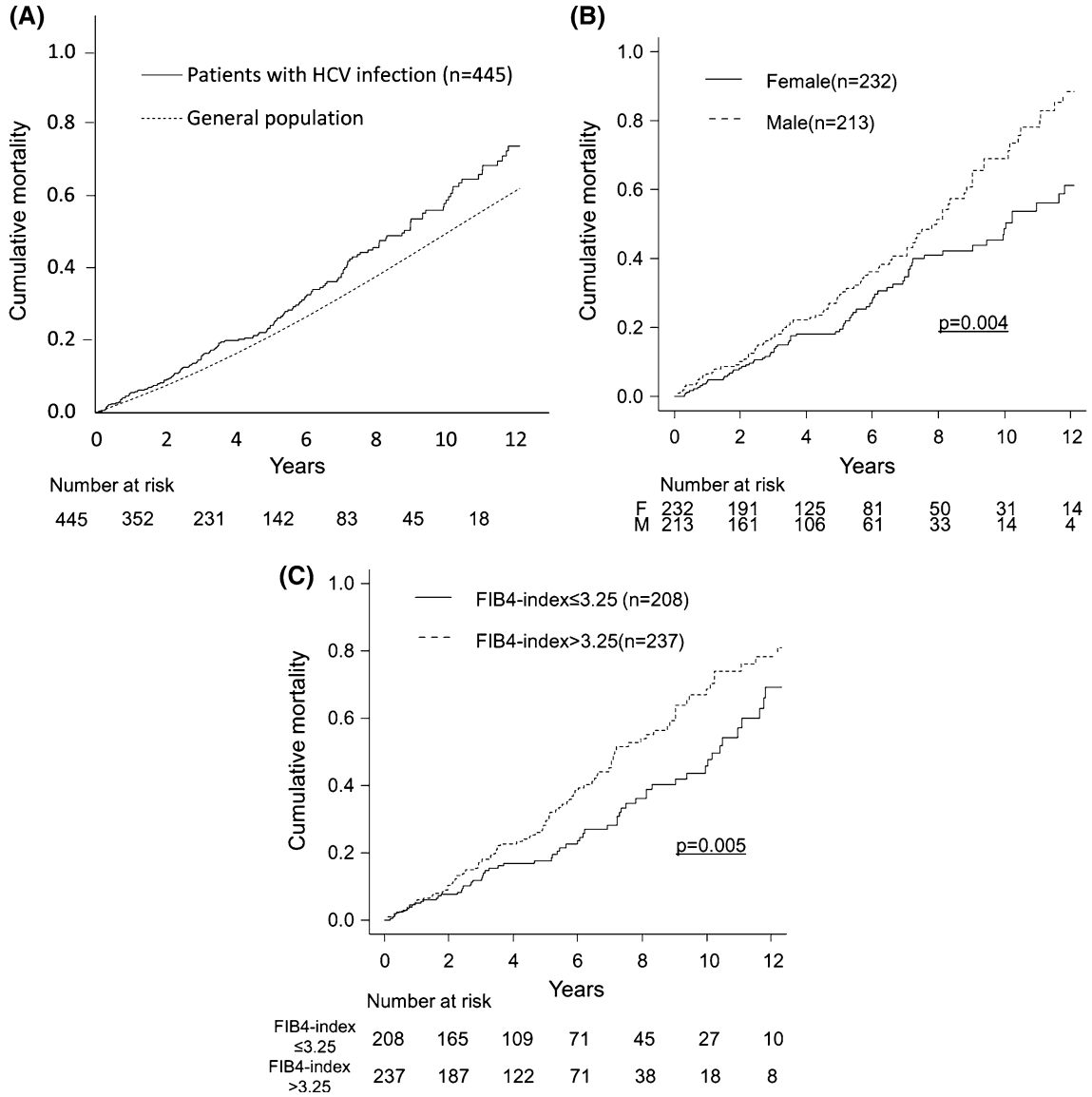

Fig. 2 Cumulative mortality of patients with persistent HCV infection who survived to age 80. **a** Comparison with the Japanese general population aged > 80 years. **b** Comparison by gender. **c** Comparison by baseline FIB-4 index. *HCV* hepatitis C virus

4.16 (IQR, 2.31–6.93) years. During the follow-up period, 164 (36.9%) patients died and 76 (17.1%) underwent anti-HCV therapy after age 80. Thirty-nine patients (23.8%) died due to HCC, 13 patients (7.9%) due to liver-related disease other than HCC, and 112 patients (68.3%) died due to non-liver-related disease.

Cumulative all-cause mortality

Figure 2a compares the cumulative all-cause mortality of HCV-infected patients after age 80 vs. the Japanese general population after age 80. The latter was calculated by matching with age and gender using "the 22nd life table" [23], which is based on the census by the Japanese government. In patients with HCV, the 5- and 10-year mortality rates were 23.4% (95% CI, 18.8–27.8%) and 58.0% (95% CI, 50.0–64.7%), respectively. They were 21.2% and 50.6%, respectively, for the Japanese general population. Median survival times (MSTs) of patients with HCV infection and the general population were 8.8 years and 10.1 years, respectively. Figure 2b compares cumulative all-cause mortality by gender. All-cause mortality was significantly higher in males than females. The 5- and 10-year mortality rates were 29.7% (95% CI, 21.1–35.5%) and 69.0% (95% CI, 56.6–77.9%) in males vs. 18.9% (95% CI, 13.1–24.3%) and 48.6% (95% CI, 37.7–57.5%) in females ($p = 0.004$). Females had significantly longer MSTs than males (10.0 vs. 7.9 years; $p = 0.004$). When all-cause mortality was compared based on the degree of liver fibrosis as assessed by the FIB-4 index, the mortality

of patients with advanced liver fibrosis (FIB-4 index > 3.25) was significantly higher than that of patients with mild liver fibrosis (FIB-4 index ≤ 3.25) ($p = 0.005$). The 5- and 10-year mortality rates were 28.3% (21.4–34.5%) and 68.6% (57.2–77.0%), respectively, in patients with FIB-4 index > 3.25. They were 17.6% (11.6–23.3%) and 45.6% (33.9–55.3%), respectively, in patients with FIB-4 index ≤ 3.25. MST was 7.1 years in patients with FIB-4 index > 3.25 and 10.2 years in patients with FIB-4 index ≤ 3.25. Despite persistent HCV infection, patients with FIB-4 index ≤ 3.25 and the general population had comparable MST.

Cumulative mortality from HCC, liver-related disease other than HCC, and non-liver-related disease

Figure 3 shows cumulative mortality from HCC, liver-related disease other than HCC, and non-liver-related disease. The 5- and 10-year cumulative mortality rates from HCC were 5.1% (3.0–7.7%) and 14.6% (10.1–20.0%) compared with 3.1% (1.6–5.3%) and 4.1% (2.2–6.9%) for liver-related disease other than HCC, and 15.4% (11.8–19.3%) and 39.2% (32.2–46.2%) for non-liver-related disease.

Factors associated with death from each cause

Univariate and multivariate analyses were conducted with Fine and Gray proportional hazards models to identify factors associated with mortality from various causes of death. Covariates included gender, baseline FIB-4 index (FIB-4 index ≤ 3.25 vs. > 3.25) as an indicator of the severity of liver fibrosis, and baseline ALBI grade (grade 1 vs. 2 or 3) as a measure of liver function. Patient age was not included, because all patients were 80 years at baseline. In the univariate analysis, FIB-4 index and ALBI grade were significantly associated with mortality from HCC. Multivariate analysis identified FIB-4 index > 3.25 as the only factor independently associated with mortality from HCC (HR, 14.27; 95% CI, 3.38–60.25; $p < 0.001$) (Table 2A).

Univariate analysis identified FIB-4 index and ALBI grade as factors significantly associated with mortality from liver-related disease other than HCC. However, in contrast to mortality from HCC, multivariate analysis identified only ALBI grade 2 or 3 as a factor independently associated with mortality from liver-related disease other than HCC (HR, 5.14; 95% CI, 1.39–19.00; $p = 0.014$) (Table 2B).

Regarding mortality from non-liver-related disease, univariate and multivariate analyses identified FIB-4 index > 3.25 (HR, 0.638; 95% CI, 0.433–0.940; $p = 0.023$) and male gender (HR, 1.796; 95% CI, 1.236–2.610; $p = 0.002$) as factors independently associated with mortality (Table 2C).

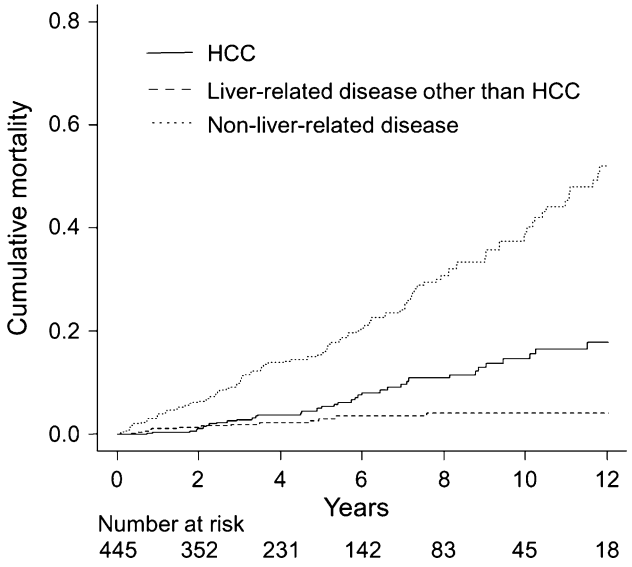

Fig. 3 Cumulative mortality of HCV patients aged > 80 years at baseline by cause of death. *HCV* hepatitis C virus

Mortality in patients with HCV infection with mild vs. advanced liver fibrosis

Figure 4 and supplementary table show the cumulative incidence of all-cause mortality and mortality by cause of death in patients with FIB-4 index ≤ 3.25, indicating mild fibrosis (Fig. 4a), and FIB-4 index > 3.25, indicating advanced liver fibrosis (Fig. 4b). A considerable proportion of patients with FIB-4 index > 3.25 died from HCC or other liver-related disease. As a result, there was a large difference in mortality from HCC between patients with FIB-4 index ≤ 3.25 vs. FIB-4 index > 3.25 ($p < 0.001$) (Supplementary figure). Mortality from HCC or other liver-related disease was low in patients with FIB-4 index ≤ 3.25; most patients with FIB-4 index ≤ 3.25 died from non-liver-related disease.

Discussion

With the marked increase in life expectancy of the general population in Japan, the number of patients with HCV infection who are surviving over 80 years is increasing. The population of Japan in 2016 is about 127 million, and people over 80 years are 10 million [24]. In addition, patients with HCV infection were predominantly high age [25, 26]. Indeed, among examinees of periodical health check-ups on 2005, HCV antibody-positive rates were

Table 2 Univariate and multivariate analyses of factors associated with mortality (A) from HCC (B) from liver-related disease other than HCC (C) from non-liver-related disease

(A) Factors	Univariate analysis		Multivariate analysis	
	Relative risk (95% CI)	*p* values	Relative risk (95% CI)	*p* values
Gender	1		1	
Female				
Male	0.993 (0.532–1.853)	0.98	0.963 (0.517–1.794)	0.91
ALBI grade				
1	1		1	
2 or 3	2.310 (1.242–4.297)	0.008	1.536 (0.819–2.880)	0.18
FIB-4 index				
≤ 3.25	1		1	
> 3.25	17.67 (4.26–73.26)	< 0.001	15.93 (3.776–67.23)	< 0.001
(B) Factors	Univariate analysis		Multivariate analysis	
	Relative risk (95% CI)	*p* values	Relative risk (95% CI)	*p* values
Gender				
Female	1		1	
Male	0.505 (0.156–1.637)	0.25	0.468 (0.142–1.546)	0.21
ALBI grade				
1	1		1	
2 or 3	6.217 (1.702–22.71)	0.006	5.149 (1.390–19.070)	0.014
FIB-4 index				
≤ 3.25	1		1	
> 3.25	4.774 (1.061–21.48)	0.042	3.231 (0.707–14.78)	0.13
(C) Factors	Univariate analysis		Multivariate analysis	
	Relative risk (95% CI)	*p* values	Relative risk (95% CI)	*p* values
Gender				
Female	1		1	
Male	1.859 (1.285–2.69)	0.001	1.807 (1.245–2.623)	0.002
ALBI grade				
1	1			
2 or 3	1.322 (0.901–1.939)	0.15	1.450 (0.978–2.151)	0.065
FIB-4 index				
≤ 3.25	1			
> 3.25	0.677 (0.468–0.979)	0.038	0.625 (0.424–0.923)	0.018

HCC hepatocellular carcinoma, *ALBI* albumin-bilirubin, *CI* confidence intervals

0.516% in patient with 50–54 years, 0.631% in patients with 55–59 years, 0.779% in patients with 60–64 years, 1.085% in patients with 65–69 years, and 1.674% in patients with 70–74 years [25]. Consequently, patients with persistently HCV infection, who are considered being candidates of DAA-based anti-HCV therapy currently, are predominantly elderly and are often 80 years or older in Japan.

Although several studies have demonstrated that DAA-based, IFN-free anti-HCV therapy has high tolerability and virological efficacy in elderly patients, it remains unclear whether the eradication of HCV reduces liver-related mortality in elderly patients aged > 80 years. The course of elderly patients with persistent HCV infection remains insufficiently characterized. HCV-related liver diseases will undoubtedly influence mortality in patients with HCC and patients have benefit from HCV eradication even elderly when patients experienced HCC. In contrast, it is unclear whether survival of elderly patients is influenced by liver complications when they did not have liver complications at baseline. The number of elderly patients with persistent HCV infection is relatively small and they are often lost to follow-up, especially they do not have liver complications. In addition, it is difficult for the hepatology department to accurately identify the cause of death when patients die from non-liver-related disease. These factors

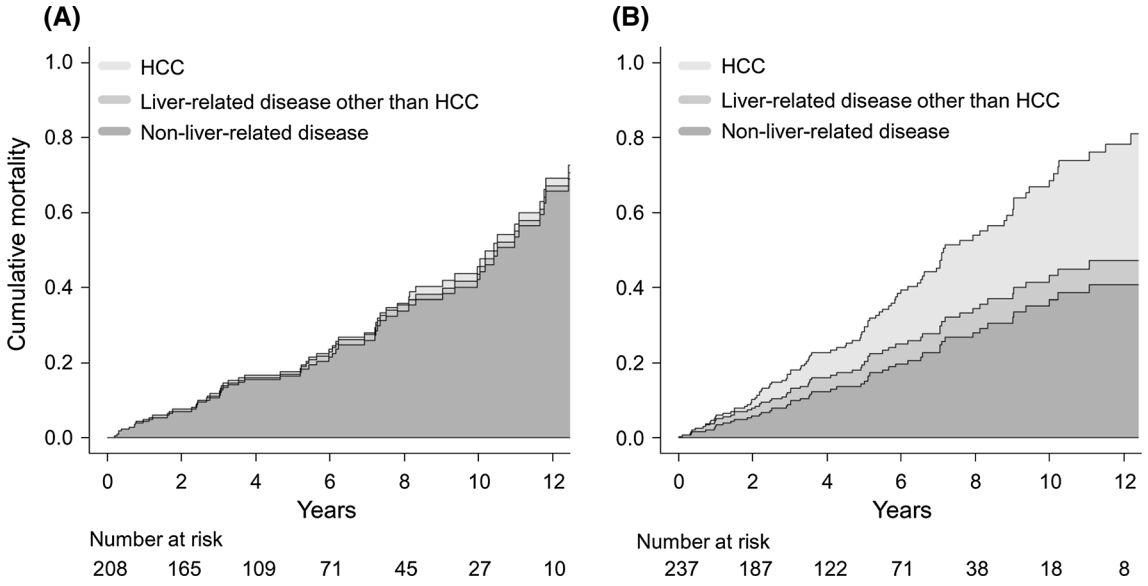

Fig. 4 Cumulative mortality of HCV patients aged > 80 years at baseline by cause of death and liver fibrosis severity. **a** Patients with mild liver fibrosis at baseline (FIB-4 index ≤ 3.25). **b** Patients with advanced liver fibrosis at baseline (FIB-4 index > 3.25). *HCV* hepatitis C virus

make it difficult to characterize the course of HCV infection in this patient population.

Our institution where this study was conducted is located in a rural area and there is relatively less migration of individuals compared to urban areas, especially among elderly patients. Therefore, we could obtain the information on long-term vital status and cause of death from most patients, making it possible to investigate the course of patients with HCV.

Our study showed that patients with persistent HCV infection had life expectancy that was not markedly inferior to that of the general population when patients have survived to age 80. The majority of patients died from non-liver-related disease despite persistent HCV infection. However, cumulative mortality of patients with advanced liver fibrosis (FIB-4 index > 3.25) was significantly higher than patients with mild liver fibrosis (FIB-4 index ≤ 3.25). Patients with advanced liver fibrosis had higher mortality from liver-related complications, especially HCC. Indeed, FIB-4 index > 3.25 is independently associated with mortality from HCC, even in elderly patients. Advanced liver fibrosis secondary to persistent HCV infection can unfavorably influence patient survival due to the emergence of liver-related complications. Therefore, HCV eradication can confer a survival benefit in this patient subpopulation.

By contrast, few elderly patients with mild liver fibrosis died from liver-related complications. Although the previous studies have reported high age as a risk factor for HCC development among patients with HCV infection despite the absence of cirrhosis [27, 28], mortality from HCC, or other liver-related complications was shown to be low in elderly patients with mild liver fibrosis; HCV eradication in this subpopulation may have less impact on the mortality than in patients with advanced liver fibrosis. However, several studies have reported that HCV eradication will have a favorable effect on extrahepatic diseases [29, 30] and it is unrevealed whether HCV eradication also reduces the mortality by non-liver-related causes or not. Given the high efficacy and tolerability of DAA therapy for elderly patients, one should be mostly careful to determine not performing DAA therapy for entire elderly patients. Further studies will be necessary for concluding whether HCV eradication will confer a survival benefit in elderly patients including those with mild liver fibrosis.

There are several limitations in this study. Some patients dropped out from the study due to the start of DAA-based anti-HCV therapy, which led to HCV eradication in most patients during the observation period; these patients were analyzed as censored cases. In addition, details about non-liver-related co-morbidities at baseline were not sufficiently available, which might have affected findings about mortality and cause of death. Finally, the results of this study were simply the course of elderly patients with persistent infection. Ideally, DAA therapy in HCV patients over 80 years will be preferable to elucidate the effect of HCV eradication on patient survivals in this patient population. However, it is actually unlikely to conduct these randomized comparisons. We believe that the course of HCV infection in elderly patients can instead provide relevant information when considering anti-HCV therapy for elderly patients.

The recent report on lenvatinib, one of the molecular-targeted drug for HCC, showed this applicability for elderly patients with HCC [31]. Thus, the emergence of DAA for HCV infection and molecular-targeted drugs for

HCC can encompass the indication of patient age to elderly, which may change the landscape of the treatment of viral hepatitis and HCC in elderly patients in near future.

In conclusion, life expectancy of patients with persistent HCV infection over 80 years of age is not markedly inferior to that of aged-matched general population. The majority of such patients die from non-liver-related disease, especially if they have mild liver fibrosis. Further studies that reveal the best cut-off of liver fibrosis index with which one can expect the benefit of HCV eradication by anti-HCV therapy in elderly patients should be necessary in the future.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Noninvasive diagnostic criteria for nonalcoholic steatohepatitis based on gene expression levels in peripheral blood mononuclear cells

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Abstract

Background Nonalcoholic fatty liver disease (NAFLD) consists of nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH); the latter progresses to liver cirrhosis and hepatocellular carcinoma. Discriminating NASH from NAFL typically involves liver biopsy. The mechanism of NASH progression is unclear but may involve immunological pathways. In this study, we examined expression levels of cytokine- and chemokine-encoding genes in peripheral blood mononuclear cells (PBMCs) from NAFLD patients and established immunological criteria for discriminating NASH from NAFL.

Methods PBMCs were obtained from 54 patients diagnosed histologically with NAFLD (NAFL, 18; NASH, 36). mRNA was extracted from PBMCs, and expression levels of cytokine- and chemokine-encoding genes were determined by quantitative real-time PCR. Statistical analysis was performed by nonparametric test.

