

Gastroenterology For General Surgeons

Matthias W. Wichmann
Timothy K. McCullough
Ian C. Roberts-Thomson
Guy J. Maddern
Editors



Springer

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*This book is dedicated to the memory of my
surgical teacher, mentor and shining example
Univ. Prof. Dr. med. Dr. h.c. Friedrich-
Wilhelm Schildberg who passed away in
September 2018 at the age of 84 years.
In gratitude, Matthias Wichmann.*

Preface

Dear colleague, life is too short for bad books, but rest assured this is not one of them.

If you are working in an environment where support by a specialist gastroenterologist is limited,

if you are concerned that your knowledge about current gastroenterological problems and their management requires updating,

or if you are interested in a good book about the current nonsurgical treatment of diseases of the gastrointestinal tract,

then this book is for you.

This volume has been a challenge to edit and write for the general surgeons. We are therefore grateful to have secured the outstanding support and contributions of our coeditor Professor Ian C. Roberts-Thomson—an outstanding gastroenterologist. Without his never-ending enthusiasm, it would have been difficult to complete this work.

The book addresses nonsurgical conditions affecting the gastrointestinal tract. We sincerely hope it meets your expectations and will help to further improve your management of these diseases.

We are indebted to a large number of colleagues who offered their knowledge and time to contribute to this book. We are all aware it is difficult to find the time in our busy work schedule. We are most grateful to our contributing authors.

We would like to thank Springer-Verlag and their staff for the opportunity to publish our work with them.

Remarkable developments have occurred in gastroenterology and gastrointestinal surgery over the past 50 years. Some of us remember the introduction of flexible endoscopy. Larger numbers can recall the introduction of ultrasonography, computed tomography, and magnetic resonance imaging. Blood tests are now more accurate at differentiating inflammatory causes for pain from non-inflammatory conditions. Laparoscopic surgery was in its infancy in 1990 but is currently the procedure of choice for many gastrointestinal disorders.

There has also been a dramatic change in the incidence of various diseases with falls in the incidence of appendicitis and peptic ulcers and rises in the incidence of nonalcoholic fatty liver disease and inflammatory bowel disorders.

Fifty years ago, there were only minor areas of overlap between the interests of gastroenterologists and general surgeons, but boundaries have been blurred by the

passage of time and then came the Internet and more knowledgeable and sometimes more demanding patients.

Aspects of medical care that have remained unchanged include the benefits of a careful evaluation of symptoms and clinical signs, the allocation of time for an adequate explanation for symptoms, and the development of a doctor-patient relationship that aids the management of chronic symptoms.

We hope that you enjoy reading this book and, more importantly, that the information contained in this book results in better outcomes for patients and greater satisfaction for surgeons.

Mount Gambier, SA, Australia
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The Editors

Contents

1	Functional Dyspepsia and the Irritable Bowel Syndrome	1
	Ian C. Roberts-Thomson	
2	Diverticular Disease	13
	Matthias W. Wichmann	
3	Gastroenteropancreatic Neuroendocrine Tumours	21
	Florian Bösch, Christoph Auernhammer, Christine Spitzweg, and Martin Angele	
4	Anorectal Disorders	35
	Timothy K. McCullough and Matthias W. Wichmann	
5	Colorectal Cancer	43
	Matthias W. Wichmann and Timothy K. McCullough	
6	Inflammatory Bowel Disease: Diagnosis and Management	55
	Madeleine Gill and Robert V. Bryant	
7	Disorders of Motility	75
	Paul Kuo and Ian C. Roberts-Thomson	
8	Gallstones	89
	Gian A. Prevost, Harsh A. Kanhere, and Guy J. Maddern	
9	Spleen	97
	Matthias W. Wichmann and Timothy K. McCullough	
10	Acute Pancreatitis, Chronic Pancreatitis and Pancreatic Neoplasms	103
	Ali Arshad and Ashley Dennison	
11	Endoscopy and Upper Gastrointestinal Disorders	119
	Marie Ooi and Nam Nguyen	
12	Gastro-esophageal Reflux Disease	133
	F. T. Kolligs and C. Kurz	

13	Surveillance and Premalignant Conditions	143
	Matthias W. Wichmann and Timothy K. McCullough	
14	Acute and Chronic Liver Failure	159
	Garry R. Nind	
15	Advanced Radiologic Imaging Techniques of the Gastrointestinal Tract	175
	Frank Voyvodic, Melissa Jenkins, and Steven James Knox	
16	Nutrition and Parenteral Nutrition	215
	Christopher K. Rayner and Marianne J. Chapman	
17	The Non-surgical Acute Abdomen	229
	Ian C. Roberts-Thomson	
18	Liver and Gastrointestinal Disorders During Pregnancy	237
	William M. Hague and Ian C. Roberts-Thomson	
19	Intestinal Failure	245
	Timothy K. McCullough and Matthias W. Wichmann	
20	Ischemic Enteritis/Colitis	253
	Matthias W. Wichmann and Timothy K. McCullough	
21	Genetics of Inherited Gastrointestinal Tumors	257
	Nicola K. Poplawski	
22	Gastrointestinal Stromal Tumors: An Update for the General Surgeon	287
	Markus I. Trochsler and Harsh A. Kanhere	
23	Gastrointestinal Disorders Induced by Medication	299
	Ian C. Roberts-Thomson	
24	Management of Obesity	309
	Harsh A. Kanhere and Markus I. Trochsler	