Results Expression levels of interferon (IFN)γ, interleukin (IL)2, IL15, C–C-motif chemokine ligand (CCL)2, IL10, and C-X-C-motif chemokine ligand (CXCL)11 were significantly upregulated in NASH patients compared with NAFL patients. Moreover, their expression levels were positively correlated with the degree of ballooning of hepatocytes but not of steatosis or lobular inflammation. We focused on those encoding IL10, IFNγ, and CCL2, and developed a scoring system to discriminate NASH from NAFL. The discriminatory power of the criteria was validated in an independent cohort.

Conclusions Expression levels of the cytokine- and chemokine-encoding genes in PBMCs were positively correlated with ballooning, suggesting their utility for the diagnosis of NASH. The data indicate that peripheral as well as intrahepatic immunity is involved in the progression of NASH. Our findings afford new insight into immunological mechanisms of NASH and will facilitate its noninvasive diagnosis.

Keywords Nonalcoholic steatohepatitis · Peripheral blood mononuclear cells · Cytokine · Chemokine

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Abbreviations

NAFLD	Nonalcoholic fatty liver disease
NAFL	Nonalcoholic fatty liver
NASH	Nonalcoholic steatohepatitis
PBMC	Peripheral blood mononuclear cells
IFN	Interferon
IL	Interleukin
CCL	C–C motif chemokine ligand
CXCL	C-X-C motif chemokine ligand
CXCR	C-X-C chemokine receptor

NAS	NAFLD activity score
LPS	Lipopolysaccharide
MCP	Monocyte chemoattractant protein
TLR	Toll-like receptor
BMI	Body mass index
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
GGT	Gamma-glutamyl transpeptidase
TG	Triglyceride
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
CRP	C-reactive protein
PT	Prothrombin time
HbA1c	Hemoglobin A1c
HOMA-IR	Homeostasis model assessment insulin resistance
cDNA	Complementary DNA
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
SD	Standard deviation
LI	Lobular inflammation
Treg	Regulatory T cells
ROC	Receiver operating characteristic
AUC	Area under curve
DC	Dendritic cells
NK	Natural killer
NKT	Natural killer T
CTL	Cytotoxic T lymphocytes
HCC	Hepatocellular carcinoma

Introduction

The incidence of nonalcoholic fatty liver disease (NAFLD) is increasing worldwide, including in Japan due to lifestyle westernization [1]. NAFLD shares with metabolic syndrome various abnormalities of glucose and lipid metabolism [2, 3]. NAFLD consists of nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH); the latter is progressive and leads to cirrhosis and hepatocellular carcinoma (HCC) [4, 5]. Early diagnosis and treatment of NASH are required to prevent its progression to life-threatening conditions; e.g., cardiovascular diseases, which can be fatal [6]. The pathogenesis of NASH is related to excessive food intake, lack of exercise [7], insulin resistance [8], oxidative stress [9], inflammatory cytokines [10, 11], intestinal bacteria [12], lipopolysaccharide (LPS) [13], and bile-acid metabolism [14]. However, the mechanism underlying the progression of NASH is unclear. The diagnosis of NASH is currently based on pathological findings and requires an invasive percutaneous liver biopsy, which in practice delays diagnosis. The establishment of noninvasive diagnostic procedures or biomarkers for NASH is, thus, eagerly awaited.

The pathogenesis of NASH involves immunological mechanisms; i.e., the production of cytokines and chemokines in the blood and liver [15, 16]. For example, LPS generated as a result of intestinal dysbiosis is transported through the portal vein to the liver and induces the production of Toll-like receptor (TLR) 4-mediated C–C motif chemokine ligand (CCL) 2, so-called monocyte chemoattractant protein (MCP) 1. This activates macrophages in the blood, liver, and adipose tissue, inducing inflammation of adipose tissues and downregulating adipokines associated with the progression of NASH [17, 18]. Furthermore, the expression level of C-X-C motif chemokine receptor (CXCR) 3, expressed mainly in activated T cells as a receptor for C-X-C motif chemokine ligand (CXCL) 9, CXCL10, and CXCL11, is significantly upregulated in the livers of NAFLD patients as well as in a mouse model of NASH, which promotes fatty-acid synthesis [19]. Therefore, immune cells in the blood are closely associated with inflammation of, and the metabolic pathways active in, the liver.

Changes in the gene expression profiles of peripheral blood mononuclear cells (PBMCs) reflect liver pathogenesis [20–23]. However, few studies have focused on PBMCs in NAFLD [24]; indeed, their role in the pathogenesis of NASH is also unclear. In this study, therefore, we focused on the expression levels of cytokine- and chemokine-encoding genes in PBMCs from NAFLD patients according to disease stage. In addition, we established immunological criteria for the noninvasive discrimination of NASH from NAFL.

Methods

Patients

From April 2015 to January 2017, a percutaneous liver biopsy was performed on patients with clinically suspected NASH at The University of Tokyo Hospital. PBMCs were obtained from patients diagnosed with NAFLD according to the Matteoni classification [25]. NAFLD was diagnosed clinically in patients who met all of following criteria: (1-A) Transient liver elastography value measured by FibroScan® (FS; Echosens™, Paris, France) of > 7.0 kPa; (1-B) serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels above the upper limits of normal for at least 6 months; (2) enhanced hepatorenal contrast by abdominal ultrasonography; (3) history of alcohol consumption of < 30 g/day for men and < 20 g/day for women [26]; (4) seronegativity for hepatitis B virus surface antigen and hepatitis C virus antibody and the

absence of other liver diseases such as primary biliary cholangitis, autoimmune hepatitis (AIH), primary sclerosing cholangitis, drug-induced liver injury (DILI), Budd–Chiari syndrome, Wilson's disease, hemochromatosis, and schistosomiasis. We enrolled patients meeting criterion 1-A or 1-B (or both), because these reflected past and current liver injury, respectively. Liver biopsy was performed on consenting patients. The exclusion criteria were: (1) symptoms of viral or bacterial infection at the time of admission; (2) malignant tumor, chronic inflammatory disease, or autoimmune disease; and (3) immunosuppressant use within 3 months. This study was approved by the Ethics Committees of The University of Tokyo and all patients provided informed consent, as required by the Declaration of Helsinki.

Comorbid diseases, particularly immunological conditions, and drug intake were recorded, and body height, body weight (BW), and body mass index (BMI) were measured on the day of admission. On the day of liver biopsy, blood samples were obtained for determination of the levels of albumin, AST, ALT, γ-glutamyl transpeptidase, total bilirubin, uric acid, creatinine, triglyceride, high-density lipoprotein, low-density lipoprotein, C-reactive protein (CRP), fasting blood glucose, hemoglobin A1c, hyaluronic acid, and type IV collagen, as well as the prothrombin time, number of platelets, and the homeostasis model assessment for insulin resistance (HOMA-IR) score. PBMCs were separated from the blood samples using a Ficoll kit [27], which has been confirmed to isolate pure PBMCs [28].

Histological assessment

Percutaneous liver biopsy was performed using a 16 G needle with a 20-mm long biopsy specimen notch. All biopsy samples were examined by one experienced hepatopathologist blinded to the clinical data and the study design. Significant hepatic steatosis was considered as present when $\geq$ 5% of hepatocytes exhibited fatty changes. Liver histology was assessed according to the Matteoni classification [25], and patients not diagnosed with NAFLD were excluded. According to the Nonalcoholic Steatohepatitis Clinical Research Network criteria, NASH progression was assessed by determining the NAFLD activity score (NAS), which is based on the degrees of steatosis, lobular inflammation (LI), and hepatocellular ballooning. According to the Matteoni classification, NASH is pathologically diagnosed when ballooning is present. Therefore, we regarded the presence of ballooning as diagnostic of NASH.

Quantitative real-time polymerase chain reaction

mRNA was extracted from PBMCs using the RNeasy Micro Kit (Qiagen, Hilden, Germany), and complementary DNA was synthesized using the RT2 First Strand Kit (Qiagen). First, a Cytokine and Chemokine PCR Array (Qiagen) was used to examine the expression levels of 84 cytokine-encoding genes in 12 patients with NASH and in 6 patients with NAFL. The list of genes examined with this array is shown in Supplementary Fig. 1. Next, the expression levels in all 54 patients of the genes identified were determined by TaqMan PCR. Expression levels were normalized to that of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and the relative expression levels were calculated. The PCR primers and probes were from Thermo Fisher Scientific (Waltham, MA, USA) (Supplementary Fig. 2).

Statistical analysis

Data were analyzed using JMP 13 software (SAS Institute Japan, Tokyo, Japan). A value of $p < 0.05$ was considered as indicative of statistical significance. We examined the correlations between the components of NAS and gene expression levels using Spearman's rank-correlation method. Nonparametric data were analyzed by Wilcoxon Kruskal–Wallis test. Data are mean ± standard deviation unless stated otherwise.

Results

Patients' characteristics

From April 2015 to January 2017, liver biopsies were performed on 103 patients, 58 of whom were diagnosed with NAFLD based on histologic findings. Four of these fifty-eight patients were excluded due to clinical suspicion of concomitant alcoholic liver disease (one patient), DILI (one patient), or AIH (two patients). Therefore, 54 patients (NASH, 36; NAFL, 18) were enrolled. The baseline characteristics of these 54 patients are listed in Table 1.

There was no significant difference in age, male: female ratio, BW, or BMI between the NASH and NAFL patients. Regarding laboratory parameters, the AST, CRP, hyaluronic acid, and type IV collagen levels were significantly increased in NASH patients. The differences in AST and CRP levels likely reflect liver inflammation, and those in hyaluronic acid and type IV collagen levels, liver fibrosis [29]. The measured FS values were also significantly higher in NASH patients.

Table 1 Clinical background of 54 NAFLD patients and pathological changes in livers

Parameter	Total (n = 54)	NAFL (n = 18)	NASH (n = 36)	p value
Age at biopsy (years)	52.4	49.8 ± 12.0	53.8 ± 15.9	0.205
Male sex (%)	55.6	68.4	48.6	
BW(kg)	73.3	71.2 ± 12.1	74.4 ± 21.6	0.978
BMI (kg/m^2)	27.8	27.3 ± 3.9	28.0 ± 5.6	0.452
Albumin (g/dL)	4.0	4.0 ± 0.3	4.0 ± 0.4	0.417
AST (U/L)	**47.2**	**32.6 ± 10.7**	**54.5 ± 31.4**	**0.002**
ALT (U/L)	69.9	49.0 ± 18.4	80.3 ± 59.5	0.139
GGT (U/L)	107.7	105.8 ± 78.5	108.6 ± 106.9	0.263
Total bilirubin (mg/dL)	0.9	1.1 ± 0.5	0.9 ± 0.3	0.09
Uric acid (mg/dL)	6.3	6.4 ± 1.4	6.2 ± 1.5	0.735
Creatinine (mg/dL)	0.7	0.8 ± 0.2	0.7 ± 0.2	0.091
Triglycerides (mg/dL)	143.1	161.1 ± 67.6	134.1 ± 88.1	0.052
HDL-C (mg/dL)	51.7	52.4 ± 15.8	51.4 ± 13.1	0.858
LDL-C (mg/dL)	117.9	112.6 ± 32.0	120.5 ± 46.7	0.769
CRP (mg/dL)	**0.3**	**0.1 ± 0.4**	**0.3 ± 0.6**	**0.015**
Platelet count (10,000/μL)	22.7	22.3 ± 5.5	22.9 ± 8.3	0.829
PT (%)	97.4	98.8 ± 2.6	96.7 ± 5.2	0.327
Fasting blood glucose (mg/dL)	100.7	103.1 ± 28.0	99.4 ± 24.1	0.878
HbA1c (N)	6.5	6.4 ± 0.9	6.6 ± 1.3	0.918
HOMA-IR	2.9	2.5 ± 1.4	3.1 ± 2.5	0.319
Hyaluronic acid (ng/mL)	**33.5**	**21.8 ± 16.7**	**39.7 ± 32.6**	**0.037**
Type IV collagen (ng/mL)	**4.4**	**3.8 ± 0.9**	**4.6 ± 1.3**	**0.027**
FS (kPa)	**10.7**	**6.6 ± 2.0**	**12.8 ± 9.8**	**0.001**
CAP (dB/m)	287.8	286.6 ± 45.3	288.5 ± 49.8	0.976
Matteoni classification				
Type I: steatosis alone		4 (22.2%)	0 (0%)	
Type II: steatosis with inflammation		14 (77.8%)	0 (0%)	
Types III–IV: steatosis with ballooning and/or fibrosis		0 (0%)	36 (100%)	
NAS				
Steatosis				
0		0 (0%)	0 (0%)	
1		8 (44.4%)	13 (36.1%)	
2		7 (38.9%)	16 (44.4%)	
3		3 (16.7%)	7 (19.4%)	
Lobular inflammation				
0		4 (22.2%)	1 (2.8%)	
1		14 (77.8%)	27 (75.0%)	
2		0 (0%)	8 (22.2%)	
3		0 (0%)	0 (0%)	
Ballooning				
0		18 (100%)	0 (0%)	
1		0 (0%)	29 (80.6%)	
2		0 (0%)	7 (19.4%)	
Fibrosis				
0		9 (50%)	1 (2.8%)	
1		9 (50%)	13 (36.1%)	
1A		8 (44.4%)	10 (27.8%)	
1B		1 (5.6%)	3 (8.3%)	

Table 1 continued

Parameter	Total (n = 54)	NAFL (n = 18)	NASH (n = 36)	p value
1C		0 (0%)	0 (0%)	
2		0 (0%)	4 (11.1%)	
3		0 (0%)	15 (41.7%)	
4		0 (0%)	3 (8.3%)	

Values are N (%) or mean ± standard deviation. The bold means the parameter is significantly upregurated in NASH compared with NAFL

Expression levels of genes encoding cytokines and chemokines

As a screening, we first examined the expression levels of 84 cytokine- or chemokine-encoding genes in randomly selected 6 NAFL and 12 NASH patients (Supplementary Table 1), using a commercially available expression array. Genes whose expression levels were > 1.5-fold higher in NASH compared to NAFL patients were regarded as being upregulated. The expression levels of IFNγ, IL2, IL15, CCL2, CXCL9, CXCL10, CXCL11, IL6, and IL10 were > 1.5-fold higher in NASH compared to NAFL patients (Table 2). However, none of the differences was significant, likely due to the small number of patients examined. On the other hand, none of the genes was more than 1.5-fold lower in NASH patients compared to NAFL patients.

We next determined expression levels of these candidate genes in all of 54 patients by real-time PCR using specific primers and probes. The expression levels of IFNγ, IL2, IL15, CCL2, CXCL11, and IL10 were significantly upregulated in NASH patients. The expression levels of CXCL9, CXCL10, and IL6 were higher, albeit not significantly so, in NASH patients (Fig. 1).

We next investigated gene expression levels according to the grade of steatosis, LI, and ballooning. The expression levels of the nine genes were not correlated with the degree of steatosis (Table 3). Only IL2 expression was positively correlated with the degree of LI. The expression levels of IFNγ, IL2, IL15, CCL2, CXCL11, and IL10 were positively correlated with the degree of ballooning, in line with their significantly increased expression in NASH patients. In addition, the expression levels of IFNγ, IL2, and IL10 were positively correlated with the degree of fibrosis (Table 3). These results suggest that PBMC-derived cytokines and chemokines are involved in the pathogenesis of NASH.

Table 2 Screening analysis of gene expression in PBMC of 18 NAFLD cases

	NAFL (n = 6)	NASH (n = 12)
IFNγ	0.93 ± 0.12	1.75 ± 0.9
IL2	0.89 ± 0.2	1.8 ± 1.1
IL15	0.82 ± 0.25	1.32 ± 0.57
CCL2	0.54 ± 0.25	1.18 ± 0.97
CXCL9	0.65 ± 0.29	2.03 ± 2.24
CXCL10	0.85 ± 0.26	2.45 ± 2.7
CXCL11	0.62 ± 0.3	2.48 ± 4.38
IL6	0.83 ± 0.26	1.64 ± 1.0
IL10	1.05 ± 0.42	1.66 ± 0.92

Values are mean ± standard deviation

Establishment of criteria for discrimination of NASH

The expression levels of IFNγ, IL2, IL15, CCL2, CXCL11, and IL10 were positively correlated with NASH progression. Based on these expression levels, we established criteria for the noninvasive discrimination of NASH from NAFL.

IL10 had the highest area under the curve (AUC) value, followed by IFNγ, CCL2, CXCL11, IL2, and IL15 (Fig. 2a). Although IL10 alone could have a relatively high AUC to discriminate NASH from NAFL, we selected IL10, IFNγ, and CCL2 for inclusion in the criteria for discrimination of NASH to enhance the sensitivity and specificity of the criteria (Fig. 2b–d). The expression levels of these three genes were scored, and the scores were combined for evaluation. Among the 54 NAFLD patients, those with a score of < 3 had NAFL and those with a score of > 3 had NASH (Fig. 2e). The AUC value of combination of IL10, IFNγ, and CCL2 was 0.9691, and higher than that of IL10, IFNγ, or CCL2 alone. However, NASH could not be distinguished from NAFL in patients with a score of 3 (Fig. 2f).

We validated the scoring system in an independent validation cohort comprising 30 NAFLD patients. In this cohort, 7 patients had a score of < 3, 16 a score of > 3, and 7 patients had a score of 3. The criteria enabled accurate diagnosis of 21 of the 23 patients with scores above or below 3; the exceptions were one NAFL patient (score 6) and one NASH patient (score 1) (Table 4). The seven patients with a score of 3 had NASH. Of the two patients

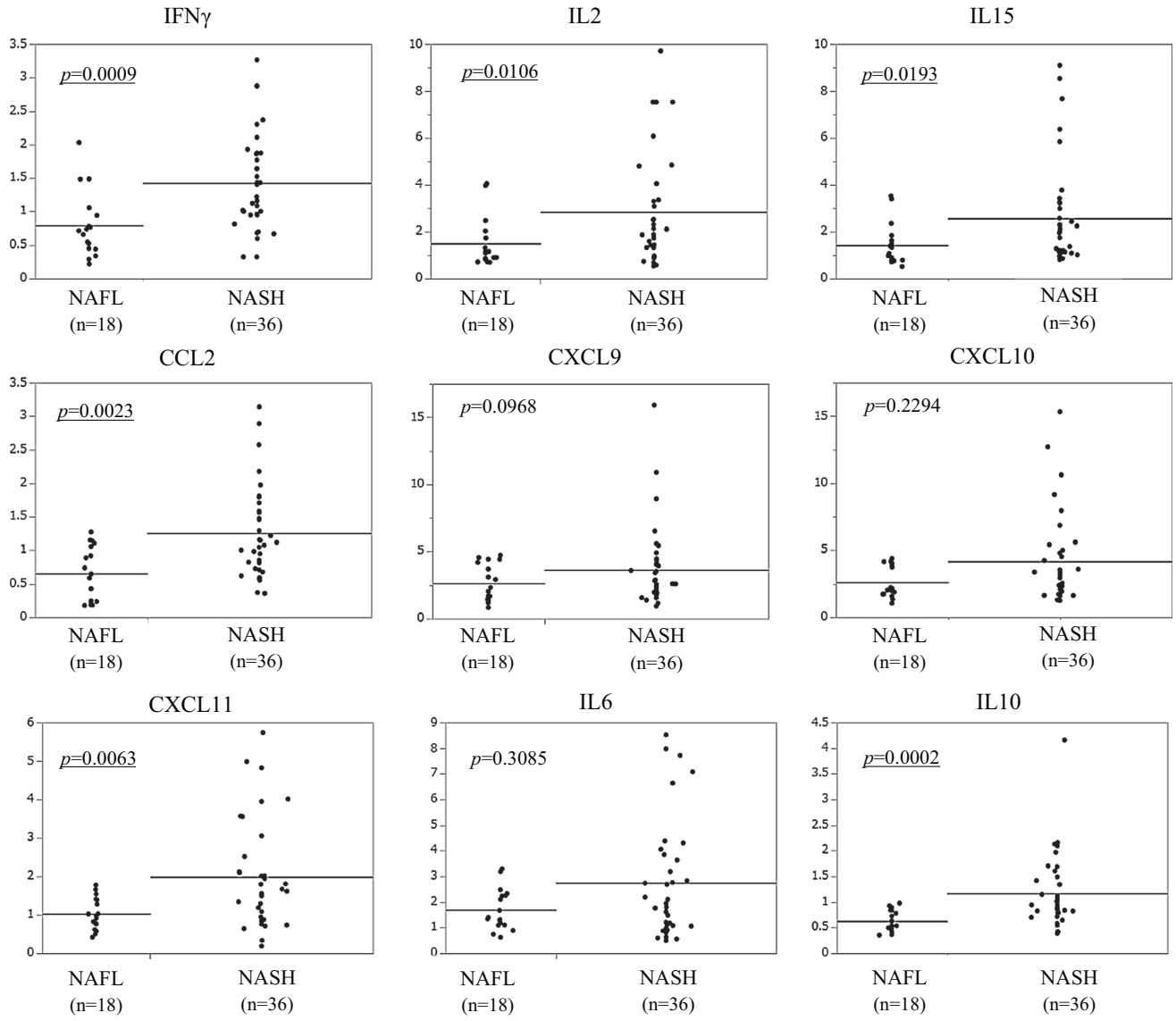

Fig. 1 Expression levels of cytokine- and chemokine-encoding genes in peripheral blood mononuclear cells (PBMCs) from patients with nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver (NAFL) as determined by real-time PCR. The expression levels of the genes encoding interferon (IFN) γ, interleukin (IL) 2, IL15, C–C-motif chemokine ligand (CCL) 2, C-X-C-motif chemokine ligand (CXCL) 11, and IL10 were significantly increased in NASH patients

who did not meet the criteria, one (NAFL) had cold symptoms around the liver biopsy, and the other (NASH) had cancer of the appendix. In this point, these two patients potentially met the exclusion criteria in the original cohort, and therefore should have been excluded from the cohort if their comorbidities had been diagnosed at the time of admission. Other patients in the validation cohort were appropriately discriminated, indicating our discrimination criteria also worked for the validation cohort, but not for patients with comorbid disorders such as inflammatory or malignant diseases. We also found that scores by our system were significantly correlated with FS values (data not shown).

To confirm that this scoring system should also work properly for patients without NAFLD, we examined 14 patients who were hospitalized with diseases such as gastroduodenal ulcer, intestinal obstruction, and gastrointestinal bleeding in our department. We confirmed normal values of serum AST and ALT and also the absence of NAFLD by abdominal ultrasonography. All of these patients also met inclusion and exclusion criteria in this study except the presence of NAFLD and elevation of serum AST and ALT. PBMCs were obtained after the patients recovered from their diseases and expression levels of IL10, IFNγ, and CCL2 were similarly examined. In our criteria, all of them had a score of < 3 and were

Table 3 Changes of gene expression in PBMC of 54 NAFLD patients according to the degree of NAS and fibrosis

NAS	Gene	Spearman's rho	*p* value
Steatosis (score 1–3)	IFNγ	0.0402	0.7749
	IL2	− 0.0205	0.15
	IL15	− 0.2589	0.0587
	CCL2	− 0.0219	0.8789
	CXCL9	− 0.1833	0.1845
	CXCL10	− 0.2503	0.0679
	CXCL11	0.0317	0.8237
	IL6	− 0.1298	0.0578
	IL10	0.1458	0.2929
LI (score 0–2)	IFNγ	0.2172	0.1182
	IL2	0.3241	**0.0191**
	IL15	0.1949	0.1578
	CCL2	0.1731	0.2244
	CXCL9	0.0822	0.5547
	CXCL10	0.2067	0.1337
	CXCL11	0.1731	0.2199
	IL6	0.1601	0.2476
	IL10	0.162	0.2419
Ballooning (score 0–2)	**IFNγ**	0.4242	**0.0015**
	IL2	0.2854	**0.0403**
	IL15	0.273	**0.0453**
	CCL2	0.3892	**0.0048**
	CXCL9	0.1982	0.1509
	CXCL10	0.2511	0.067
	CXCL11	0.461	**0.0006**
	IL6	0.0651	0.6399
	IL10	0.5764	**< 0.0001**
fibrosis (staging 0–4)	**IFNγ**	0.4004	**0.003**
	IL2	0.3045	**0.0282**
	IL15	0.1315	0.3431
	CCL2	0.0189	0.9003
	CXCL9	0.0287	0.8367
	CXCL10	0.1106	0.4258
	CXCL11	0.2445	0.0807
	IL6	− 0.0646	0.6428
	IL10	0.3407	**0.0117**

The bold means the parameter is significantly upregurated in NASH compared with NAFL

regarded as non-NASH (Supplementary Table 2), indicating that cases without NAFLD were classified in NAFL, not NASH.

Discussion

In this study, we examined the expression levels of cytokine- and chemokine-encoding genes in PBMCs from patients with NAFLD with the aim of establishing immunological diagnostic criteria for NASH. Several proteins; e.g., S100A9 and cytokeratin, have been reported as candidate biomarkers of NASH [30, 31]. However, only an increased level of activated plasminogen activator inhibitor 1 (PAI1) was independently associated with NASH in a multivariable analysis [32]. Discriminating NASH from NAFL using these factors is likely problematic, and thus, other biomarkers or criteria for the noninvasive diagnosis of NASH are needed.

In this study, we focused on expression of cytokines and chemokines and found that the expression levels of the genes encoding IFNγ, IL2, IL15, CCL2, CXCL11, and IL10 were significantly upregulated in PBMCs from NASH patients. This is consistent with several prior reports [33–35]. We, thus, hypothesize that these PBMC-derived cytokines and chemokines contribute to the pathogenesis of NASH.

There were some concerns that gene expression of PBMC may reflect intrahepatic expression. We examined mRNA expression levels of several cytokines in liver tissues of these patients and found expression levels of IFNγ and IL10 were correlated with those in PBMC (unpublished data). Concerning IFNγ, one previous study using chimpanzee model of HCV infection demonstrated the correlation of intrahepatic IFNγ expression with peripheral IFNγ-positive CD8 cells [36]. To our knowledge, there are no studies demonstrating that intrahepatic expression level of IL10 is correlated with that in PBMC, but considering that IL10 and IFNγ are secreted from similar immune cells including those infiltrating into the liver, it is not strange that IL10 expression level in PBMC might be also correlated with that in the liver. On the other hand, the correlation of CCL2 expression level between liver and PBMC was not observed (unpublished data). The reason remains to be determined, but it is possible that expression level of CCL2 from liver-resident CCL2-producing cells such as bile duct epithelial, endothelial, and other perisinusoidal cells might be changed according to the progression to NASH [34].

CCL2 is produced by LPS-stimulated or pathogen-infected monocytes, macrophages, and dendritic cells, and activates macrophages [37]. Moreover, in NASH patients, CCL2 is also produced by adipose tissue [17, 18, 38]. IL15 and IFNγ are secreted from immune cells mentioned above, leading to migration of natural killer (NK) and natural killer T (NKT) cells and activation of the Th1 immune response [39–41]. By contrast, IL15 inhibits hepatic steatosis by suppressing gluconeogenesis and promoting lipolysis [42, 43]. IL2 is produced by NK cells, NKT cells, and CD4+ T cells, and activates CD8+ cytotoxic T lymphocytes to produce CXCL9, CXCL10, and CXCL11 [44–46]. These chemokines activate T cells via CXCR3, leading to steatosis, inflammation, and fibrosis in

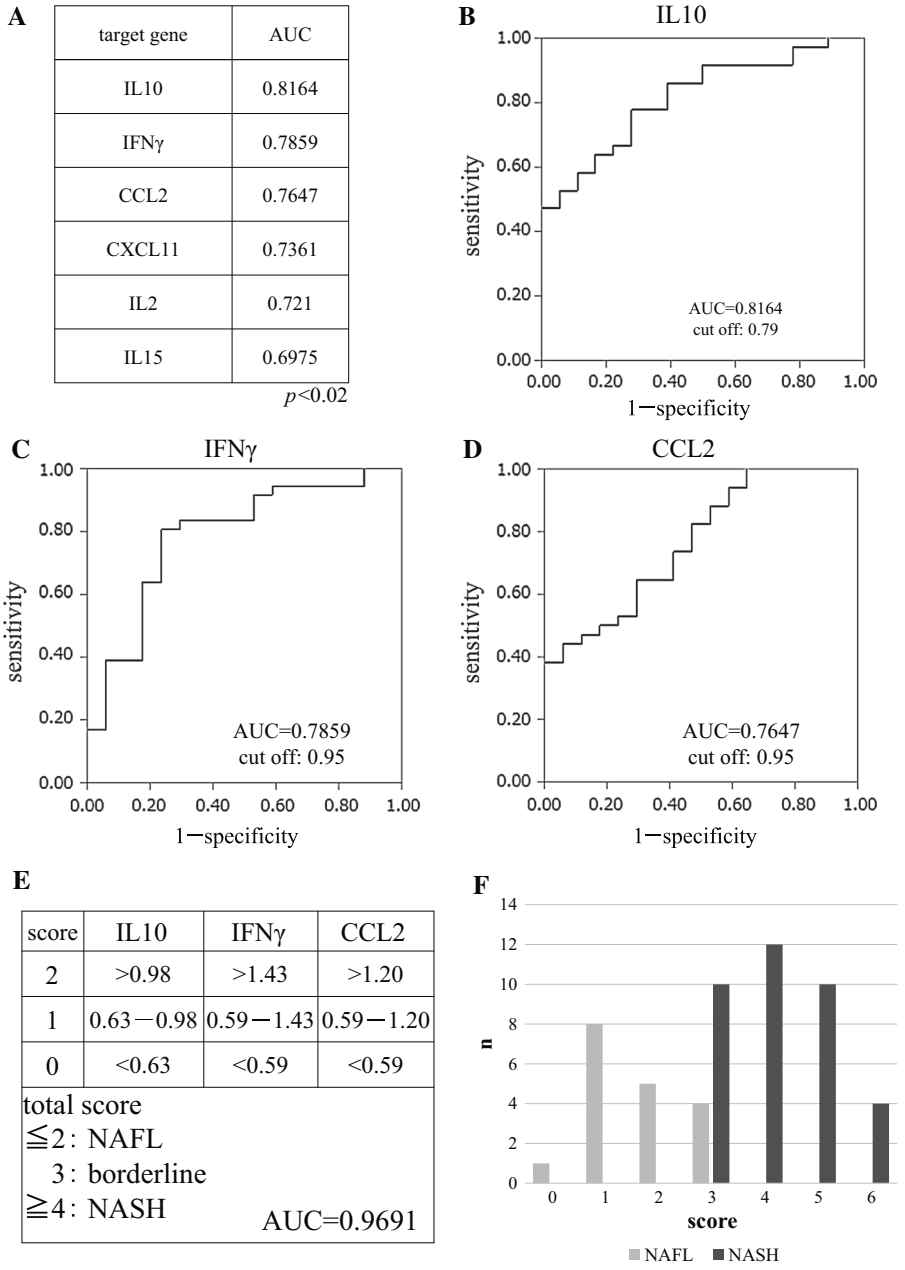

Fig. 2 Determination of diagnostic criteria for discrimination of NASH from nonalcoholic fatty liver disease (NAFLD). **a** AUC values of the genes. **b–d** ROC curves for the expression levels of IL10, IFNγ, and CCL2. **e** Scoring system based on the expression levels of IL10, IFNγ, and CCL2. **f** Number of NAFLD cases according to score

the liver [19, 47–49]. In fact, CXCR3 expression level in liver tissue was significantly upregulated in NASH patients, and CXCL11 expression level in PBMCs was positively correlated with that of CXCR3 in liver tissue (data not shown), suggesting that liver cells respond to increased production of CXCL11 in PBMCs. IL10, which suppresses the production of IFNγ, IL2, CXCL9, CXCL10, and CXCL11, is secreted by Th2 and regulatory T cells and inhibits the LPS-induced production of proinflammatory cytokines such as tumor necrosis factor-α, IL6, and IL1β [50–52]. IL10 causes accumulation of abnormal proteins and mitochondria in vitro and increases the risk of lipoapoptosis in NASH patients [53–55]. As the upregulation of IL10 expression was most significantly correlated with the degree of ballooning, we speculate that IL10 induces cytopathic changes (e.g., ballooning) and liver fibrosis, which contributes to the progression of NASH [56, 57]. These results suggest that cytokines and chemokines produced by PBMCs cooperatively contribute to the pathogenesis of NASH.

Criteria for discriminating NASH from NAFL were developed based on the expression levels of IL10, IFNγ, and CCL2, as these had the highest AUC values. Initially, we tried to regard IL10 as a single biomarker for discrimination of NASH from NAFL. In the validation cohort, 28 out of 30 NAFLD patients were accurately

Table 4 Validation of the NASH discrimination criteria

Case	Age	Sex	Pathological diagnosis	IL10	IFNγ	CCL2	Score	Diagnosis by the score
1	66	Male	NASH	1.34	1.99	0.84	5	NASH
2	57	Male	NASH	2.39	4.73	0.76	5	NASH
3	59	Female	NASH	2.3	1.48	0.91	5	NASH
4	69	Male	NAFL	3.26	2.29	1.71	6	NASH
5	57	Male	NASH	0.92	2.58	0.83	4	NASH
6	25	Female	NASH	4.92	1.62	0.73	5	NASH
7	43	Male	NAFL	0.62	1.09	1.2	2	NAFL
8	64	Female	NASH	2.18	1.5	0.36	4	NASH
9	35	Female	NASH	1.53	1.43	1.4	5	NASH
10	79	Male	NASH	2.74	0.84	0.2	3	Borderline
11	63	Female	NASH	1.42	1.19	0.92	4	NASH
12	57	Male	NASH	1.34	3.15	0.32	4	NASH
13	27	Male	NASH	2.82	0.94	2.14	5	NASH
14	58	Male	NASH	1.47	2.93	0.32	4	NASH
15	27	Female	NASH	2.09	0.93	0.24	3	Borderline
16	65	Female	NASH	0.79	1.08	1.11	3	Borderline
17	40	Female	NAFL	0.98	1.25	0.32	3	Borderline
18	51	Female	NASH	0.63	0.34	0.33	1	NAFL
19	35	Male	NASH	1.09	0.58	0.84	3	Borderline
20	61	Male	NASH	1.24	1.14	0.84	4	NASH
21	42	Male	NASH	5.5	4.33	1.84	6	NASH
22	25	Male	NASH	2.34	1.53	3.71	6	NASH
23	35	Male	NASH	0.67	0.73	0.71	3	Borderline
24	35	Male	NASH	1.12	2.25	1.23	6	NASH
25	61	Male	NASH	0.84	0.8	1.16	3	Borderline
26	46	Female	NAFL	0.49	0.65	0.67	2	NAFL
27	52	Male	NAFL	0.38	0.17	0.11	1	NAFL
28	62	Male	NAFL	0.18	0.3	0.2	0	NAFL
29	29	Male	NAFL	0.55	0.49	0.21	2	NAFL
30	33	Female	NAFL	0.21	0.31	0.19	1	NAFL

discriminated when the proposed cut-off value 0.63 in the expression level of IL10 in PBMCs was applied. However, in the original cohort, 14 out of 54 NAFLD patients were not accurately discriminated by the same cut-off value. Therefore, we established the criteria by combining levels of IL10, IFNγ, and CCL2 to divide most of 54 NAFLD patients into NAFL and NASH groups in the original cohort. In fact, the criteria properly discriminated all of the patients with a score of more or less than 3. In the validation cohort, the criteria also worked similarly, even for the patients whose FS values could not be measured due to obesity. By our scoring system, however, 4 NAFL and 10 NASH patients in the original cohort and 1 NAFL and 6 NASH patients in the validation cohort had a score of 3. Our criteria cannot discriminate patients with a score of 3. We are currently engaged in developing a more detailed scoring system for discriminating NASH from NAFL in such patients. So far, IL10 might be a candidate for discrimination of patients with borderline. At least in our original and validation cohorts, borderline patients with IL10 expression level more than 0.63 were all NASH, while that less than 0.63 all NAFL. In this point, we should have a further examination.

Since it is slightly complicated to examine mRNA expression of PBMC for the clinical application in the future, we sought to measure serum levels of these cytokines and chemokines by commercially available ELISA kits. However, as far as we examined, serum levels of IL10 and IFNγ were both below the detection limit in all of the samples. Concerning CCL2, we could detect serum levels, but there were no significant changes between patients with NASH and NAFL (data not shown). The reason is unclear, but it is possible that CCL2 is secreted from not only PBMCs but also other cells such as vascular endothelial cells, fibroblasts, and osteoblasts, which may

affect serum CCL2 levels. In this point, the method should be improved to evaluate patients more conveniently.

Several cytokines, as well as PBMCs expressing particular sets of surface markers, are reportedly associated with the pathogenesis of NASH. CCL5 promotes liver fibrosis in patients with NAFLD [58–60]. Antagonists of CCR2 and CCR5, the receptors for CCL2 and CCL5, respectively, suppress liver fibrosis and are currently under evaluation in clinical trials involving NASH patients in the United States [61]. In this study, the expression levels of CCL5 and CCL2 were significantly upregulated in NASH patients (Fig. 1 and data not shown); therefore, CCL5 may also be useful for the diagnosis of NASH. Segregated nucleus-containing atypical monocytes (SatM), Ceacam1+ Msr1+ Mac1+ monocytes with granulocyte properties, are associated with liver fibrosis [62]. The function of SatM is unclear, but the cytokines or chemokines produced by these cells may be included in future diagnostic criteria for NASH.

This study had several limitations. First, we excluded patients with HCC or other malignancy, as these entities can influence the systemic immune status and the expression levels of IL10, IFNγ, and CCL2 in PBMCs, leading to incorrect evaluation of liver pathology. Indeed, one case with cancer of the appendix in the validation cohort was misdiagnosed using the criteria. Therefore, modified criteria should be developed, since patients with NASH sometimes accompany potential HCC. Secondly, the validation cohort included few patients with NAFL. In our hospital, patients with NAFLD suspicious for NASH were recommended to undergo percutaneous liver biopsy; this increased the number of NASH patients in the cohort. In a future study, we will examine more PBMCs from patients with NAFL as well as those with other diseases or healthy controls. Finally, patients with a score of 3 cannot be discriminated using the criteria developed in this study.

We did not identify the cell types responsible for the upregulation of cytokines in this study. We finally aimed to establish criteria to discriminate patients with NASH from those with NAFL; therefore, we used the whole PBMCs so that the criteria will be more accessible in clinical practice. We are at present engaged in an investigation of this aspect of the pathogenesis of NASH by fluorescence-activated cell sorting. Identification of the responsible cell types would assist the development of novel and effective therapeutic strategies for NASH.

In conclusion, the expression levels of several cytokines and chemokines in PBMCs differed between NASH and NAFL patients, and we used these differences to establish criteria for discriminating NASH from NAFL. Moreover, the criteria were validated in an independent cohort. Our data suggest that PBMC-derived cytokines and chemokines contribute to the pathogenesis of NASH and that differences in their expression levels could be used to discriminate NASH from NAFL. We believe that our criteria will be useful in clinical practice. Finally, our findings will facilitate the development of novel therapeutic strategies for NASH.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Esophagus (PG Iyer, Section Editor)

Predictors of Progression in Barrett's Esophagus

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Abstract

Purpose of review To review recently published data on factors that predict the risk of progression of Barrett's esophagus (BE) to high grade dysplasia (HGD) or esophageal adenocarcinoma (EAC).
Recent findings Computer models have been developed that could help predict the risk of progression with greater accuracy. The progression of BE score (PIB) is one such model based on clinical and endoscopic features, while a second uses automated image analysis of formalin-fixed and paraffin-embedded tissues looking for morphologic features and immunostaining patterns for molecular markers. Panels of genes such as those regulated by Myc and hypermethylated genes have been recently described.
Summary EAC remains a cancer with a poor 5-year survival of less than 20%. Screening for BE, the only known precursor of EAC is recommended only in high-risk individuals. Clinical, endoscopic, and molecular predictors of progression have been identified but require validation. These tools could in turn help focus screening and surveillance efforts to reduce mortality from EAC.