Functional Dyspepsia and the Irritable Bowel Syndrome

1

Ian C. Roberts-Thomson

1.1 Introduction

Intermittent gastrointestinal symptoms are a normal component of human life. Common examples include epigastric discomfort after larger meals, apparent intolerance of foods such as spices and coffee and a bowel habit that is somewhat irregular in response to variation in diet, alcohol use and stress. These symptoms are interpreted as a consequence of lifestyle factors by most people and only rarely as a reason to seek medical advice. However, some individuals have more prominent symptoms, either intermittently or persistently, which are perceived as abnormal and that impair the expectation of a “normal” quality of life. When investigations are unhelpful, these symptoms are often labelled as “functional” although this term sheds little light on the nature of pathogenic mechanisms. Symptoms that focus on the upper gastrointestinal tract are usually called either functional or non-ulcer dyspepsia. Symptoms that focus on the lower gastrointestinal tract are typically called the irritable bowel syndrome. Additional categories include functional biliary-type pain, discussed in Chapter 17, and chronic abdominal pain of unknown cause, often called the functional abdominal pain syndrome. While some patients readily fit into one of the above categories, many are more difficult to categorize because of symptoms that include both the upper and lower gastrointestinal tracts.

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1.2 Epidemiology

Intermittent dyspepsia is common, particularly in adults. The prevalence in Caucasian populations has been estimated at 5–15%, but this varies considerably depending on the survey method [questionnaire or interview], methods for the definition of symptoms and the length of the observation period. Even higher prevalence rates occur when symptoms are expanded to include those of esophageal reflux such as regurgitation and heartburn. Most studies indicate that the prevalence in women is modestly higher than that in men. Prevalence rates do not appear to be influenced by age as there is a similar number with new-onset symptoms to those whose symptoms resolve spontaneously.

The proportion of patients with dyspepsia who seek medical attention has been estimated at approximately 50%. This probably includes those with more severe symptoms of recent onset, but other factors can be relevant including fear of serious illness, serious illness in a friend or relative and anxiety or psychological stress. Other people with dyspepsia simply tolerate their symptoms, experiment with over-the-counter products or consult a variety of non-medical practitioners.

In contrast to dyspepsia, there is more reliable data on the prevalence of the irritable bowel syndrome. Using criteria agreed by an international panel [Rome I–IV criteria], the global prevalence of the irritable bowel syndrome is approximately 10%. Prevalence rates may be highest in South America and lowest in Africa. In Western populations, the prevalence in women is somewhat higher than that in men with the majority of patients in the age group 30–50 years. In Asia, the irritable bowel syndrome is more prevalent in younger age groups but is equally common among males and females.

Not all people with irritable bowel symptoms consult medical practitioners. In Western countries, women are more likely to seek help than men, perhaps because symptoms are more frequent and severe. Women are also less likely to attribute symptoms to anxiety and stress. In contrast, men are more likely to consult medical practitioners in some parts of Asia [e.g. India], perhaps because of cultural differences in the interpretation and response to symptoms.

The functional abdominal pain syndrome is much less common than functional dyspepsia or the irritable bowel syndrome with a population prevalence of approximately 1%. The majority of these patients are women who often exhibit chronic pain behaviour and significant psychological disturbance.

The financial burden of functional gastrointestinal disorders on personal and national health budgets is substantial. The National Health Insurance database in South Korea estimated that 6% of the population sought medical care for irritable bowel symptoms at least once per year. This generated outpatient visits, investigations and hospitalization that accounted for approximately 0.5% of the total medical budget. In many other countries without national insurance schemes, these costs are borne by the patient, sometimes by diverting funds from critical areas such as food and housing. In the USA, direct costs associated with functional bowel disorders have been estimated at \$20 billion per year.

1.3 Symptoms of Functional Gastrointestinal Disorders

The term dyspepsia describes a variety of symptoms localised to the epigastric region. The major symptoms are those of postprandial fullness, early satiety, epigastric pain and epigastric burning. However, additional symptoms may be present such as nausea, prominent burping and abdominal bloating. The presence of esophageal symptoms is relatively common in clinical practice, but significant esophageal symptoms would place patients outside the relatively strict category of functional dyspepsia. This difficulty with terminology has led to the development of consensus views on definitions [Rome criteria] that have particular relevance for the development and interpretation of clinical studies. In the Rome III consensus, functional dyspepsia was subdivided into two groups: a postprandial distress syndrome that included postprandial fullness and early satiety and an epigastric pain syndrome characterized by epigastric pain or burning. This subdivision was supported by epidemiologic studies showing that there was no major overlap of symptoms between the two groups.