Introduction

The incidence and mortality of esophageal adenocarcinoma (EAC) in the USA have been steadily rising since the early 1970s. The 5-year overall survival rate for patients with EAC remains poor, at < 20%, and median survival after diagnosis is only 11 months. Barrett's esophagus (BE) is the only known precursor to EAC and can be detected endoscopically. Screening and surveillance to detect BE and dysplasia/EAC are hence recommended to enable prevention (by endoscopic treatment of dysplasia) and/or treatment of early stage EAC

[1]. Endoscopic surveillance is however only modestly effective likely due to a variety of reasons [2]. Compliance with endoscopic surveillance guidelines is poor, dysplasia distribution in BE mucosa is patchy and often subtle, leading to missed dysplasia [3]. Additionally, interobserver agreement among pathologists for the diagnosis of dysplasia (especially low-grade dysplasia) is moderate to poor. These limitations likely negatively impact the effectiveness of surveillance as currently practiced.

The degree of dysplasia on biopsy specimens obtained during upper endoscopy (EGD) is currently the only method utilized to predict progression to EAC and thereby determine surveillance intervals. Currently, progression (i.e., development of HGD or EAC) is defined as the detection of HGD or EAC more than 12 months after the initial diagnosis of BE. Population studies show that most patients with BE do not have dysplasia (80%) and the absolute risk of progression in non-dysplastic BE (NDBE) is low at 0.33% each year [4, 5]. Endoscopic surveillance in those with NDBE is recommended every 3 to 5 years, and biopsies are recommended every 2 cm in a four-quadrant fashion (Seattle protocol). Modeling studies have found surveillance in those with NDBE to not be cost-effective [6].

Hence, there is a strong clinical need to define predictors of progression in BE, in order to risk stratify patients into low- and high-risk categories, such that their surveillance and management can be tailored to this classification. In this review, we aim to comprehensively review and summarize the literature on predictors of progression in BE.

Patient characteristics that predict progression

Patient factors reported to increase risk of progression in BE patients include male gender and advancing age [7]. In a recent systematic review and meta-analysis (SRM) of cohort studies, significant associations between risk of progression and increasing age (OR 1.03, 95% CI 1.01–1.05, $I^2 = 45$) as well as male gender (OR 2.16, 95% CI 1.84–2.53, $I^2 = 0$) were reported.

While obesity is an established risk factor for BE and EAC [7], data on its direct impact on progression in those with known BE are more limited. In a large population-based cohort of BE patients, being overweight (BMI 25–29.9) conferred an increased risk of progression to EAC (OR 1.64). However, there was no effect of higher grades of obesity on progression [8]. Similarly, in another SRM, obesity as measured by BMI did not associate with the risk of progression [9••]. However, in a prospective cohort study, increased levels of serum Leptin and insulin resistance (which are associated with central obesity) were associated with progression, particularly in men [10]. Central obesity or visceral abdominal fat may be more closely associated with esophageal carcinogenesis than BMI which is a measure of overall adiposity [11].

Smoking is also a well-established risk factor for BE [12]. In a SRM of cohort studies, smoking was associated with an increased risk for progression of almost 50% [9••]. In this SRM, when analysis was restricted to the five studies that reported multivariate analyses adjusted for age and sex, smoking remained predictive of progression. However in the two studies adjusting for age, sex, and BE characteristics (baseline dysplasia and/or BE length), smoking was not predictive of progression. Additional studies have also consistently shown that smoking is a risk factor for EAC (OR 1.96, 95% CI 1.64–1.34, $I^2 = 24$) [13] along with a dose response effect. Hence, smoking may be one of the few modifiable risk factors influencing BE progression.

Medications such as aspirin/nonsteroidal anti-inflammatory drugs (NSAIDs), statins, and proton pump inhibitors (PPIs) have been reported to protect against progression of BE. In a SRM, the use of proton pump inhibitors (PPIs) and statins was associated with decreased odds of progression (ORs 0.55 and 0.48, respectively). While there is some evidence on the role of metformin, the chemoprevention of other malignancies, evidence for its role in preventing EAC in BE, appears to be limited [8, 14, 15].

Alcohol use does not appear to affect the risk of progression [8]. Another meta-analysis including 882 cases of BE progression in 6867 patients also found that alcohol consumption was not associated with the risk of neoplastic progression in BE [15, 16].

Endoscopic predictors of progression

BE segment length has been fairly consistently associated with increased risk of progression (Table 1). In an SRM data from 10 studies, the risk of progression increased by 25% (HR 1.25, 1.16–1.36) for every 1-cm increase in the length of BE (heterogeneity was moderate, $I^2 = 47$). This association remained significant even when the analysis was limited to six studies adjusting for age and sex and the three studies adjusting for baseline dysplasia as well. Indeed, in a recent multicenter cohort study, the annual risk of progression to HGD/EAC in those with long segment BE (≥ 3 cm) of 0.91% was substantially higher than that with short segment BE (1–3 cm) of 0.29% [17].

Endoscopic evidence of nodularity may reflect the presence of prevalent dysplasia or EAC and predict progression to HGD/EAC. In a retrospective cohort study, patients with NDBE and low-grade dysplasia (LGD) progressed to HGD/EAC at a rate of 0.97% per year (0.59% per person years in NDBE and 1.23% per person years in LGD). Nodularity on endoscopy predicted a 5-fold higher risk of progression (HR 4.98; 95% CI 1.80–11.7). In another cohort study of patients with LGD, nodularity increased the risk of progression more than 6-fold: HR 6.4 (0.98–24.3) [1, 18–20].

Dysplasia as a predictor of progression

NDBE

The rate of progression of NDBE to HGD or EAC is low. In a large Danish cohort, the annual risk of progression from NDBE to EAC was 0.1%. However, this was a pathology database study, with no information provided on the length of the BE segment, raising the possibility of misclassification bias (patients with intestinal metaplasia of the cardia being classified as BE). A somewhat similar rate of 0.17% was also observed among patients with NDBE in Northern Ireland although the latter included tumors arising in the gastric cardia in their calculation. A more comprehensive SRM reported that the annual risk of progression in NDBE is 0.33% [21]. In a retrospective cohort study of 1400 participants, the persistence of NDBE over consecutive endoscopies was associated with progressively decreasing odds of progression to EAC, though this has been refuted in other reports [4, 22].

Table 1. Models to predict progression in BE

Corresponding author	Type of predictors	Predictors	Technique	Outcome	Categories of risk progression	Accuracy of model
Sharma, P	Clinical features plus degree of dysplasia	Gender, cigarette smoking, length of BE, confirmed LGD	Assign points to each predictor and add up the points to calculate risk score	Annual risk of progression to HGD/EAC	Low risk (0.13%) Intermediate risk (0.73%) High risk (2.1%)	
Critchley-Thorne R.J.	Tissue morphology and biomarker	p16INK4a, AMACR, p53, HER2, K20, CD68 COX-2, HIF-1a, CD45RO	Automated analysis of FFPE slides for 15 morphologic features and IF pattern followed by calculation of risk scores	Progression from ND, IND or LGD to HGD or EAC within 12 months	Low risk (OR 1-reference) Intermediate risk (OR 7.7) High risk (OR 46)	AUROC progressors vs. non-progressors: 0.89

Indefinite for dysplasia

Indefinite for dysplasia is referred to "epithelial abnormalities insufficient to diagnose dysplasia or epithelial abnormalities that are unclear due to inflammation or sampling". The natural history of IND is still being elucidated. In a retrospective cohort study, 66 patients without prevalent dysplasia underwent surveillance endoscopy more than 1 year after the diagnosis of IND. Two (3%) developed HGD 16.5 and 28 months after the initial diagnosis of IND. Patients with incident dysplasia had a longer Barrett's segment and were more likely to report a history of smoking. Another retrospective study found that nearly 13% of patients with IND had prevalent dysplasia (seven LGD, two HGD) or EAC (two). Further, 17 of 82 patients (21%) progressed to dysplasia (82% LGD, 18% HGD) and two (0.2%) developed EAC. The incidence of advanced neoplasia (HGD/EAC) was 1.2 cases per 100 patient-years, which approximates that of LGD. Multi-focal IND and longer length of BE on the index biopsy predicted progression to advanced neoplasia [23]. Another retrospective cohort study from the Netherlands reported that the rate of progression from IND to HGD/EAC was 1.4 per 100 person years [24]. Hence, the preponderance of data seems to suggest that the risk of progression in IND may be comparable to that of BE-LGD.

LGD

The rate of progression of LGD to HGD or EAC varies based on the agreement between pathologists. In a SRM, the pooled annual incidence of EAC and EAC/HGD in patients with LGD was 0.54% and 1.73%, respectively. Stratifying the studies by proportion of LGD diagnosed in each study, denominator being total number of BE cases, less than or more than 15%), the annual incidence of EAC was 0.76% for a LGD/BE ratio less than 0.15 and 0.32% if the ratio was more than 0.15: suggestive of a low threshold for an LGD diagnosis. Substantial heterogeneity was observed in the overall analysis [5]. A key limitation of using LGD as a predictor of progression is the inter-observer variation among pathologists in diagnosing the presence of and grade of dysplasia. Studies where the proportion of LGD is high are expected to have a lower incidence of EAC given the over diagnosis of LGD. Conversely, the studies where proportion of LGD is low are expected to have a higher incidence of EAC because of more stringent diagnosis of LGD [5]. Additionally, the correlation between community pathologists and expert GI pathologists in making a diagnosis of LGD is poor, with most LGD diagnoses downgraded to NDBE on GI pathology review. In these downgraded patients, the risk of progression approximates that of NDBE patients (0.49%), while those with confirmed LGD, the rates of progression are substantially higher (13.4%) [25]. Hence, it is recommended that the diagnosis of LGD be confirmed by another pathologist with expertise in gastrointestinal pathology. Several studies have shown that persistent LGD (LGD demonstrated on more than surveillance endoscopy), confirmation of LGD by multiple GI pathologists and nodularity predict higher rates of progression [18, 26]. More recent studies have

also demonstrated that LGD may be a marker for prevalent HGD or IMC, and hence detection of LGD should prompt careful endoscopic follow-up [27, 28].

Genetic predictors of BE progression

EAC is a cancer with high mutation burden approaching that of cancers associated with known carcinogens like lung cancer and melanoma. It is also a genetically heterogeneous cancer, in that there are only a handful of genes including tumor suppressors *TP53* and *SMAD4* that are mutated consistently across multiple cases. *p16* mutation occurs independent of progression, while *p53* mutation is mostly seen in HGD and EAC and the *SMAD4* mutation is seen in EAC. A field effect has also been described in BE epithelium: *p53* mutation is often seen in the non-dysplastic area adjacent to EAC, more commonly in progressors than in non-progressors (18% vs. 7%).

In addition to point mutations, copy number changes and gene gains or deletions have also been described in progressors (summarized in Table 2). In one study, while the copy number profile of non-progressors remained relatively stable over time, in progressors, there was a marked increase from 0% at baseline to nearly 100% within 48 months of diagnosis of EAC. A panel comprising *TP53* loss of heterozygosity (LOH), *CDKN21* LOH, and presence of tetraploidy increased the risk of progression by nearly 39-fold [29]. In a prospective study, p53 protein expression was assessed using immunohistochemistry (IHC) and loss of p53 gene locus by fluorescent in situ hybridization (FISH) in 116 patients with BE. p53 overexpression (defined as 4+ expression on a scale of 0–4) was more common in LGD than in HGD or EAC, while p53 overexpression and loss of p53 gene locus together were more common in LGD, HGD, and EAC (Fig. 1). On multivariable analysis, overexpression of p53 and loss of TP53 gene locus were independent predictors of progression to HGD/EAC (HR = 17, 95% CI 3.2–

Table 2. Individual genetic biomarkers of progression in BE

Marker	Type of change	Type of study	Relative risk for progression
P53	Increased p53 expression by IHC	Nested case control	11.7 (1.9–71.4)
		Retrospective	5.6 (3.1–10.3)
	Absent p53 staining		14 (5.3–37.2)
	Absent p53 staining plus confirmed LGD		33% compared to 15% for absent p53 alone
TP53 LOH, CDKN2A LOH, and tetraploidy		Retrospective analysis of prospectively collected samples	38.7 (10.8–138.5)
Abnormal DNA ploidy, expression of *Aspergillus oryzae* lectin	No LGD at baseline		3.3 (1.8–6.1)
	LGD at baseline		3.9 (2.4–6.4)

From [19]

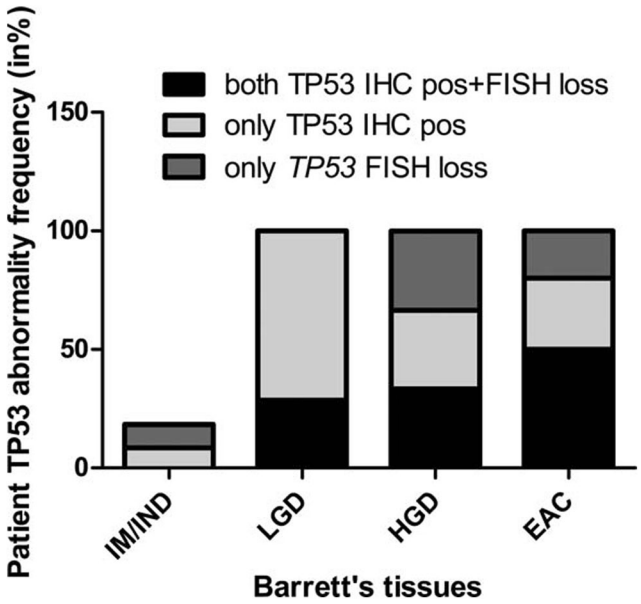

Fig. 1. Frequency distribution of p53 overexpression (by immunohistochemistry) and loss of TP53 gene locus by FISH by Barretts histologic categories [30].

96 and 7.3, 95% CI 1.3–41), respectively [30]. In a case-control study, 720 patients with BE were classified as cases if they developed HGD/EAC or as controls.

Overexpression of p53 was associated with increased risk of progression after adjusting for age, gender, length of BE, and esophagitis (adjusted RR 5.6, 3.1–10.3). Loss of p53 expression, although less common (5% vs 44% with p53 overexpression) was associated with an even higher risk of progression (RR 14, 5.3–37.2). Compared to normal p53 expression, aberrant p53 expression was associated with higher risk of progression in both NDBE (OR 4.5, 2.0–9.0) and LGD (11.2, 5.7–22.0) [31]. Finally, in a SRM, aberrant p53 expression was associated with increased risk of progression to EAC (OR 7.04, 3.68–13.46, $I^2 = 56\%$), remaining significant for both non-dysplastic BE (OR 6.12, 2.99–12.52) and LGD (OR 8.64, 3.62–20.62) (Fig. 2) [34].

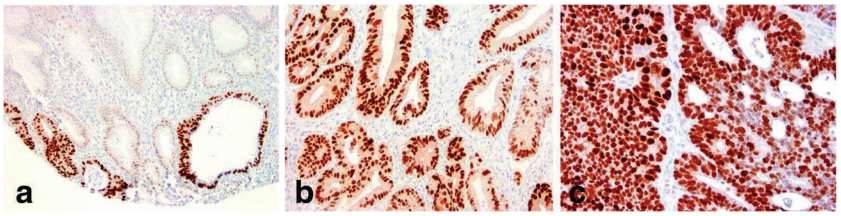

Fig. 2. p53 expression can be increased or is sometimes absent in BE. Top panel: **a** Negative control (no primary antibody) (× 200). **b** Barrett's mucosa with low-grade dysplasia, entire sample negative for p53 (× 400). **c** Barrett's mucosa with low-grade dysplasia, positive for p53 (× 400). **d** Barrett's mucosa with high-grade dysplasia, positive for p53 (× 400) [32]. *Bottom panel*: p53 immunostaining in a tissue array made from resected esophageal specimens. p53 expression in an area of high-grade dysplasia with adjacent mucosa negative for p53. **b** High-grade dysplasia with p53-positive immunostaining. **c** EAC with positive p53 immunostaining. In this study, 11% of NDBE, 0% of LGD, 57% of HGD, and 100% of EAC were positive for p53 [33].

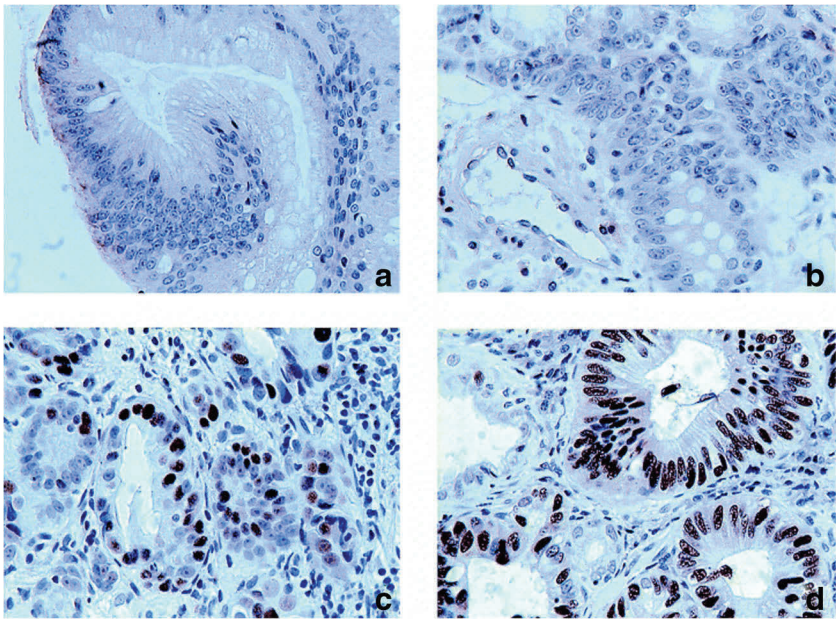

Fig. 2 continued.

A risk score that utilized LOH and microsatellite instability status of 10 specific loci also predicted progression to HGD. A combination of abnormal ploidy and expression of *Aspergillus oryzae* lectin (AOL) increased the odds of progression by 3–4-fold, with greater risk of progression in those with LGD [35]. A panel of four hypermethylated genes could stratify patients into low, intermediate, or high risk of progression with 94% sensitivity and 97% specificity, while another panel of eight genes distinguished progressors from non-progressors with an AUC of 0.84 and 0.83 at 2 and 4 years [36, 37].

A meta-analysis to identify genetic markers associated with susceptibility and progression of BE identified chromosomal instability as being significantly associated with increased odds of progression (Table 3). ORs for progression adjusted for length of BE and dysplasia ranged from 1.36–5.98. While LOH for

Table 3. Panel of biomarkers to predict risk of progression in BE

Marker	Number or genes	AUC
MYC-regulated genes	90	0.87 (0.82–0.93) to distinguish dysplastic from non-dysplastic BE 64% of LGD correctly at higher risk of progression correctly identified
Hypermethylated genes	4 (SLC22A18, PIGR, GJA12, RIN2)	Stratified patients into low, intermediate, high risk of progression with 94% sensitivity and 97% specificity
	8 genes (p16, RUNX3, HPP1, NELL1, TAC1, SST, AKAP12, CDH13)	AUC for BE progression 0.84 at 2 years and 0.83 at 4 years

From [19]

TP53 and *p16* and presence of a mutant *p53* were associated with higher odds of progression (ORs 5.4, 2.4 and 1.27, respectively), their odds ratios were not adjusted for degree of dysplasia.

Another prospective study from the Netherlands followed patients with NDBE with serial endoscopic biopsy surveillance (every 2–3 years for NDBE and 6 months for dysplastic BE) and brush cytology for fluorescence in situ hybridization (FISH). Four hundred ninety-eight patients were followed for a cumulative 2277 patient-years. Twenty-two patients progressed: nine developed HGD and 13 EAC (rate of progression to HGD/EAC was 0.97% per patient year). Univariate analysis revealed that loss of *p16*, gain of *MYC*, and aneusomy detected by FISH (using centromeric probes for chromosomes 7 and 17) were the genetic markers significantly associated with progression in NDBE. Age and length of circumferential BE were the other factors associated with progression. Age and the number of abnormal FISH markers remained significant predictors of progression on multivariable analysis. A model comprising of age, length of circumferential BE, and the number of abnormal markers had a 99% negative predictive value—i.e., 99% of patients would be correctly classified as non-progressors. Its positive predictive value, however, was only 9%. Hence, the panel appeared to be more helpful in identifying a low-risk group than a high risk group [38].