In the Rome consensus, postprandial fullness describes an unpleasant sensation of prolonged persistence of food in the stomach after meals. Early satiety is a sensation that the stomach is full or overfull soon after starting a meal with the result that the meal cannot be finished. Epigastric pain describes an intense and unpleasant sensation in the epigastrium which can lead to concern about the presence of significant disease. Epigastric burning describes an unpleasant sensation of heat or discomfort in the epigastrium, often but not always related to meals.

In contrast, the major symptoms of the irritable bowel syndrome are recurrent abdominal pain [often related to defecation], a change in the frequency of defecation and changes in the appearance of stools. These are often accompanied by abdominal bloating and sometimes by other gastrointestinal symptoms such as nausea. Again, patients have been subdivided according to bowel habit into those with diarrhea as a prominent symptom [IBS with diarrhea], constipation as a prominent symptom [IBS with constipation], alternating diarrhea and constipation [IBS with mixed symptoms] and unsubtyped IBS. These subtypes may improve the homogeneity of patients in clinical trials and assist with the study of pathophysiologic mechanisms and therapy. Rome IV criteria for the diagnosis of functional dyspepsia and irritable bowel syndrome are listed in Table 1.1.

Care needs to be taken in categorizing the presence of diarrhea and constipation in individual patients. For example, most patients appropriately describe diarrhea as the presence of loose stools, but diarrhea may be an alternative description for fecal incontinence. Other important historical features are the duration of symptoms, the presence or otherwise of fluctuating symptoms, stool characteristics, associated symptoms, diet and medication. Constipation can be even more difficult as assessment is complicated by issues such as hard stools, difficult defecation and laxative use. One definition of a normal bowel habit ranges from two stools per day to two stools per week, but this is more complex in individuals who “only have a bowel action with laxatives”. The prevalence of self-perceived constipation in adult communities usually ranges from 10% to 20% and is more common in women than in men.

Table 1.1 Rome IV criteria for the diagnosis of functional dyspepsia and the irritable bowel syndrome

<i>Functional dyspepsia – postprandial distress syndrome</i>
<ul style="list-style-type: none"> • Bothersome postprandial fullness, occurring after ordinary-sized meals, at least several times per week • Early satiation that prevents finishing a regular meal, at least several times per week
Supportive criteria include upper abdominal bloating, postprandial nausea and excessive belching. The epigastric pain syndrome may coexist
<i>Functional dyspepsia – epigastric pain syndrome</i>
<ul style="list-style-type: none"> • Pain or burning localized to the epigastrium, of at least moderate severity, at least once per week. Pain is intermittent, not generalized and not relieved by defecation and does not fulfil the criteria for biliary pain
Supportive criteria include pain induced or relieved by ingestion of a meal. The postprandial distress syndrome may coexist. A component of retrosternal pain excludes the strict definition of functional dyspepsia but is common in clinical practice. Many older studies have defined dyspepsia as predominant epigastric pain for at least 1 month, sometimes associated with epigastric fullness, nausea, vomiting or mild heartburn
<i>Irritable bowel syndrome</i>
<ul style="list-style-type: none"> • Recurrent abdominal pain on most days associated with at least two of the following three symptoms: pain related to defecation, changes in the frequency of stool and changes in the form [appearance] of stool
Supportive criteria include the absence of warning symptoms. For both functional dyspepsia and the irritable bowel syndrome, patients included in contemporary clinical trials have usually fulfilled criteria for 3 months and describe the onset of symptoms as >6 months

Whether patients with functional disorders are more likely than control subjects to have symptoms outside the gastrointestinal tract is still being debated. However, some authors highlight unexplained symptoms such as headaches, urinary symptoms and other pain syndromes as evidence for a more generalized pain disorder not restricted to the gastrointestinal tract. There is also the issue of psychiatric disorders that could be of primary importance or secondary to persistent gastrointestinal symptoms.

1.4 Pathogenesis

Several factors appear to influence susceptibility to functional disorders. These include genetic factors, psychosocial distress, psychiatric disorders, visceral hypersensitivity, activation of mucosal immunity, altered gastrointestinal motility, dietary influences and changes in the intestinal microbiome and intestinal permeability. Although mutations influencing intestinal fluid transport and carbohydrate metabolism have been identified, these mutations are rare and only account for symptoms in a small minority of patients.

A controversial area is the importance of psychiatric disorders and changes in the brain-gut axis. Patients with functional disorders have a higher than expected frequency of childhood abuse, anxiety and depression and frequently describe abdominal symptoms that are aggravated by stress. In addition, some show an exaggerated

response to stress with higher circulating levels of corticotropin-releasing factor. These observations support the hypothesis of brain-to-gut pathways, but a primary role for the central nervous system seems likely in fewer than 50% of patients.