Models to predict risk of progression

Some investigators have attempted to develop models to predict the risk of progression using multiple clinical and biomarker-related variables. Using data from 2697 patients from a multicenter cohort, a risk assessment score using only clinical variables was recently proposed to predict the risk of progression to HGD or EAC (Table 4). This score has four components, each given a specific score—male gender (9 points), cigarette smoking (ever smoker getting 5 points), and length of BE segment (1 point for every 1-cm increase in length, up to a maximum of 10 points) and confirmed LGD (11 points). The total score is the sum of these four variables. Patients are divided into three categories stratified by annual risk of progression—low risk (0–10 points, 0.13%/year), intermediate risk (11–19 points, 0.73%/year), and high risk (> 20 points, 2.1%/year). The study was limited by lack of histological confirmation of the presence and degree of neoplasia by expert pathologists. Risk factors such as age, BMI, and medications (e.g., aspirin, NSAIDs, statin, and PPIs) were not significant predictors of progression of BE in this model [39••]. This score needs to be externally validated.

A second proposed BE progression prediction model is based on the field effect of cancer—i.e., pre-neoplastic changes in morphology and gene expression that surround areas of HGD or EAC (Table 4). The premise of this model is that detection of these alterations before progression (e.g., at index endoscopy which shows either NDBE, IND, or LGD) could potentially guide closer surveillance in those predicated to be at higher risk of progression. Using a case (patients who had HGD/EAC on repeat endoscopy within 1 year, or had prior history of treatment for HGD/EAC downgraded to NDBE/IND/LGD and then

Table 4. Models to predict progression in BE

Corresponding author	Type of predictors	Predictors	Technique	Outcome	Categories of risk progression	Accuracy of model
Sharma, P	Clinical features plus degree of dysplasia	Gender, cigarette smoking, length of BE, confirmed LGD	Assign points to each predictor and add up the points to calculate risk score	Annual risk of progression to HGD/EAC	Low risk (0.13%) Intermediate risk (0.73%) High risk (2.1%)	
Critchley-Thorne R.J.	Tissue morphology and biomarker	p16INK4a, AMACR, p53, HER2, K20, CD68 COX-2, HIF-1a, CD45RO	Automated analysis of FFPE slides for 15 morphologic features and IF pattern followed by calculation of risk scores	Progression from ND, IND or LGD to HGD or EAC within 12 months	Low risk (OR 1-reference) Intermediate risk (OR 7.7) High risk (OR 46)	AUROC progressors vs. non-progressors: 0.89

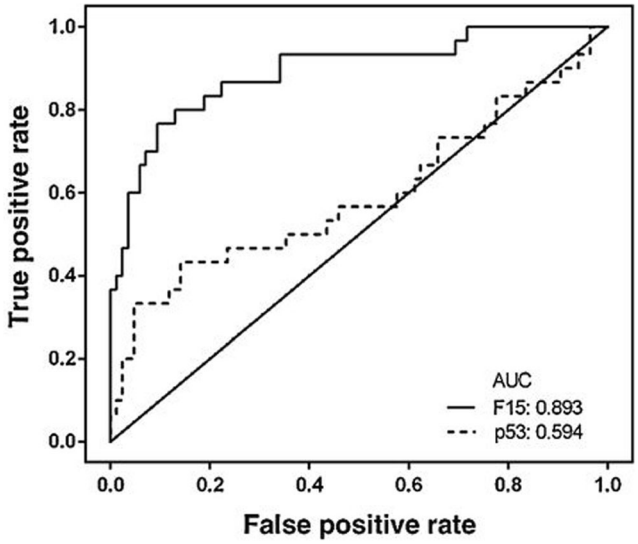

Fig. 3. An AUC curve compares the performance of a score using 15 features derived from automated image analysis to that of p53 in distinguishing progressors (HGD/EAC on repeat endoscopy within 1 year or previously treated HGD/EAC that returned to NDBE/LGD/IND followed by HGD/EAC on repeat endoscopy) from non-progressors (no HGD/EAC on follow-up).

had recurrent HGD/EAC) and control (i.e., patients who did not progress to HGD/EAC) study design and 15 variables including a combination of morphologic features and molecular marker expression, the authors created a model that could distinguish progressors from non-progressors with an area under the curve of 0.89 (Fig. 3). When progressors were subdivided into (a) those that were previously treated for HGD/EAC followed by regression to NDBE/IND/LGD or (b) those with no prior history of treatment for HGD/EAC, the model still predicted the development of HGD/EAC with good accuracy in either group (AUC 0.93 and 0.88, respectively). The advantage of this method was that it used automated image analysis of paraffin-embedded sections of mucosal biopsies thereby reducing inter-observer variability. Biomarker expression was assessed by immunofluorescence. The features extracted by the image analysis program were used to create a computer model which assigned a score from zero to 10. Based on the score, patients were divided into one of three categories—low, intermediate, or high risk for progression to HGD/EAC. Interestingly, the study found that in a patient with NDBE at one level and LGD at another level who progressed to HGD, the risk score was the same for the areas with NDBE and LGD, suggesting that the molecular changes due to the field effect do precede morphologic changes. One of the strengths of this model was that the diagnosis of BE and dysplasia was evaluated by three expert GI pathologists [40••].

Conclusions

Progression of BE to HGD or EAC is affected by patient demographics, lifestyle, medications, endoscopic features, and molecular markers. Recently, models have been described that help to stratify risk of progression better. Further studies are needed to validate these models and identify optimal strategies for

surveillance or therapy in patients at high risk of progression as well as determine their true negative predictive value.

Compliance with Ethical Standards

Conflict of Interest
Subhankar Chakraborty declares that he/she has no conflict of interest. Prasad Iyer reports grants from Exact Sciences, Pentax Medical, Intromedic, non-financial support from Medtronic, and is a consultant for Medtronic and CSA Medical.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

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Endoscopy (P Siersema, Section Editor)

Durability of Endoscopic Treatment for Dysplastic Barrett's Esophagus

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Keywords Barrett's esophagus · Dysplasia · Ablation · Long-term results · Durability

Abstract

Purpose of review This review discusses the durability of the neo-squamous esophageal epithelium following endoscopic eradication therapy of dysplastic Barrett's esophagus. Our review will focus primarily on patients treated with radiofrequency ablation; however, we describe the known durability of cryotherapy. Additionally, we discuss the utility of novel imaging technologies and the efficacy of chemopreventive medications following endoscopic ablation.

Recent findings Mounting data describe the durability of the post-ablation esophagus. Dysplastic Barrett's esophagus and adenocarcinoma following ablation are rare. New data emphasize that most recurrent disease occurs in the initial year following treatment. Additionally, recent publications suggest that a much-attenuated surveillance interval may provide adequate detection of neoplasia with many fewer surveillance endoscopies.

Summary Future guidelines will likely liberalize surveillance intervals following endoscopic eradication therapy. Additionally, further longitudinal studies will need to assess the length of time for which surveillance is indicated. The utility of chemopreventive strategies and adjunctive imaging modalities in the maintenance and surveillance of the post-ablation esophagus also remain unclear and will be areas for future investigation.

Introduction

Barrett's esophagus (BE) is a premalignant condition whereby intestinal metaplasia (IM), a specialized columnar epithelium, replaces the usual stratified squamous epithelium of the distal esophagus [1•]. BE represents a commonly encountered finding. In population-based cohort studies, the prevalence of BE was 1–2% [2, 3] and 15% [4] in all patients referred for endoscopy and in patients referred specifically for symptoms of gastroesophageal reflux, respectively. BE also increases the risk for esophageal adenocarcinoma (EAC) [1•]. Once diagnosed with EAC, less than 20% of patients survive to 5 years [5].

Significant advances have occurred in the management of BE over the last two decades. These advances include new techniques for endoscopic resection and ablation, collectively termed endoscopic eradication therapy (EET) [6–8]. Radiofrequency ablation (RFA) is the most frequently utilized EET given its substantial evidence base, efficacy, and infrequent complications [9]. High-quality data from clinical trials consistently show that EET reliably produces complete eradication of intestinal metaplasia (CEIM) and dysplasia with an acceptable safety profile [7, 10]. Moreover, newer data derived from cohort studies [11–15], RCTs [16], and systematic reviews [17•, 18] describe the long-term durability of the neo-squamous esophageal epithelium following EET. Though IM not infrequently recurs in the post-ablation esophagus [12, 19], most recurrent IM is amenable to further EET [12] and is associated with a benign course [20].

In this review, we discuss the durability of the neo-squamous esophageal epithelium following EET of dysplastic BE. The available body of literature will focus our discussion on patients treated with RFA, though the durability of cryotherapy will be briefly considered. In addition, we discuss the use of novel imaging technologies in the surveillance of BE following CEIM, as well as the efficacy of chemopreventive strategies in the prevention of recurrent disease.

Variable definitions are utilized to describe the durability of the post-ablation neo-squamous esophagus

Significant heterogeneity exists in the literature describing the durability of the post-ablation esophagus. This heterogeneity principally derives from three sources. First, no consensus definition of CEIM exists. In addition, investigators variably define recurrent disease. Finally, the designs of the relevant studies also differ. Variable surveillance protocols, patient populations, and treatments underscore the latter point.

The complete eradication of dysplasia and intestinal metaplasia defines success in the application of EET. However, given concern over sampling error intrinsic to random biopsies, some investigators have required two negative biopsy sessions to define complete eradication, while others require only one such exam. For instance, papers analyzing data from the AIM Dysplasia Trial [21, 22•] and the US RFA Patient Registry [11] required complete histologic and endoscopic remission of IM on a single biopsy session following treatment to define CEIM. Alternatively, papers from the Barrett's Esophagus Translational Research Network (BETRNet) Consortium required at least two sessions with histologic and endoscopic remission of IM to define CEIM [12]. Though the latter definition may partially mitigate sampling error, no data objectively describe an ideal number of biopsy sessions devoid of recurrent disease. Certainly, if two is better than one, three should be better than two. Therefore, by using this rationale, it is difficult to know the "right" definition of durability, and no matter which number is chosen, the specter of residual sampling error persists, albeit to a presumably lesser degree. Furthermore, papers from the AIM

Dysplasia Trial and US RFA Patient Registry also conducted sensitivity analyses assessing the impact on recurrent rates of disease using the alternative definition of CEIM, and these rates did not differ significantly [11, 22•]. These sensitivity analyses argue that a definition incorporating a single normal endoscopy session optimizes the amount of follow-up time without markedly impairing data quality.

Investigators also variably define recurrent disease, and these differences pertain to anatomic loci. Some investigators have defined recurrent disease as IM or dysplasia located solely within the tubular esophagus [13], while others have termed recurrent disease to be IM located within both the tubular esophagus and the gastroesophageal junction and cardia [23], or even disease located solely in the cardia [20]. Significant uncertainly exists as to the optimal disease definition for recurrent disease. Dysplasia confined to the cardia following CEIM may suggest recurrent disease or dysplasia missed on pre-CEIM biopsies, owing to sampling error. Because few investigators contest the clinical relevance of dysplasia of the cardia, most clinicians consider this finding to be a failure of EET, and therefore include it in a definition of recurrent disease. IM of the cardia, on the other hand, is common place in patients with chronic GERD; approximately 20% of patients with chronic GERD symptoms without BE have non-dysplastic IM of the cardia [24]. The natural history of IM of the cardia is unclear, and the clinical data we do have on this entity suggest that, at least in the chronic GERD population, the risk of malignant progression is low. Therefore, the finding of IM of the cardia alone on surveillance biopsies after CEIM is not considered recurrent disease by most investigators. It is important to further note that in order to discover dysplasia or IM of the cardia, one must take biopsies of the cardia, and biopsy regimens in durability studies have varied considerably both in number and location.

Subsquamous Barrett's esophagus following endoscopic eradication therapy

Buried BE, also known as subsquamous IM, refers to the presence of IM beneath a normal layer of squamous esophageal epithelium (Fig. 1). Debate exists regarding the malignant potential of this finding. Moreover, the rate of detection of subsquamous IM following CEIM varies drastically by EET modality and means of detection. For instance, rates of buried BE post-RFA and photodynamic therapy have been estimated at 0.9% and 14.2%, respectively [24–26]. The addition of a novel imaging technology, such as three-dimensional optical coherence tomography, increased detection to as high as 63% of patients [27].

Though the prevalence of buried Barrett's esophagus remains in dispute, this finding apparently represents a benign lesion in the vast majority of patients. Subsquamous EAC following CEIM has seldom been reported despite a large body of literature. Furthermore, the risk of subsquamous IM appears to decrease following endoscopic ablation. Data from the AIM Dysplasia Trial showed that, using a highly protocolized standard biopsy technique, the prevalence of subsquamous IM decreased from 25.2 to 5% and subsequently 3.8% following 12 and 24 months of surveillance post-RFA [7]. For these reasons, although subsquamous IM is a common occurrence after apparently successful EET, the clinical significance remains unclear. Because of the unclear significance of this finding, the most appropriate clinical response to subsquamous IM is similarly not understood. While some endoscopists further treat such patients with EET,

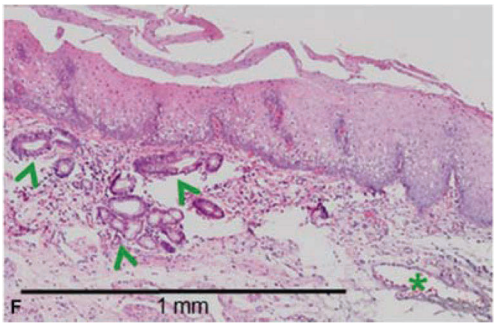

Fig. 1. Arrowheads indicate buried Barrett's glands in a patient with Barrett's esophagus in surveillance following radiofrequency ablation. From Swager A, Boerwinkel D, de Bruin DM, et al. Detection of buried Barrett's glands after radiofrequency ablation with volumetric laser endomicroscopy. Gastrointest Endosc. 2016;83(1):80–8. Figure 3F. Used with permission from Elsevier.

others perform endoscopic surveillance in this population and only intervene further if dysplastic changes are noted.

The durability of the neo-squamous epithelium following the complete eradication of intestinal metaplasia

Data from multiple cohort studies [11–15], RCTs [16, 28, 29], and systematic reviews [17•, 18] describe the durability of CEIM and complete eradication of dysplasia. Though EETs effectively achieve CEIM, recurrent IM is common and occurs in approximately 25% of patients at a rate of 8–10% per patient-year of follow-up [12, 19, 30]. However, most recurrences are associated with a benign clinical course [20], as recurrent dysplastic IM or recurrent BE with histologic progression (i.e., recurrent disease with a histologic grade more advanced to pre-CEIM grade) occurs in a minority of cases [11]. Moreover, EAC is rare in post-ablation surveillance cohorts [31•], and <1% of patients treated with EET require esophagectomy [32].

Overall durability of Barrett's esophagus and incidence of non-dysplastic IM following the complete eradication of intestinal metaplasia

Multiple studies document that the predominant histologic subtype for recurrence after CEIM is non-dysplastic IM. One study analyzing data from the US RFA Patient Registry, a multi-center collaboration documenting outcomes of care for patients treated with RFA for BE at 148 US institutions [11], assessed 1634 patients for 2.4±1.3 years subsequent to CEIM. Of these, 668 (31%) of the cohort had non-dysplastic BE prior to ablation. In this cohort, recurrence of any disease was seen in 334 (20%) patients (Fig. 2a, b). Non-dysplastic or indefinite for dysplasia recurrence accounted for 287/335 (86%) recurrences. Similarly, data from the AIM Dysplasia Trial analyzed the rate of recurrent disease in patients achieving CEIM following EET for dysplastic BE [22•] (Fig. 3a, b). In this trial, 110/127 (92%) subjects achieved CEIM and were subsequently followed for a mean time of 2.9 years (range 0.2–5.5). Of these 110 patients, 35 (32%) experienced any recurrent disease. Twice as many patients in this study recurred with NDBE than with dysplasia. A second study

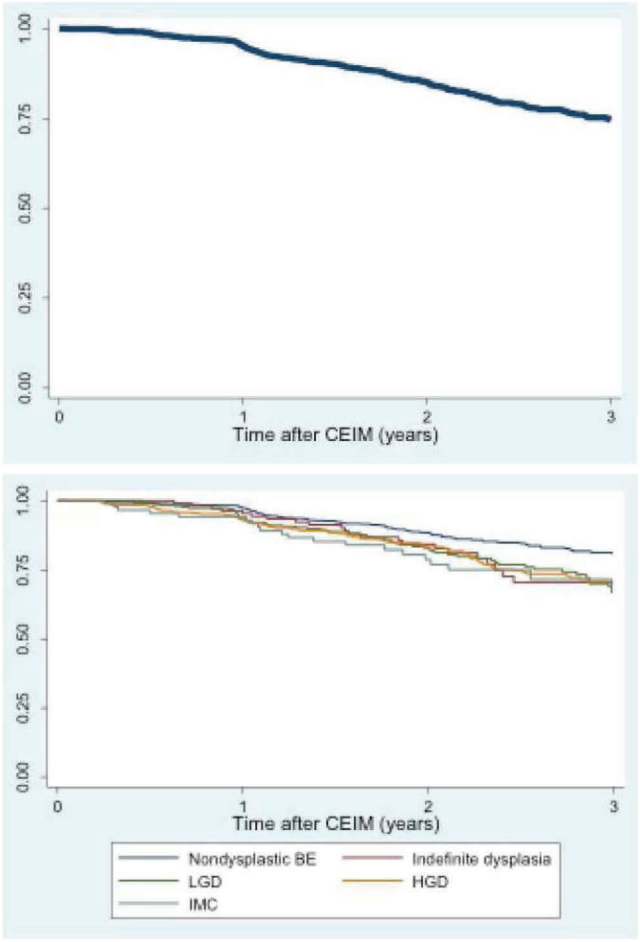

Fig. 2. a Kaplan-Meier plot of intestinal metaplasia recurrence among patients who achieved complete eradication of intestinal metaplasia after RFA (*n*=1634). From Pasricha S, Bulsiewicz WJ, Hathorn KE, et al. Durability and Predictors of Successful Radiofrequency Ablation for Barrett's esophagus. Clin Gastroenterol Hepatol. 2014;12(11):1840–1847. Figure 2a. Used with permission from Elsevier. **b** Kaplan-Meier plot of IM recurrence among patients who achieved CEIM after RFA, with pretreatment histology non-dysplasic BE, low-grade dysplasia (LGD), and high-grade dysplasia (HGD). From Pasricha S, Bulsiewicz WJ, Hathorn KE, et al. Durability and Predictors of Successful Radiofrequency Ablation for Barrett's esophagus. Clin Gastroenterol Hepatol. 2014;12(11):1840–1847. Figure 2b. Used with permission from Elsevier.

of patients in the BETRNet Consortium, additionally, described outcomes for patients treated with RFA [12]. Most of the 448 patients in this study had baseline dysplastic BE; there were 385 (86%) with dysplastic BE or EAC. Ultimately, 229 (51%) achieved CEIM, and 37/229 (16%) patients were found to have recurrent disease. However, the mean follow-up time was short with an average of 3 months (range 0 days–4.6 years) per patient. The majority of the 37 documented recurrences (78%) were also non-dysplastic. Pooled estimates for the overall incidence of recurrent disease have also been reported in systematic reviews and meta-analyses [14]. The overall pooled incidence rate for any recurrent disease following RFA was estimated at 8.6/100 PY (95% CI 6.7–10.5/100 PY).

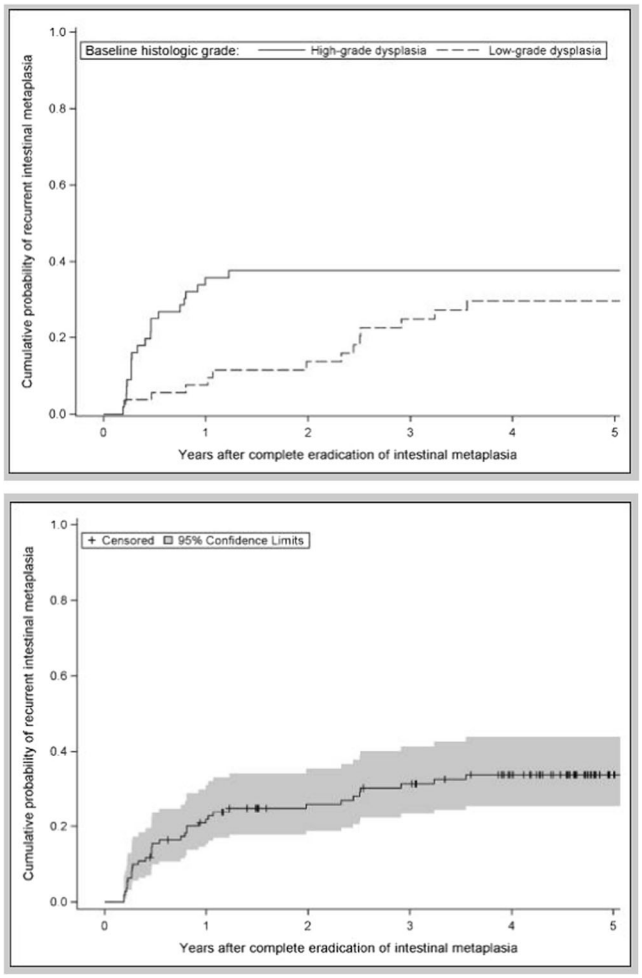

Fig. 3. a Estimated proportion of subjects with any recurrence of intestinal metaplasia recurrence stratified by baseline histologic grade after complete eradication of intestinal metaplasia now allowing interim "touch-up" treatments. From Cotton CC, Wolf WA, Overholt BF, et al. Late Recurrence of Barrett's Esophagus After Complete Eradication of Intestinal Metaplasia is Rare: Final Report From Ablation in Intestinal Metaplasia Containing Dysplasia Trial. *Gastroenterology*. 2017;153(3):681–688. Figure 2. Used with permission from Elsevier. **b** Estimated proportion of subjects with any recurrence after complete eradication of intestinal metaplasia not allowing interim touch-up treatments. From Cotton CC, Wolf WA, Overholt BF, et al. Late Recurrence of Barrett's Esophagus After Complete Eradication of Intestinal Metaplasia is Rare: Final Report From Ablation in Intestinal Metaplasia Containing Dysplasia Trial. *Gastroenterology*. 2017;153(3):681–688. Figure 3. Used with permission from Elsevier.

Recurrence of dysplastic Barrett's esophagus following the complete eradication of intestinal metaplasia

As opposed to non-dysplastic recurrent disease, dysplastic disease following CEIM with RFA is a rarer finding. In the aforementioned US RFA Registry study [11], there were 34/334 (10%) recurrences containing dysplasia. Low-grade dysplasia (LGD) and high-grade dysplasia (HGD) comprised 19 (6%) and 15 (4%) of these findings. In the paper by Cotton et al. assessing data from the AIM Dysplasia Trial, following 363.1 person-years of follow-up (mean 3.3 years per patient), there were 19 (17%) dysplastic recurrences. The overall incidence rate

Table 1. Recurrent disease by preradiofrequency ablation histology in selected studies. From Reed CC, Shaheen NJ. Natural History of the Post-ablation Esophagus. Dig Dis Sci. 2018;63(8):2136–2145. Table 1. Used with permission from Springer Nature

Study	Preradiofrequency ablation histology, *n* (%)						
	Total patients	NDBE	IND	LGD	HGD	IMC	EAC
Gupta et al. [12]							
Pretreatment number	229	NR	NR			NR	
Any post-RFA recurrence	37 (16)						
HR and 95% CI				0.66 (0.25, 1.76)	0.53 (0.23, 1.19)		0.52 (0.14, 1.91)
Cotton et al. [22•]							
Pretreatment number	NR	NR	NR	54	55	NR	NR
Any post-RFA recurrence				14 (26)	21 (38)		
Orman et al. [20]							
Pretreatment number	107	NR	NR	23	67	17	NR
Any post-RFA recurrence	8 (7)			1 (4)	5 (7)	2 (12)	
Small et al. [48]							
Pretreatment number	158	NR	NR	NR	95	64	NR
Any post-RFA recurrence	81 (51)				48 (51)	33 (52)	
Wolf et al. [31•]							
Pretreatment number	4982	2346	368	1020	990	195	63
Post-RFA EAC	100 (2)	3 (0.1)	2 (0.5)	12 (1)	83 (8)	–	–
Small et al. [48]							
Pretreatment number	24	NR	NR	NR	95	64	NR
Any post-RFA recurrence	81 (51)				48 (51)	33 (52)	
Pouw et al. [49]							
Pretreatment number	24	NR	NR	NR	NR	NR	NR
Any post-RFA recurrence	4 (17)						

NDBE non-dysplastic Barrett's esophagus, *IND* indeterminate for dysplasia, *LGD* low-grade dysplasia, *HGD* high-grade dysplasia, *IMC* intramucosal carcinoma, *EAC* esophageal adenocarcinoma, *RFA* radiofrequency ablation, *HR* hazard ratio, *95% CI* 95% confidence interval for recurrence, *NR* not reported

of dysplastic recurrence was 5.2/100 PY (95% CI 3.3–8.2) [22•]. Of the 37 patients included within the BETRNet Consortium study with documented recurrence, 8/37 (22%) were dysplastic [12]. These individual findings were reflected in the pooled estimated recurrence rate of dysplastic IM described in a systematic review and meta-analysis of 1.9/100 PY (95% CI 1.3–2.5/100 PY) [14].

Risk of disease recurrence stratified by pretreatment histologic grade

The most severe pretreatment grade of BE prior to CEIM consistently associates with post-treatment outcomes (Table 1). Data derived from the AIM Dysplasia Trial illustrate this finding. These investigators documented incidence rates for any recurrence of 10.8 per 100 PY (95% CI 8.7–15.0/100 PY), 8.3 per 100 PY (95% CI 4.9–14.0/100 PY), and 13.5 per 100 PY (95% CI 8.8–20.7/100 PY) for all baseline histologic grades, baseline LGD, and baseline HGD, respectively [22•]. When considering dysplastic recurrence specifically, similar findings were reported. Here, an overall rate of dysplastic recurrence of 5.2 per 100 PY (95% CI 3.3–8.2/100 PY) was documented. The rates of dysplastic recurrence among patients with baseline LGD and HGD were 3.3 per 100 PY (95% CI 1.5–7.2/100 PY) and 7.3 per 100 PY (95% CI 4.2–12.5/100 PY). Increasingly severe pretreatment histologic grade was also associated with overall recurrence rates in data from the US RFA Patient Registry [11]. Yearly recurrence rates were 7% for patients with baseline non-dysplastic BE, 11% for patients with baseline LGD, 10% for patients with baseline HGD, 12% for patients with baseline IMC, and 19% for patients with baseline EAC.

Risk for histologic progression and esophageal adenocarcinoma following endoscopic eradication therapy

In the setting of BE with CEIM, histologic disease progression denotes the recurrence of BE with a histologic grade more advanced than that found prior to treatment. This finding occurs infrequently. As noted in the previously described US RFA Registry study, recurrent disease with histologic progression occurred in 6% (20/334) of cases with recurrent disease, and 1.2% of the total number of patients treated [11]. Histologic progression was also rare in the BETRNet Consortium study. These investigators found a single (1/37) recurrent case with progression. In this case, the patient, who had HGD at baseline, progressed to IMC [12].

An additional study analyzing data from the US RFA Registry estimated the incidence of EAC following RFA in a cohort of 4698 patients [31•]. Of these 4698 patients, 3946 (84%) with CEIM were followed for on average for 2.7 ±1.6 years. There were 100 (2%) with diagnoses of EAC. A slight majority (54 patients) was IMC with the rest being invasive EAC (46 patients). Through the follow-up period described in this paper, 9/157 (0.6%) deaths were attributed to EAC.

A systematic review collated the risk for EAC following EET [14]. Of 1000 relapses included within this systematic review, 54/1000 (5.4%) contained EAC. It is worth noting that 25/39 studies included within the systematic review solely assessed RFA. The remainder examined stepwise complete endoscopic mucosal resection, and as such, the aforementioned estimate of 5.4% derives from both procedure types.

Risk of recurrent intestinal metaplasia or Barrett's-associated neoplasia as a function of time following EET

The risk of recurrent IM and BE with dysplasia likely varies with time from initial ablative therapy, though papers variably report this association. For instance, a retrospective cohort study examined time to recurrence of disease following CEIM with RFA in 218 patients [21]. For these 218 patients, 24% had recurrence of IM or Barrett's-associated neoplasia in 540.6 PY of follow-up time. The mean time to recurrence was 1.88 years (SD±1.42), with an average of 2.32 surveillance endoscopies (SD±1.35) prior to recurrence, and an incidence rate of 9.6% per year. From this analysis, the authors concluded that the rate of recurrence and proportion of patients with recurrence were constant over time. Other data [12, 22•] suggest that the rate of recurrent IM and dysplastic BE differs with increasing time from ablation. In a study utilizing data from the AIM Dysplasia Trial [22•], recurrent disease was overwhelmingly found in the first year or surveillance (e.g., 24 of 35 recurrences). A survival analysis [12] similarly found that the incidence of recurrent disease in year 1 was 20% and only 33% by year 2. It is unclear whether these differences reflect underlying differences between the patient populations, or perhaps a type 2 error due to inadequate patient numbers in some trials.

Durability of the post-ablation neo-squamous epithelium in patients treated with cryotherapy

Cryotherapy, utilizing liquid nitrogen or carbon dioxide, is an alternative EET for BE. This method consists of the application of a cryogen (e.g., liquid nitrogen, nitrous oxide, or carbon dioxide) through a low-pressure catheter directly upon affected tissue. Though RFA represents an effective means of producing CEIM, treatment-related strictures occur in approximately 5% of patients [32]. Cryoablation, as opposed to RFA, leaves the tissue architecture of the superficial squamous layers relatively intact and may result in a decreased rate of treatment-related stenosis. Additionally, some data suggest that patients treated with cryotherapy may suffer less post-procedural pain [33].

Data from a single-center retrospective cohort study reported outcomes following liquid nitrogen spray cryoablation at 3 and 5 years [34•]. This study describes a cohort of 50 patients with HGD followed for 3 years and 40 patients followed up to 5 years following therapy. The authors report 98% (49/50) with complete eradication of HGD, 90% (45/50) with complete eradication of dysplasia, and 60% (30/50) with CEIM initially. In the 45 patients with initial complete eradication of dysplasia, 11/45 (24%) were found to have recurrent dysplasia at 3 years. For the 30 patients with initial CEIM, 12/30 (40%) had recurrent IM at 3 years. Following 5 years in the 40 patients, the authors documented that the durability of complete eradication of HGD was 96%, the durability of complete eradication of dysplasia was 92%, and the durability of CEIM was 81%. Overall, there were two cases of EAC with no reported deaths.

This data must be considered in light of the much larger body of literature pertinent to the utilization of RFA for BE. The role of cryotherapy in the treatment of dysplastic BE remains to be fully elucidated and ultimately may require head-to-head trials with RFA.

Surveillance endoscopy intervals following the complete eradication of intestinal metaplasia

Current recommendations for surveillance endoscopy following the complete eradication of intestinal metaplasia

At present, consensus guideline recommendations endorse indefinite surveillance at intervals determined by the highest pretreatment histologic grade preceding CEIM [1•]. The data supporting these guidelines derive largely from cohort studies and expert opinion [13, 20]. Current recommendations include surveillance endoscopy every 3 months in the first year following CEIM for patients with baseline HGD or IMC. This is followed by every 6 months in the second year and additional surveillance endoscopy yearly. For patients with LGD at baseline, recommendations include surveillance every 6 months in the first year after CEIM followed by annual assessment [1•].

Surveillance intervals following complete eradication of intestinal metaplasia as informed by new data on the durability of the post-ablation esophagus

Though effective in producing low rates of unresectable EAC following CEIM [35], current consensus recommendations [1•] are likely too aggressive. This supposition makes intuitive sense given that post-ablation recommendations mirror identically the intervals recommended for patients who have not undergone treatment. RFA lowers incident cancer risk, so surveillance protocols should reflect this decreased risk with less intense surveillance. Data from the AIM Dysplasia Trial, US RFA Registry, and UK National Halo Registry (UK NHR) were utilized to propose new surveillance intervals following CEIM [15•, 22•].

An analysis of data from these two registries allowed investigators to build and validate models to predict the risk of neoplasia (e.g., LGD, HGD, or EAC in

Table 2. Recommended time after complete eradication of intestinal metaplasia to perform surveillance endoscopy based on new data. From Cotton CC, Haidry R, Thrift AP, et al. Development of Evidence-Based Surveillance Intervals After Radiofrequency Ablation of Barrett's Esophagus. *Gastroenterology*. 2018;155(2):316–326.e6. Table 2. Used with permission from Elsevier

Risk category	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Low-grade dysplasia	1 years	3 years	>5 years[a]	a	a	a	a	a
High-grade dysplasia or adenocarcinoma in situ	3 months	6 months	1 year	2 years	3 years	4 years	5 years	>5 years[a]

[a]Surveillance times were estimated to a limit of 5 years for the higher two-risk categories and 7 years for the lower risk categories to avoid extrapolation beyond the data

Table 3. Comparing the number of surveillance endoscopies that would be performed in the US Radiofrequency Ablation Registry and the UK National Halo Registry Under Current Surveillance Regimens and Newly Proposed Regimens. From Cotton CC, Haidry R, Thrift AP, et al. Development of Evidence-Based Surveillance Intervals After Radiofrequency Ablation of Barrett's Esophagus. *Gastroenterology*. 2018;155(2):316–326.e6. Table 3. Used with permission from Elsevier

Surveillance risk group	Patients in surveillance	Endoscopies under current recommendations	Endoscopies under proposed recommendation	Actual reduction in stratum %	Total reduction for population (%)
US Radiofrequency Ablation Registry					
2: Low-grade dysplasia	658	3948	1316	67	38
3: High-grade dysplasia or intramucosal adenorcarcinoma	767	6903	5369	22	
UK National Halo Registry					
2: Low-grade dysplasia	83	498	166	67	29
3: High-grade dysplasia or intramucosal adenocarcinoma	290	2610	2030	22	

the esophagus or cardia) after CEIM by RFA [15•]. Using their model to predict histologic recurrence of neoplasia, they found that HGD and IMC overlapped in the estimated risk of recurrence. This was also true for patients with baseline non-dysplastic BE and indeterminate for dysplasia. Annual rates of recurrence with neoplasia was 0.19% (95% CI 0.09–0.40) in those with pre-CEIM non-dysplastic BE and indeterminate for dysplasia, 1.98% (95% CI 1.34–2.93) in those with pre-CEIM LGD, and 5.93% (95% CI 4.77–7.36) in patients with pre-CEIM HGD or IMC. The investigators subsequently choose 2.9% as the rate of neoplastic recurrence per surveillance endoscopy to produce an estimated rate of invasive EAC of 0.1%. This level of risk was chosen in light of the complication rate associated with endoscopic surveillance. Their analysis allowed them to propose surveillance endoscopy at 1 and 3 years after CEIM for patients with baseline LGD. For patients with baseline HGD or IMC, suggested surveillance endoscopy intervals of 3 months, 6 months, and annually to 5 years were proposed. Given limitations in their data, recommendations could not be extrapolated beyond the fifth year (Table 2). These attenuated surveillance intervals should provide a low constant rate of incident recurrence with neoplasia, while accomplishing a sizable reduction in the overall number of upper endoscopies necessary to survey post-ablation populations, when compared with current recommendations (Table 3).

Management of recurrent Barrett's esophagus following the complete eradication of intestinal metaplasia

Following CEIM, recurrent IM and BE with dysplasia may be treated with further EET [13, 22•, 23, 25]. In a 2017 study, second CEIM was obtained in 58% of subjects with recurrence of IM or Barrett's-associated neoplasia. It is worth noting that 37% of the patients with recurrent disease were still completing EET when the paper was published. As such, the success of EET in this setting was likely under reported. Of the 30 patients achieving second CEIM, a third recurrence was found in 13%. However, a minority (4%) of patients in this study ultimately failed endoscopic re-treatment and progressed to EAC [21].

Novel imaging and sampling modalities in the surveillance of Barrett's esophagus patients obtaining complete eradication of intestinal metaplasia

Random biopsies of the esophagus can miss areas of dysplasia or IMC as a consequence of sampling error [1•, 36–38]. Careful endoscopic examination and advanced imaging and sampling technologies, including volumetric laser endomicroscopy (VLE) and wide-area trans-epithelial sampling (WATS), represent potential solutions to this problem.

At present, careful endoscopic examination of the esophageal mucosa under high-resolution white light endoscopy following CEIM represents the standard

of care for detection of residual or recurrent BE. Careful examination of both the tubular esophagus, in the region of the prior BE segment, and the GEJ junction in both antegrade and retrograde views is essential [1•]. Most studies suggest obtaining four-quadrant biopsies through the previous area of BE as well as obtaining targeted biopsies of abnormal areas [1•]. A substantial proportion of patients treated in the community setting, however, do not undergo adequate biopsies during surveillance examinations compromising dysplasia detection [39].

Recent data documented that recurrent IM is most common at or near the gastroesophageal junction. Recurrent disease within the tubular esophagus greater than a centimeter proximal to the gastroesophageal junction generally recurs with visible abnormalities, not as an incidental finding on surveillance biopsies [35]. Additionally, recurrence of disease within the cardia is common, and biopsies should be obtained from this anatomic location. Recurrence within the cardia, though, also tends to occur within 1 cm of the gastroesophageal junction [21].

Advanced modalities, such as VLE and WATS, may better identify residual IM and neoplasia after ablation and increase diagnostic yields for recurrent disease relative to random biopsies [40]. Data exist for both VLE [41] and WATS [42, 43], but these findings require further confirmation.

Chemopreventive strategies for patients following esophageal ablation

The efficacy of chemopreventive medications for the prevention of recurrent IM or dysplastic BE following CEIM remains unknown. However, poor reflux control in this setting is believed to increase the risk for recurrent disease [14]. Current consensus recommendations promote control of reflux symptoms as well as the prevention or healing of reflux esophagitis [1•]. Typical recommendations include twice daily PPI in this cohort. Though not assessed in the setting of CEIM, data from a recent RCT suggest that high-dose PPI, over standard dosing, may safely improve outcomes in patients with BE [44•]. Performance of pH testing while on PPI is reasonable to assess treatment efficacy in patients desiring discontinuation of these medications [45]. Though data specifically addressing this question remain sparse, a standardized reflux management protocol for patients obtaining CEIM may provide improved durability of the neo-squamous esophagus when compared with historical controls [17•].

Prior studies associate the use of non-steroidal anti-inflammatory drugs (NSAIDs) with a reduction in risk for EAC in the general population [46, 47]. Moreover, though again assessed in a patient population naïve to BE treatment, aspirin in combination with high-dose PPI may reduce the time to progression in BE. However, this finding was non-significant [44•]. Given the relatively low risk of EAC following CEIM, the bleeding risk associated with NSAIDs/aspirin may very well exceed the use of these medications as a chemopreventive strategy in this setting [1•].

Conclusion

In most cases, EET is the preferred treatment strategy for patients with BE and early neoplastic changes. These modalities are effective with an acceptable side effect profile. Mounting data describe the durability of CEIM in the post-ablation esophagus. Dysplastic BE and EAC post-CEIM are rare, though recurrent IM following EET is relatively common. Recent studies underscore this finding and suggest that current surveillance intervals following CEIM are too aggressive. Future investigation will better determine the length of time for which surveillance is indicated post-CEIM, the efficacy of chemopreventive strategies in preventing recurrent disease, and the utility of advanced technologies during surveillance to reduce sampling error.

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Compliance with Ethical Standards

Conflict of Interest

Nicholas Shaheen reports grants from Medtronic, CSA Medical, C2 Therapeutics, CDx Medical, and Interpace Diagnostics and personal fees from Pfizer and Boston Scientific.
Craig Reed declares no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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REVIEW

Uncommon imaging evolutions of focal liver lesions in cirrhosis

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Abstract

Objective The purpose of this article is to describe and illustrate uncommon imaging evolutions of benign (i.e., cyst, hemangioma, focal nodular hyperplasia-like nodules, and hepatic angiomyolipoma) and malignant (i.e., HCC and non HCC malignancies) lesions in a cirrhotic liver. The content highlights relevant pathogenesis and imaging clues for proper differential diagnosis. Revision of prior imaging and knowledge of these scenarios may help the abdominal radiologist to reach a noninvasive diagnosis and direct the patient to the most appropriate clinical management.