An interesting subgroup of patients develops an irritable bowel syndrome after an episode of gastroenteritis. Various infectious agents have been implicated including bacteria, viruses and protozoa, but bacterial infections with *Salmonella* and *Campylobacter* species have been most prominent in the UK. The frequency of persistent irritable bowel-type symptoms after an episode of gastroenteritis has been estimated at 10–20%. Many of these patients have histological features of persistent, low-grade inflammation with an increase in mucosal lymphocytes and mast cells in the small and large bowel. For functional dyspepsia, a consensus view is that gastric infection with *Helicobacter pylori* [*H. pylori*] causes or aggravates symptoms in a minority of patients. There is also some evidence for an increase in mucosal eosinophils in the upper gastrointestinal tract in the subgroup of patients with postprandial distress syndrome.

Some patients with functional disorders have changes in gastrointestinal motility. For example, approximately 25% of patients with functional dyspepsia have delayed gastric emptying. In the irritable bowel syndrome, transit time through the small and large bowel is often accelerated with diarrhea and delayed with constipation. Another area is the sensory function of the gastrointestinal tract that appears to be hypersensitive [visceral hypersensitivity] to stimuli such as balloons that inflate various parts of the bowel. In most patients, this is not associated with hypersensitivity to stimuli applied to the skin.

Other factors include diet, the intestinal microbiome and gastrointestinal permeability. Functional symptoms are aggravated by food in up to 50% of patients, particularly those with functional dyspepsia. Intolerance of specific foods is also common although blinded trials only show resolution of symptoms during withdrawal and reproduction of symptoms during rechallenge in a minority of patients. These non-immune mechanisms need to be distinguished from food allergy [e.g. peanuts, cows' milk and eggs] mediated by IgE. More recently a group of poorly absorbed, short-chain carbohydrates have been implicated in the pathogenesis of irritable bowel symptoms. These compounds described under the acronym FODMAPs include fructose, lactose, fructans, galacto-oligosaccharides and polyols. They may aggravate irritable bowel symptoms by osmotic activity in the small bowel and gas production with distension in the large bowel. The role of the intestinal microbiome in the pathogenesis of functional symptoms has not yet been clarified. Some patients appear to have mild bacterial overgrowth in the small bowel, while others have evidence of reduced microbial diversity in faeces but no characteristic microbial marker. There is also evidence of abnormal intestinal permeability in some patients, particularly those with diarrhea, but whether this is related to changes in the intestinal microbiome remains unclear. Greater intestinal permeability could explain mild bowel inflammation and changes in visceral sensitivity.

Functional gastrointestinal symptoms cannot be explained by a single algorithm. In some patients, it seems likely that the central nervous system is the primary mediator with secondary effects on the enteric nervous system. Whether these effects are

related to overactivity of the hypothalamic-pituitary-adrenal axis, the autonomic nervous system or other pathways remain unclear. In other patients, the primary stimulus arises in the gut with a gut-to-brain axis. This applies to the postinfectious irritable bowel and diet-induced symptoms and may apply to changes in the intestinal microbiome with potential changes in intestinal permeability.

1.5 Towards a Positive Diagnosis of Functional Syndromes

Surveys suggest that up to 50% of patients seen by specialist physicians or surgeons because of unexplained abdominal symptoms have a functional disorder. The challenge for both the general practitioner and the specialist is to avoid missing important diagnoses and, at the same time, to avoid unhelpful and expensive investigations. At one end of the spectrum is the younger adult with long-standing symptoms who has had a number of negative investigations. At the other end is the older adult with symptoms of recent onset who may have had only limited or no investigation. Clearly, the probability of a non-functional disorder is higher in the latter group.

Guidance on the probability of non-functional disorders, particularly cancer, has resulted in the publication of alarm or “red flag” symptoms. For upper gastrointestinal symptoms, these include dysphagia, severe pain, protracted vomiting, unintentional weight loss, anaemia and a positive fecal occult blood test [guaiac test]. Unfortunately, the reality is that most cancers exhibiting one or more of these symptoms are relatively advanced and sometimes have a poor prognosis. For lower gastrointestinal symptoms, alarm features include age over 50 years with no previous colon cancer screening, a recent change in bowel habit, overt gastrointestinal bleeding, nocturnal pain or passage of stools, unintentional weight loss and a positive fecal occult blood test [usually an immunochemical test].

A short list of non-functional disorders that can cause upper gastrointestinal symptoms is provided in Table 1.2. Chronic duodenal or gastric ulcers are found at endoscopy in up to 10% of patients. A further 10% have endoscopic evidence of reflux esophagitis with at least some inflammation or mucosal ulceration in the lower esophagus. Gastric or esophageal cancers are diagnosed in fewer than 2% of patients.

In patients with lower gastrointestinal symptoms, the differential diagnosis is influenced by the nature of the presenting symptoms, particularly the presence of diarrhea or constipation. One difficulty is the role of diverticulosis in the pathogenesis of symptoms. Diverticula are uncommon below the age of 50 years but increase in frequency thereafter to affect up to 50% of adults by the age of 70 years. While the majority of affected individuals are asymptomatic, a minority with more extensive disease can have an irregular bowel habit, intermittent pain and changes in the appearance of stools. A short list of non-functional disorders presenting with either diarrhea or constipation is provided in Table 1.3.