Conclusion Uncommon imaging evolutions of focal liver lesions in cirrhosis may represent a challenge for the abdominal radiologist, with atypical changes in size, and internal vascularization changes that may lead to misdiagnoses.

Keywords Hepatocellular carcinoma · Magnetic resonance imaging · Computed tomography · Liver cirrhosis · Liver neoplasms

Introduction

The detection and characterization of focal liver lesions in cirrhotic patients is a daily, challenging task for the abdominal radiologist. One of the most important clinical scenarios is the differentiation of hepatocellular carcinoma (HCC)—which is the most common malignant lesion arising in a cirrhotic liver—from other focal lesions that may be encountered in cirrhosis including cysts, hemangiomas, focal confluent fibrosis, regenerative nodules, dysplastic nodules, and non-HCC malignancies. When the typical imaging features are visualized (i.e., arterial phase hyperenhancement, portal-venous phase, or delayed phase washout and enhancing capsule), it is possible to make a definitive diagnosis of HCC without the need of a pathological confirmation [1]. However, in a cirrhotic liver, both benign and malignant lesions may lack typical imaging features. The definitive diagnosis may therefore require comparison with prior studies, imaging follow-up, or tissue sampling.

Prior and serial follow-up imaging examinations allow for the evaluation of lesion stability or size change, with lesion growth suggesting a diagnosis of malignancy [1], while size stability or reduction suggesting benignity [2].

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However, the increase in size of a benign or non-HCC lesion, although uncommon, may occur [3, 4], resulting in a false positive rate of 17% when using threshold growth as major imaging feature for the diagnosis of HCC in cirrhosis [2]. Conversely, hepatic malignancies may uncommonly show spontaneous shrinkage or disappearance without treatment [5]. These atypical evolutions add several clinical challenges for the radiologists and hepatologists and may induce pitfalls in imaging interpretation with significant implications for patients' management.

In this review article, we report our experience with uncommon or very rare cases of imaging evolution of benign lesions (i.e., hepatic cyst, hemangioma, angiomyolipoma) as well as malignant lesions (i.e., HCC, cholangiocarcinoma, metastases) in cirrhotic patients. Uncommon evolution of these lesions in cirrhosis include atypical changes in size, imaging evolution of the enhancement pattern, as well as, unexpected very long-term recurrence of malignancy.

Benign liver lesions

Atypical size changes

Lesion stability or shrinkage in cirrhotic liver has a reported specificity of 99% for the diagnosis of benignity in untreated lesions [2]. This high specificity allows for a confident diagnosis of benign lesions even when typical imaging features are lacking. As an example, hepatic cyst may demonstrate spontaneous increased attenuation which may limit the evaluation of contrast enhancement on CT and MRI. In these cases, the signal intensity on T2-weighted images, the evaluation of subtracted images, as well as the stability or decrease in size in the long term generally permits a confident diagnosis (Fig. 1). Pseudolesions in a cirrhotic liver may appear as enhancing nodules on hepatic arterial phase, thus mimicking malignancy (Fig. 2) [6, 7]. However, the lack of visibility on MR images acquired during the hepatobiliary phase and the absence of diffusion restriction [7], stability, or decrease in size at imaging follow-up are usually sufficient to suggest a diagnosis of benignity. In cirrhosis,

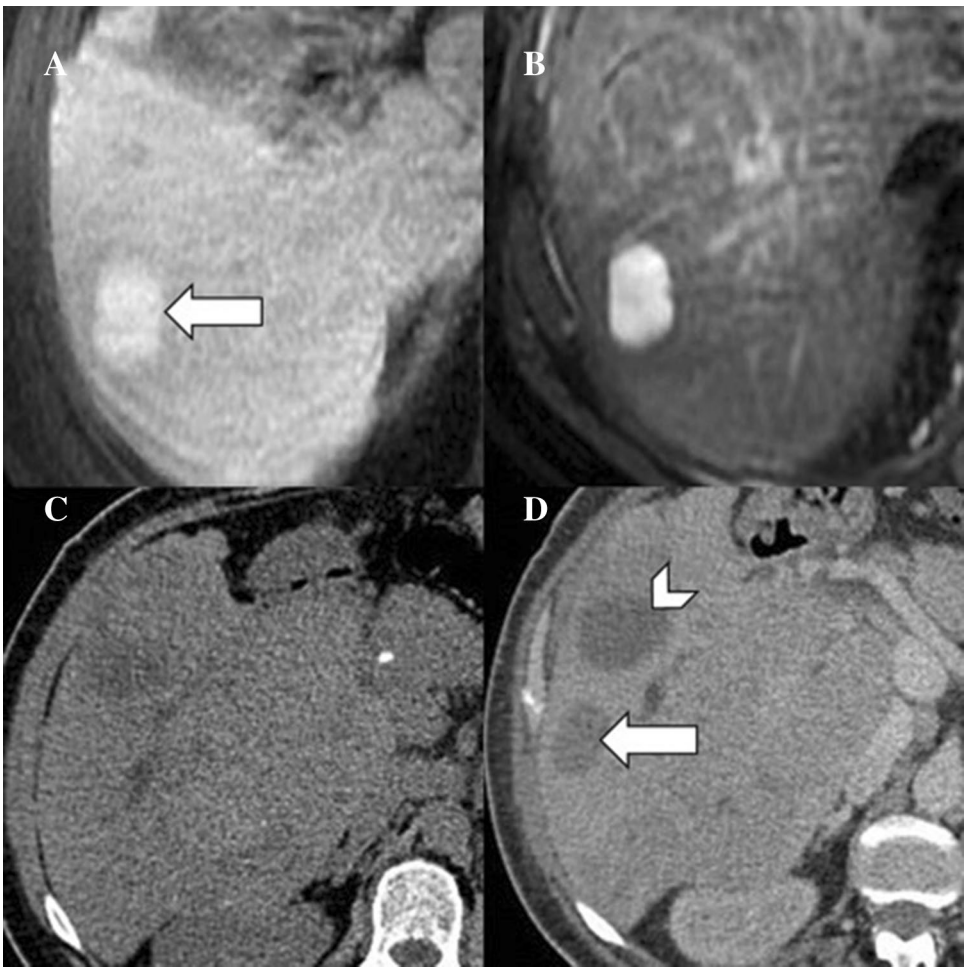

Fig. 1 63-year-old man with nonalcoholic cirrhosis. Axial baseline MRI scan shows a 3.6 cm cyst (arrow) hyperintense on T1-weighted image (**a**) and hyperintense on T2-weighted image (**b**), consistent with hemorrhagic cyst. At 5-year CT follow-up (C and D), the cyst (arrow) slightly reduces in size (3.0 cm), and it is iso-attenuating to the liver on unenhanced (**c**) and hypoattenuating (arrow) on portal-venous phase (**d**) CT images. Please note an adjacent observation (arrowhead) representing a treated HCC

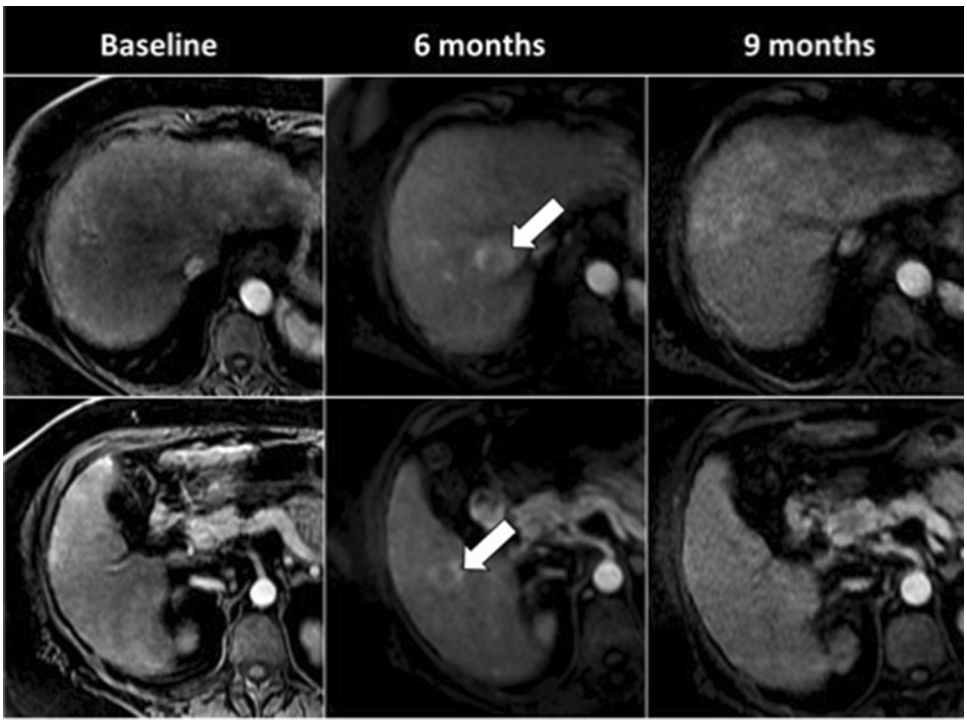

Fig. 2 72-year-old woman with NASH cirrhosis. On baseline MRI examination, no focal liver lesion is noted on the images obtained during the hepatic arterial phase. At six-month follow-up MRI, two lesions (arrows) with rim arterial phase hyperenhancement in segments 8 and 6 are categorized as LR-M observations (i.e., high likelihood of being malignant but with imaging presentation not typical for HCC). These lesions disappeared on the follow-up MRI performed at 9 months with no interval treatment. Ultrasound target liver biopsy obtained after the six-month follow-up MRI showed active steatohepatitis without evidence of tumor

pseudolesions are likely to represent perfusion alterations, hypertrophic or inflammatory pseudomasses, regenerative nodules, or artifacts after contrast injection [6, 7].

Hepatic cysts—which are the most common nonhepatocellular focal lesions in cirrhosis [8]—and hemangiomas—which occur in 0.6% of cirrhotic patients at CT [3]—may also increase in size, but the prevalence of this atypical evolution is unknown in the literature. Although lesion growth has a high specificity for malignancy (83–91%) [2], growth of benign lesions in cirrhotic patients may occur (Fig. 2). While it is known that benign hepatic cysts may enlarge in the general population without chronic liver disease [4], there are no studies on the natural history of cysts in cirrhosis. In our experience, hepatic cysts in cirrhosis are usually stable or decrease in size over time (Fig. 3). When enlargement occurs (Fig. 4), it usually does not reach threshold growth according to the definition of LI-RADS v. 2018 [1]. In these cases, the differential diagnosis with malignancies—i.e., HCC with cystic degeneration due to internal necrosis or cystic metastases—may be challenging,

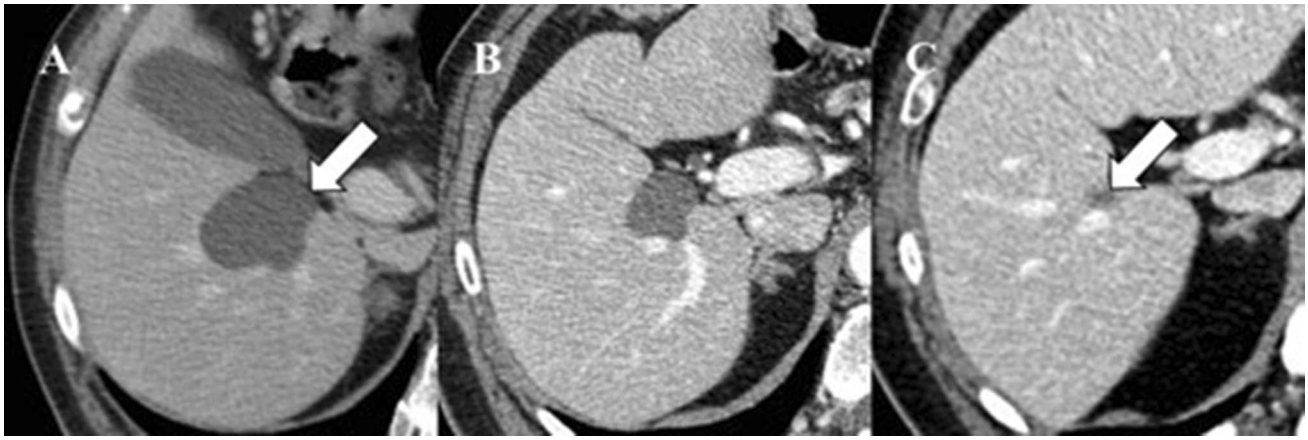

Fig. 3 74-year-old man with cirrhosis. Baseline contrast-enhanced CT on portal-venous phase **a** shows a 4.5 cm hepatic cyst (arrow) in segment 6. Follow-up CT imaging demonstrates shrinkage of the cyst (arrow) measuring 2.3 cm and 1.0 cm after 2 years (**b**) and 4 years, respectively (**c**). At subsequent 1-year follow-up CT (not shown), the lesion completely disappeared

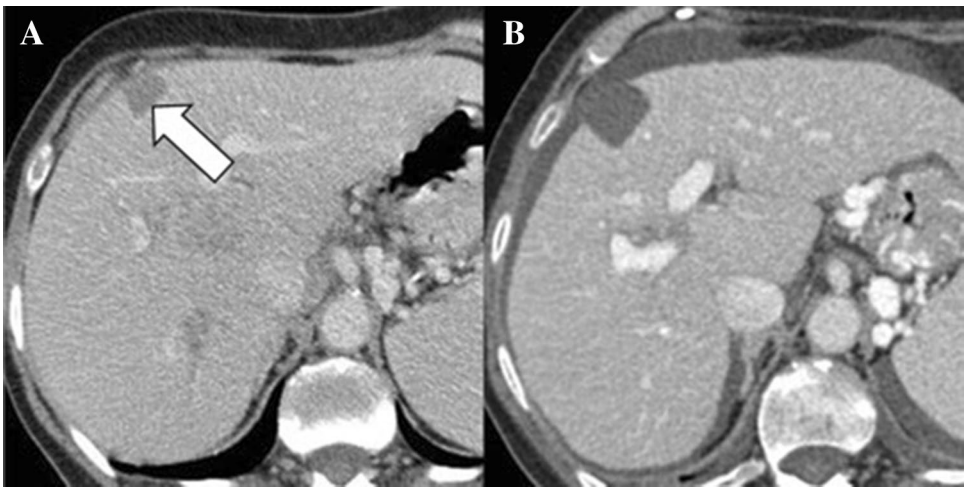

Fig. 4 93-year-old woman with cirrhosis and history of breast cancer. Baseline contrast-enhanced CT on portal-venous phase **a** shows a 2.0 cm hepatic cyst (arrow) in segment 8. Seven-year CT follow-up **b** demonstrates enlargement of the cyst, measuring 2.7 cm

and other imaging features, including homogeneity of lesion attenuation and lack of any contrast enhancement, should be considered to narrow the differential diagnosis [1]. To our knowledge, enlargement of hepatic hemangiomas in cirrhosis has never been reported in the literature. In our practice, we have encountered a hepatic hemangioma in cirrhosis enlarging over time, although we do not have a convincing hypothesis to explain this phenomenon (Fig. 5).

Other less-common benign lesions in cirrhotic patients include focal nodular hyperplasia-like nodules [8] and

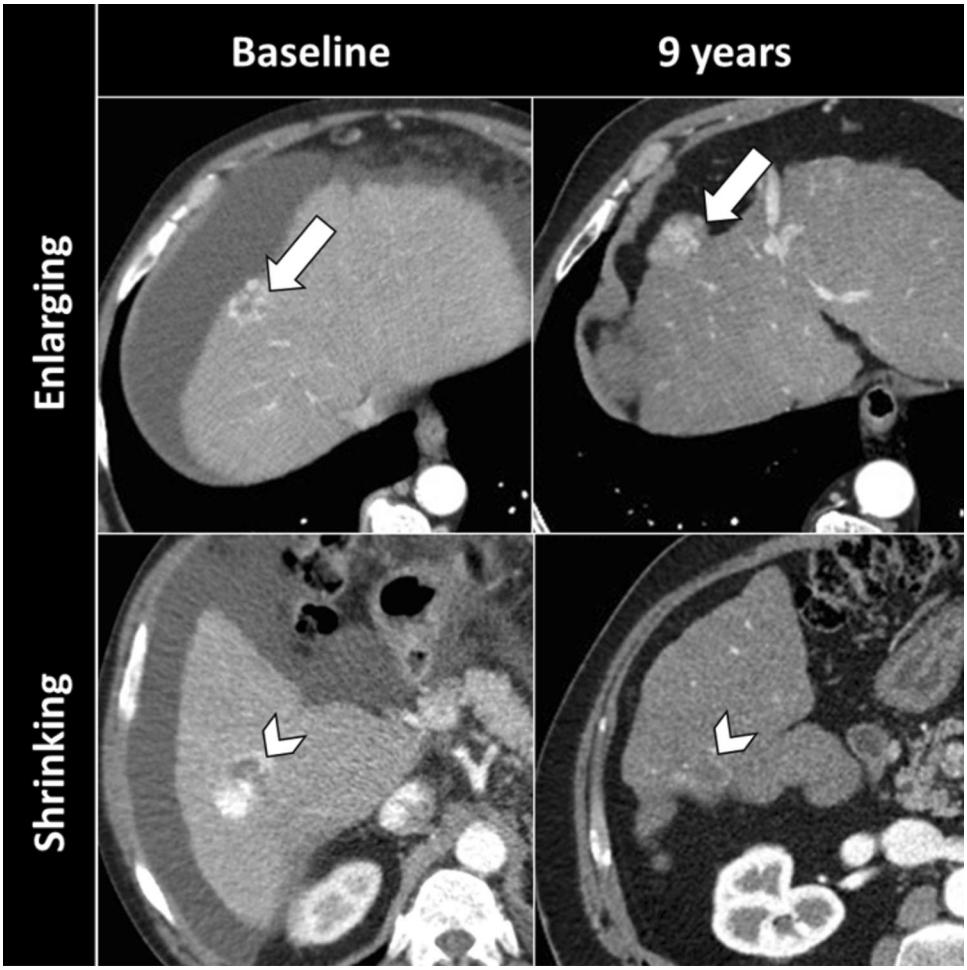

Fig. 5 63-year-old man with alcoholic cirrhosis. Baseline axial CT scan in the arterial phase shows a 2.0 cm hemangioma in segment 8 (*upper row*) and a 3.7 cm hemangioma in segment 6 (*bottom row*). At 9-year follow-up, the segment 8 hemangioma enlarges (from 2.0 to 3.0 cm, arrows), while the segment 6 hemangioma shrinks (from 3.7 cm to 2.0 cm, arrowheads) and shows new arterial phase hyperenhancement. The patient also had another hepatic hemangioma on the baseline CT scan that disappeared at 9-year follow-up (not shown). Note also the evolution of hepatic morphologic changes of cirrhosis on the follow-up CT scan

hepatic angiomyolipoma [9], but, to our knowledge, only scant data exist in the literature about their natural history [10, 11]. In our experience, we observed an uncommon case of growth of a lesion mimicking an HCC according to LI-RADS [1] which unexpectedly turned out to be an angiomyolipoma in cirrhosis at explant (Fig. 6).

Internal and vascularization changes

In a cirrhotic liver, hemangiomas may demonstrate a fibrotic involution—also known as "sclerosed hemangiomas" or "hyalinized hemangiomas" [12]. This fibrotic involution may root in the altered blood flow due to obliteration of vascular channels and in the modified intrahepatic environment, and may lead to fibrotic degeneration or hemorrhage and thrombosis [12–14]. The process of sclerosis generally starts in the center and then extends to the entire lesion. These changes may result in size reduction of the hemangiomas (Fig. 7) and might explain the significantly lower size of hemangiomas in cirrhosis compared to normal liver [3, 15]. Furthermore, the fibrotic degeneration may lead to peripheral capsular retraction or concavity over the lesion (Fig. 7), and loss of the typical imaging features of hemangiomas, including T2 hyperintensity, nodular peripheral enhancement with centripetal filling and the enhancement parallel to blood vessels [3, 16, 17]. Central fibrotic degeneration may result in central hypointensity on T2-weighted images and lack of T2-shine-through effect compared to lesions

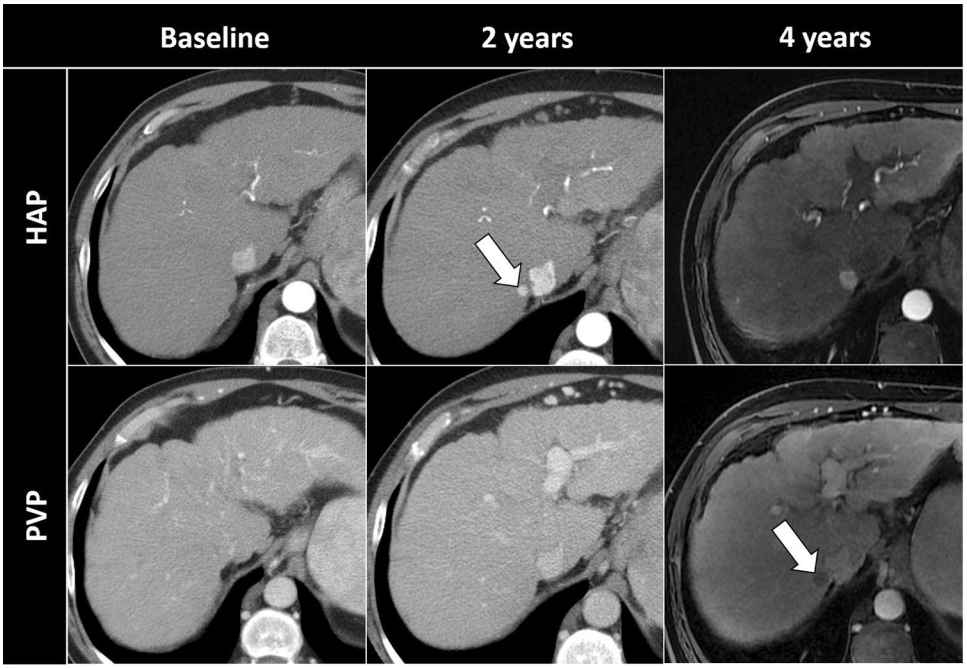

Fig. 6 58-year-old man with HCV and alcoholic cirrhosis. Contrast-enhanced CT and MR images obtained during the hepatic arterial (upper row) and portal-venous phase (bottom row) show a progressively slow-growing lesion during 4-year follow-up. A new arterial phase hyperenhancing lesion is clearly appreciated at 2-year follow-up (arrow) and a washout (arrow) of this lesion appeared at 4-year follow-up. The lesion was isointense on all other MR sequences (not shown). A dominant nodule (arrow) is easily visible at macroscopy specimen after orthotopic liver transplantation. At immunohistochemistry (not shown), the lesion was strongly HMB-45 positive and diagnosed as angiomyolipoma

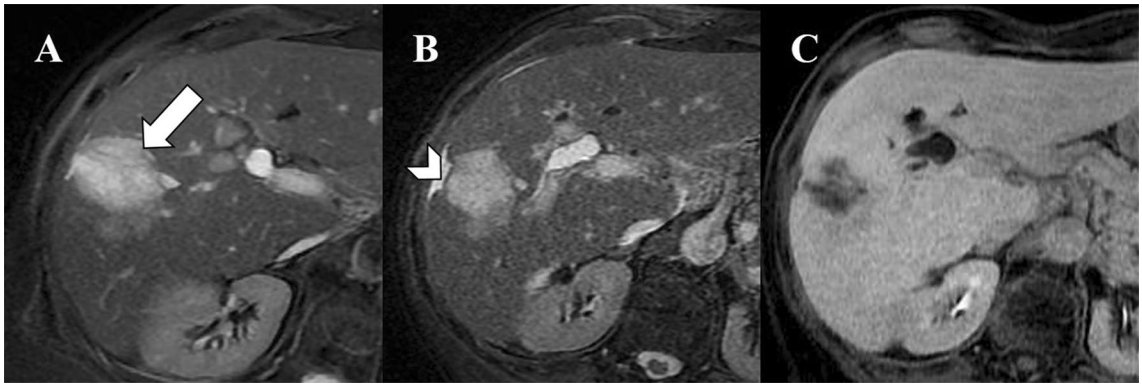

Fig. 7 74-year-old woman with cirrhosis. Axial T2-weighted MR images shows a hemangioma (**a**, arrow) in segment V. Spontaneous shrinkage of the lesion with progressive capsular retraction (arrowhead) **b** with incomplete globular peripheral enhancement in the delayed phase **c** is noticed at 1-year MRI follow-up

occurring in normal or mildly fibrotic liver [4, 15]. Sclerosed hemangioma may appear as a hypoenhancing lesion or may show rim arterial phase hyperenhancement (Fig. 5). The decreased enhancement in the dynamic study correlates with the histological degree of sclerosis [12, 13, 17]. These imaging changes may lead to a false positive diagnosis of LR-M (i.e., probably or definitely malignant but not HCC specific). Indeed, almost 6% of LR-M include benign lesions, and the analysis of prior imaging may be considered as a problem solving tool with lesion stability or decrease in size for at least 24 months favoring benignity, and unequivocal increase in lesion size (e.g., at least 50% before or at 6 months, 100% or greater increase in size after 6 months) favoring malignancy [1, 2].

Malignant liver lesions

Atypical size changes

Lesion growth remains one of the most concerning feature for malignancy. Threshold growth is currently regarded as one of the major imaging features for the definitive diagnosis of HCC according to LI-RADS, and American Association for the Study of Liver Diseases (AASLD) guidelines [1, 18, 19]. The LI-RADS definition of growth is based on an established "threshold" for the definitive diagnosis of HCC which has been modified and simplified over time. The latest LI-RADS v2018 definition—which includes a size increase of at least 50% in less than 6 months—is based on a median tumor volume doubling time of 178 days [1, 20]. However, threshold growth is not specific for HCC as it may also occur in 7.1% of non-HCC malignancies arising in cirrhosis [21].

Despite size increase is the most common scenario, spontaneous tumor regression has been described [22] (Fig. 8). The two major underlying mechanisms that may explain untreated HCC shrinkage include tumor hypoxia—caused by spontaneous hepatic artery or portal vein thrombosis, rapid tumor growth, hemodialysis, or massive gastrointestinal hemorrhage—and systemic immunological reactions which may inhibit tumor growth [5, 22].

Internal and vascularization changes

The typical imaging features of HCC on contrast-enhanced CT and MRI are nonrim arterial phase hyperenhancement

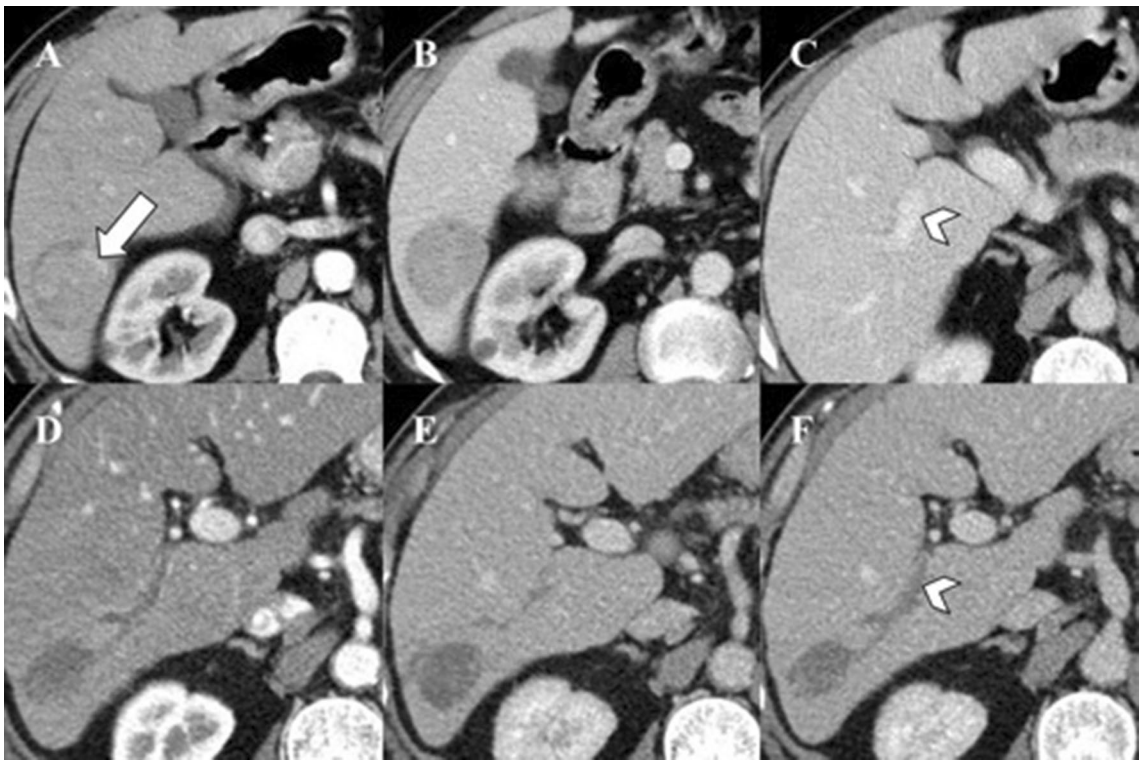

Fig. 8 56-year-old man with HCV cirrhosis. Baseline contrast-enhanced CT (upper row) shows a 4.3 cm lesion with arterial phase hyperenhancement (**a**, arrow) and washout on portal-venous phase (**b**). Note a patent right portal vein (**c**, arrowhead). At six-month CT follow-up (bottom row), without interval treatment, demonstrates spontaneous decrease in size of the lesion, with loss of arterial phase hyperenhancement (**d**) and hypoattenuation on portal-venous phase **e** with newly developed portal vein thrombosis (arrowhead) (**f**). Percutaneous biopsy of the lesion showed no evidence of viable HCC

and nonperipheral "washout" on portal-venous or delayed phases. The nonrim arterial phase hyperenhancement is due to the neoangiogenesis and formation of nontriadal or unpaired arteries in progressed HCC [23, 24]. The nonperipheral "washout" on portal-venous or delayed phases is likely the result of a combination of phenomena, including diminished portal-venous blood supply, high tumor cellularity with associated small extracellular volume, and expanded extracellular space of the surrounding cirrhotic parenchyma [20, 23–25]. These typical imaging features have to be differentiated from the rim arterial phase hyperenhancement and the peripheral "washout" more commonly encountered in non-HCC malignancies, including metastases, intrahepatic mass-forming cholangiocarcinoma, and combined hepatocellular-cholangiocarcinoma. Rim APHE and peripheral washout probably reflect the peripheral tumoral cellularity and central fibrous stroma or necrosis [26]. However, emerging data reported that up to 15% of overall non-HCC malignancies, and up to 50% of non-HCC malignancies smaller than 2 cm may show nonrim arterial phase hyperenhancement [21, 27, 28]. In our practice, we have occasionally noted liver observations initially showing a nonrim arterial phase hyperenhancement progressing to a rim arterial phase hyperenhancement at imaging follow-up (Fig. 9) and vice versa (Fig. 10). Although Tanabe et al [29] showed that 2%-5% of LR-4 may progress into LR-M—which includes rim arterial phase hyperenhancement lesions—no data exist in the literature on the evolution of nonrim arterial phase hyperenhancement into rim arterial phase hyperenhancement. We speculate that these changes in imaging presentation at contrast-enhanced CT/MR might be due to histologic changes within the lesion—i.e., necrosis, fibrosis—and/or to variable CT/MR acquisition protocol or timing.

Unusual tumor recurrence

Intrahepatic recurrence of HCC occurs in 8–54% of cirrhotic patients after surgical resection with a median time of 22-32 months [30, 31], and in 10–45% following

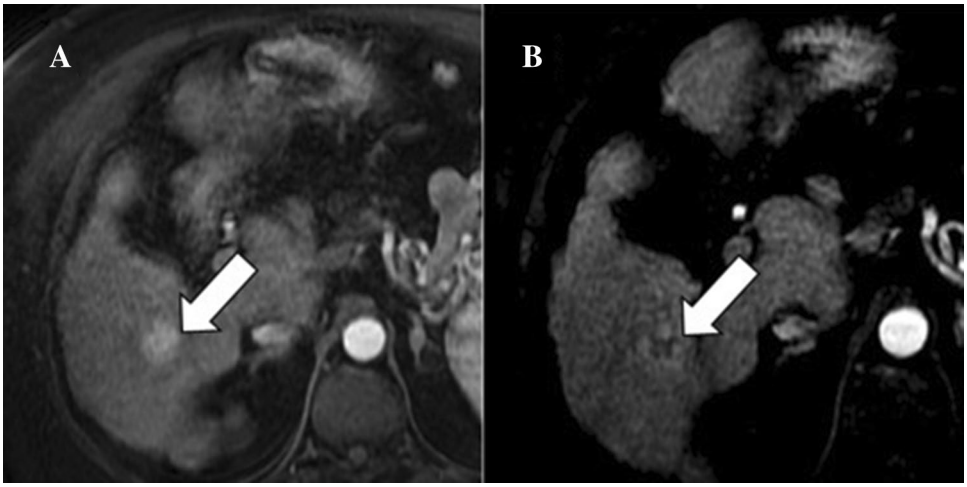

Fig. 9 58-year-old woman with HCV cirrhosis. **a** Baseline MRI on hepatic arterial phase shows a 2.0 cm lesion in segment 6 (arrow) with nonrim arterial phase hyperenhancement. At 3-month MRI follow-up **b** without interval treatment, the lesion (arrow) demonstrates rim arterial phase hyperenhancement and was classified as LR-M, highly concerning for malignancy but not typical for HCC

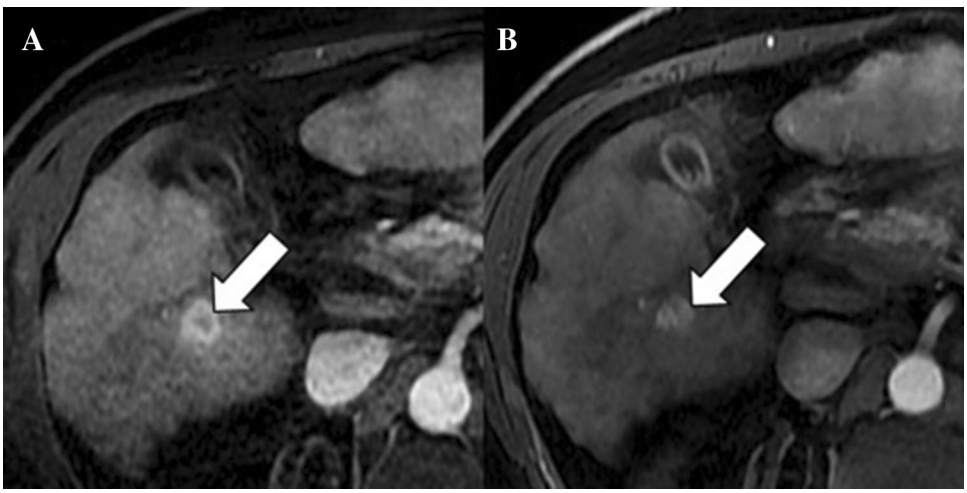

Fig. 10 62-year-old man with NASH cirrhosis. **a** Baseline MRI on hepatic arterial phase shows a 1.6 cm lesion (arrow) in segment 6 with rim arterial phase hyperenhancement. At 3-month MRI follow-up (**b**) without interval treatment, the lesion demonstrates nonrim arterial phase hyperenhancement (arrow). The lesion was a pathologically proven HCC

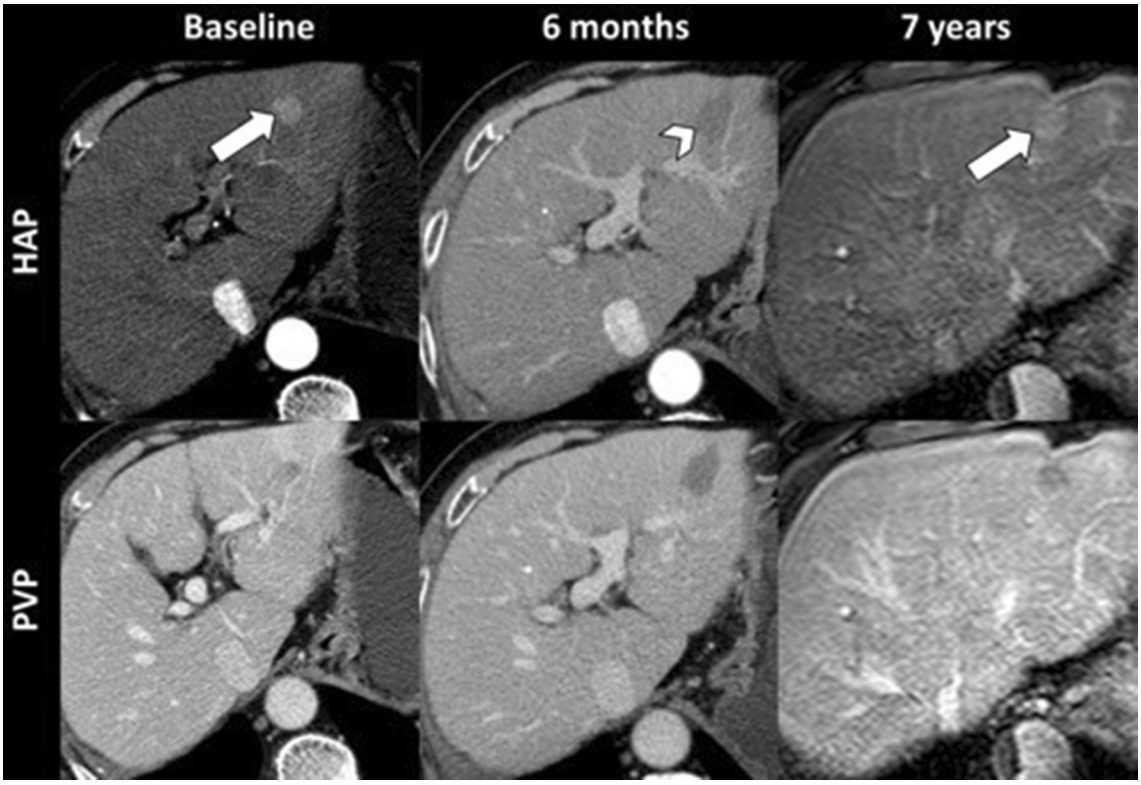

Fig. 11 83-year-old man with HCV cirrhosis. Baseline, 6-months and 7-years follow-up CT and MR images obtained on hepatic arterial (HAP, upper row) and portal-venous (PVP, bottom row) phase. Baseline CT demonstrated a nonrim arterial phase hyperenhancing lesion (arrow) with washout on portal-venous phase. The lesion underwent radiofrequency ablation with no evidence of local recurrence (arrowhead) at 6-month imaging follow-up. The 7-year MRI follow-up demonstrates nodular arterial phase hyperenhancement (arrow) at the ablation site compatible with tumor recurrence

locoregional treatments. The median tumor volume doubling time of recurrent HCC is 82 days [32–34]. Although HCC recurrence after radiofrequency thermal ablation usually develops within the first 3 years after treatment [32], we encountered local tumor recurrence more than 5 years following locoregional treatment (Fig. 11).

Summary

In conclusion, we described benign and malignant lesions in cirrhosis with an uncommon evolution. Lesions showing unusual size change, loss of typical imaging features, and late tumor recurrence represent a diagnostic challenge. Knowledge of these scenarios may help the abdominal radiologist to reach a noninvasive diagnosis and direct the patient to the most appropriate clinical management.

Compliance with ethical standards

Disclosures Federica Vernuccio, Roberto Cannella, Giorgia Porrello, Alberto Calandra, Massimo Midiri, Alessandro Furlan, and Giuseppe Brancatelli have no conflicts of interest to disclose for this study. Alessandro Furlan: Research Grant with General Electric; Elsevier/Amirsys author.

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Notes:-

Clopidogrel and low doses of aspirin may cause a similar degree of gastric mucosal damage[1]

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- Prevents gastric mucosal damage without reducing the antiplatelet function of clopidogrel[1]
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1.Clin Gastroenterol Hepatol. 2012;10(8):879-885.e2
2.J Cardiovasc Pharmacol Ther. 2017;22(2):142-152
* MACE – Major Adverse Cardiac Events

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