Screening tests for the presence of non-functional disease have been recommended by several authors. For functional dyspepsia-type symptoms, these may include a full blood examination, ESR, urea, electrolytes and liver function tests.

Table 1.2 Non-functional disorders that can cause intermittent upper gastrointestinal symptoms^a

- Reflux esophagitis
- Chronic duodenal ulcer
- Chronic gastric ulcer
- Gallstone disease
- Adverse effects from medication
- Diabetic gastroparesis
- Chronic pancreatitis
- Gastric cancer
- Pancreatic neoplasms
- Miscellaneous: hernias, mechanical disorders, angina and others

^aIn approximate order of frequency**Table 1.3** Non-functional disorders that can cause intermittent lower gastrointestinal symptoms^a

- Severe diverticulosis
- Colorectal cancer [and larger polyps]
- Inflammatory bowel disease
- Microscopic [lymphocytic] colitis
- Adverse effects from medication
- Celiac disease
- Radiation colitis
- Rectal prolapse and solitary rectal ulcer syndrome
- Fecal impaction and incontinence
- Laxative abuse
- Ovarian cancer
- Miscellaneous: thyroid disease, bacterial overgrowth syndromes, neuroendocrine tumours of pancreas and others

^aIn approximate order of frequency

Other options include serological tests for *H. pylori* antibodies and celiac disease. A negative test for *H. pylori* largely excludes duodenal ulceration, but gastric ulceration may still occur in those who use non-steroidal, anti-inflammatory drugs. Patients with persistent symptoms often proceed to endoscopy, but abnormalities are unusual in younger adults.

For irritable bowel-type patients, screening tests will be influenced by the presence of constipation or diarrhea. A full blood examination, ESR and/or C-reactive protein and urea, electrolytes and liver function tests are appropriate in most individuals. In those with diarrhea, additional tests may include fecal occult blood, fecal calprotectin, fecal microscopy and culture, celiac serology and thyroid function tests. In older women, a pelvic ultrasound study may be appropriate in those with symptoms of short duration to exclude ovarian cancer. The majority of older patients, especially those with diarrhea, will proceed to colonoscopy to exclude colorectal cancer, inflammatory bowel disease and microscopic colitis. The role of bile acid malabsorption in the pathogenesis of chronic diarrhea remains uncertain, and testing is not readily available at present.

Unfortunately, there is no accurate diagnostic test for either functional dyspepsia or the irritable bowel syndrome. Nevertheless, these functional disorders should not be simply a diagnosis of exclusion. Evidence for the stability of functional diagnoses comes from several longitudinal studies indicating that the emergence of important new diagnoses in patients previously diagnosed with functional disorders is rare. Furthermore, another study showed that patients diagnosed with functional disorders on the basis of symptoms rarely had positive findings from more extensive investigation.

1.6 Research Investigations in Functional Disorders

Several techniques have been described in an attempt to define mechanisms of potential relevance to the pathogenesis of both functional dyspepsia and the irritable bowel syndrome. Some of these relate to motility and sensation in the gastrointestinal tract, while others have explored potential changes in the function of parts of the central nervous system. In functional dyspepsia, gastrointestinal investigations have included motility in the stomach and duodenum, rates of gastric emptying and accommodation and sensation, mostly in the stomach. Similar studies have been performed in the colon and rectum in the irritable bowel syndrome.

The major methods for the assessment of gastric emptying have included scintigraphy of radiolabelled solid and liquid meals, breath tests using radiolabelled octanoic acid and specialized tests using ultrasound and magnetic resonance imaging. Although some patients have delayed gastric emptying [approximately 25%], a consensus view is that there is no clear relationship between delayed emptying and subtypes of functional dyspepsia. Similarly, research studies using a gastric balloon [barostat] have revealed gastric hypersensitivity and impaired accommodation in 30%–40% of patients but no or only weak correlations between test abnormalities and symptoms. Manometry of the stomach and duodenum is a highly specialized area but does not, as yet, appear to assist with the diagnosis of functional dyspepsia.

Similar studies have been performed in individuals with the irritable bowel syndrome. In the diarrhea-predominant group, several studies have shown that the majority have rapid transit through the colon and that some have rapid transit through the small bowel. In the constipation-predominant group, transit through the colon may be normal or slow. Visceral hypersensitivity is also a common feature with more prominent symptoms after balloon distension, gaseous distension or standard meals. Changes in motility have also been confirmed by manometric studies in the colon, but none have been specific for subtypes of the irritable bowel syndrome.

Yet another area of interest has been brain structure and function because of the likelihood of central influences on abdominal symptoms. Subtle changes have been noted on neuroimaging studies such as positron emission tomography and magnetic resonance imaging, but the significance of these changes remains unclear. A particular area of interest is the role of the autonomic nervous system which is linked to both the enteric nervous system and to states of arousal and emotion. However, activation of the autonomic nervous system is difficult to study, and it is possible

that activation can be restricted to particular organs such as the gastrointestinal tract. Finally, it is difficult to ignore the association between functional syndromes and psychological issues that include personality profiles, family relationships, physical and sexual abuse, societal myths and cultural differences.

1.7 Treatment

As both functional dyspepsia and the irritable bowel syndrome are heterogeneous disorders, it comes as no surprise that there is no simple algorithm in relation to therapy. One important aspect is an effective doctor-patient relationship that provides reassurance, a positive diagnosis and at least a partial explanation for symptoms. Referral to a psychiatrist or psychologist is often resisted by patients although a meta-analysis showed some benefit from cognitive behavioural therapy and hypnotherapy. Regular exercise programmes, meditation and other stress-reduction methods also appear to be of some help. Another consideration in the interpretation of randomized trials of medication is improvement in symptoms in 30–40% of patients treated with placebo.

Recognition of the potential role of FODMAPs has led to renewed interest in the dietary management of functional disorders. In functional dyspepsia, this may include small regular meals and limits on the intake of coffee, alcohol, fatty foods and other foods identified as potential aggravating factors. For the irritable bowel syndrome, insoluble fibre in the form of bran may improve constipation but aggravate pain and bloating. These adverse effects do not appear to occur with soluble fibre in the form of psyllium husks. In randomized trials, the low-FODMAP diet was of similar or greater benefit for irritable bowel symptoms than conventional dietary recommendations. Additional data on these specialised diets is awaited with interest.

A wide range of prescription and over-the-counter medication is available for the treatment of functional disorders. These include agents with effects on gastrointestinal motility, gastric acid secretion and gut microbiota as well as agents with effects on anxiety and depression. Some of these drugs have been superior to placebo in randomized trials, but the degree of benefit is often small. As a result, it is common for patients to experiment with alternative therapies such as herbal preparations, probiotics and other products such as melatonin. Some of these preparations appear to be helpful in individual patients, but large randomized trials have not been reported.

In functional dyspepsia, it is common for patients to be treated with drugs that reduce gastric acid secretion such as histamine [H₂] receptor antagonists or proton pump inhibitors. Currently, proton pump inhibitors are more widely used, but efficacy is modest and is largely restricted to those with heartburn and the subgroup with epigastric pain. In a typical study, improvement occurs in 50% of patients treated with anti-secretory drugs versus 30% of those treated with placebo. The number needed to treat [NNT] for one to have significant benefit over treatment with placebo has been estimated at six. Another option is a serological test for *H. pylori* followed by therapy in those with positive results. Although different results

have emerged from different trials, a consensus view is that eradication of *H. pylori* is of benefit with a NNT of between 7 and 13. As functional dyspepsia is sometimes associated with delayed gastric emptying, there has been a continuing interest in drugs that enhance gastric motility. Potential agents include metoclopramide, cisapride, mosapride and domperidone, but the former three drugs are unsuitable for long-term use because of side-effects. Domperidone appears to be relatively safe, but there is a debate as to efficacy, and the drug has not been approved for use in the USA. In contrast, there is good evidence for benefit from tricyclic antidepressant drugs although improvement in symptoms is not necessarily accompanied by improvement in features such as delayed gastric emptying. Various drugs have been used in clinical trials including amitriptyline, nortriptyline, imipramine and desipramine with an NNT of approximately six. Reasons for benefit remain unclear but include a degree of sedation and improvement in sleep patterns. However, some patients are reluctant to take medication for “depression”, while others have anticholinergic side-effects such as dry mouth, constipation and urinary retention. Interestingly, serotonin reuptake inhibitors do not appear to be helpful, perhaps because the medication sometimes results in nausea and dyspepsia.

Drug therapy for patients with the irritable bowel syndrome often needs to be individualized because of variation in symptoms, particularly in relation to bowel habit. In those with diarrhea as the major symptom, the intermittent or regular use of loperamide may suffice. When diarrhea is accompanied by significant pain, tricyclic antidepressants usually slow intestinal transit and often have beneficial effects on pain. Alternative agents for those with more difficult diarrhea include alosetron, a 5-hydroxytryptamine type 3 receptor agonist, and eluxadoline, a novel drug that acts on opioid receptors. Both drugs are expensive and have been associated with significant adverse events. Rifaximin, a poorly absorbed antibiotic, also appears to be helpful in patients with the irritable bowel syndrome who are not troubled by constipation. In randomized trials, the drug was superior to placebo for global symptoms and abdominal bloating.

For the irritable bowel syndrome with constipation, initial measures usually focus on the treatment of constipation. This may involve an increase in dietary fibre although this is sometimes accompanied by a temporary increase in abdominal pain and bloating. Alternative measures include the use of soluble fibre [psyllium husk], lactulose or polyethylene glycol. For patients with difficult constipation, options include the novel drugs, lubiprostone and linaclotide, that increase fluid secretion into the gastrointestinal tract. Both drugs usually improve constipation but are expensive and only have modest effects on pain and global symptoms. Antispasmodic drugs including peppermint oil appear to be helpful in some individuals but have rarely been exposed to randomized trials.

1.8 Conclusion

Functional gastrointestinal disorders are common throughout the world with significant effects on the quality of life of affected individuals. Furthermore, they generate a substantial economic burden because of costs associated with medical consultation,

investigation, hospitalization and therapy. The major disorders are functional dyspepsia and the irritable bowel syndrome, but there is heterogeneity in relation to symptoms and overlap between the two disorders. Although functional disorders are broadly seen as disorders of the brain-gut axis, there is evidence that the primary event resides in the brain in some patients and the gut in others. The challenge for medical research is to define biological mechanisms in more detail and to integrate these pathways with factors such as genetic and epigenetic influences, gender, early life stressors and psychological and psychiatric disorders.

There is no simple algorithm for the management of functional disorders. Arguably, the most helpful measure is a good doctor-patient relationship with appropriate advice on diet and lifestyle. Medication is beneficial in up to 60% of patients, but this compares with placebo benefit in 30%. In functional dyspepsia, relatively inexpensive therapies of established benefit include acid suppression medication, eradication of *H. pylori* and tricyclic antidepressant drugs. For the irritable bowel syndrome, tricyclic antidepressants are helpful for diarrhea, and several other agents are useful in individual settings. The prospect of a highly effective therapy for functional syndromes seems remote at present unless visceral sensation can be modified without the emergence of major adverse events.

Recommended Reading

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Diverticular Disease

2

Matthias W. Wichmann

2.1 Epidemiology/Risk Factors/Pathogenesis

Diverticulosis of the large bowel is defined by the presence of multiple diverticula in the bowel wall (Fig. 2.1). A colonic diverticulum is a protrusion of the bowel wall at the position where the vasa recta penetrate the circular muscle layer of the colon. Since only the mucosa and submucosa herniate, the colonic diverticulum is a “false” or pulsion diverticulum. This defect of the bowel wall is only covered by serosa.

During recent years there has been a continuous increase of hospital admissions for both uncomplicated and complicated diverticular disease, with approximately 100 new cases per 100,000 population diagnosed annually. At age 60, 40–60% of the population have developed diverticula. Male and female patients are equally affected. Of interest, the distribution of diverticulosis within the colon varies by geography. Patients from western and industrialized nations have sigmoid diverticula in 95% of all cases. In Asia, diverticulosis is predominantly localized in the ascending colon.

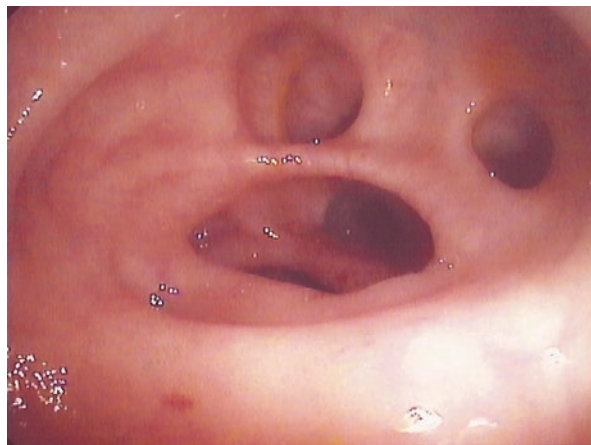
Risk factors for the development of diverticulosis and subsequent progression to diverticular disease include environmental and lifestyle factors, but the connection between disease and exposure to potential risk factors is largely unclear. The role of *fiber* in the development of diverticulosis is unclear. While early studies suggested that a diet low in fiber would contribute to the development of diverticular disease, this has not been confirmed in more recent publications. A diet low in fiber and high in total *fat* or *red meat* however significantly increases the risk of diverticular disease. Lack of *physical activity* combined with low dietary fiber intake increases the risk of symptomatic diverticular disease. *Obesity* increases the risk of complicated diverticular disease (infection, bleeding). *Smoking* increases the risk for

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Fig. 2.1 Colonoscopic impression of uncomplicated diverticulosis



complicated diverticular disease (perforation, abscess). *Medications* associated with increased risks of diverticular disease (infection, bleeding) are nonsteroidal anti-inflammatory drugs, steroids, and opiates.

No increased risk for the development of diverticular disease has been associated with the following lifestyle choices: caffeine, alcohol, nuts, corn, and popcorn consumption.

No single risk factor will cause the development of diverticular disease, but the combination of several of the “classical” risk factors (lack of fiber, fat, red meat, lack of physical activity, obesity, smoking, NSAIDs, steroids, opiates) can be identified in most patients with symptomatic diverticular disease.

There is no effective *secondary prophylaxis* once diverticular disease has developed.

The *pathogenesis* for the development of diverticula is not completely clear. It appears that abnormal colonic motility with hypersegmentation of the large bowel (exaggerated segmentation contractions) and subsequently increased intraluminal pressure predispose to the development of diverticula. This hypothesis makes sense when looking at diverticular disease of the sigmoid colon (smallest diameter, high pressure zone at rectosigmoid junction). Higher intraluminal pressures in this segment of the bowel can be explained with Laplace’s law according to which pressure is proportional to wall tension and inversely proportional to the radius. The “high pressure zone hypothesis” does not help to explain the higher prevalence of right-sided diverticular disease in the Asian population. The development of *complicated diverticular disease* with bleeding and/or infection/perforation is somewhat easier to explain. Bleeding occurs due to the close proximity of the vasa recta to the diverticulum. Structural changes of the artery and mechanical injury can lead to rupture and blood loss into the lumen. Infection results from a perforation of the diverticulum through erosion of the wall. Smaller infections are usually contained, but free perforations or fistulating processes can also occur.

2.2 Diagnosis/Differential Diagnosis

Acute diverticulitis is a clinical diagnosis based on lower abdominal pain (usually left lower quadrant), worsening pain on palpation, and inflammatory changes in blood testing (white blood cell count, C-reactive protein). The diagnosis should be confirmed by computed tomography (CT) of the abdomen and pelvis. The CT also identifies noncomplicated acute diverticulitis (Fig. 2.2) versus complicated (perforation, abscess, obstruction, fistula) (Figs. 2.3 and 2.4).

Differential diagnoses to be considered in patients presenting with suspected acute diverticulitis include:

- Irritable bowel syndrome
- Colon cancer
- Inflammatory bowel disease
- Urinary tract infection
- Infectious/neoplastic conditions of the ovaries/adnexa

Fig. 2.2 CT scan of uncomplicated acute diverticulitis (patient TB—day 1)

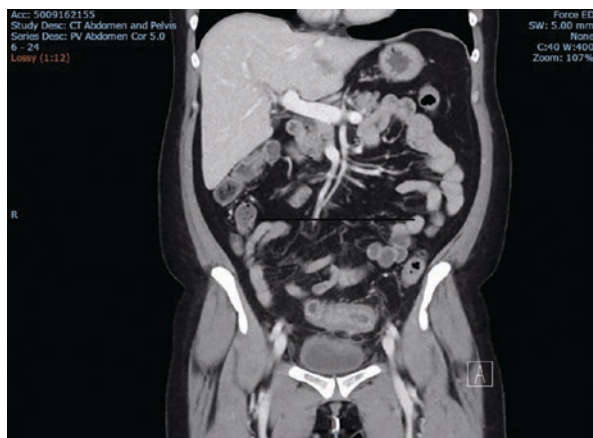


Fig. 2.3 CT scan of complicated acute diverticulitis (patient TB—day 3)

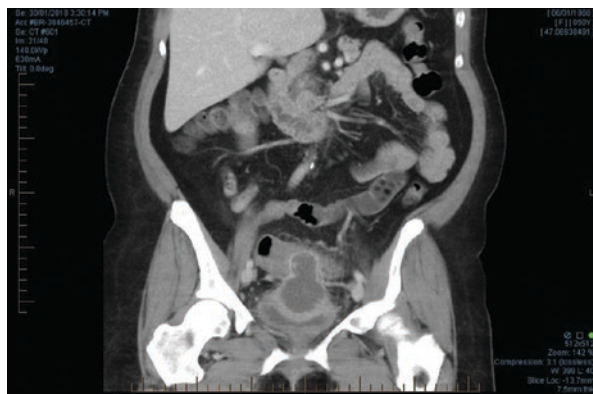
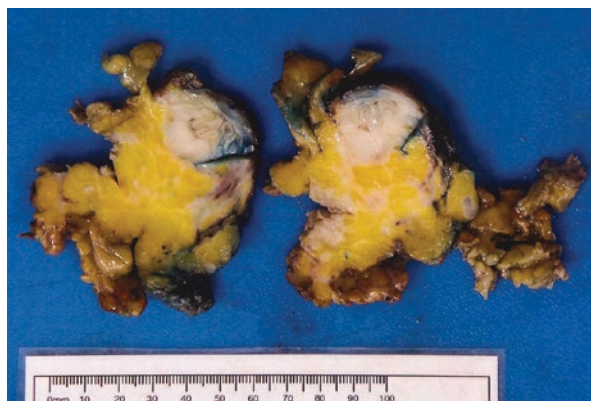


Fig. 2.4 Perforated diverticulum with impacted bone (postoperative diagnosis) causing obstruction



2.3 Nonsurgical Management

Acute diverticulitis can be managed with inpatient or outpatient treatment depending on the patient's presentation, the severity of disease, and other circumstances (remoteness, time of presentation, available support structures).

Acute uncomplicated diverticulitis can usually be treated conservatively. Conservative treatment may include one initial dose of IV antibiotics followed by oral antibiotics and subsequent outpatient reassessment (3 days after initial presentation, until complete resolution of symptoms). Alternatively, the patient may need to be admitted for IV antibiotics and clinical observation. Hospital admission for management of uncomplicated acute diverticulitis is necessary in patients with immunosuppression, fever, uncontrolled pain, advanced age, or significant comorbidities.

Successful conservative management of acute uncomplicated diverticulitis carries the risk of recurrent disease in approximately 2% of all patients per annum. Only patients with increased risks of complications or mortality should be discussed for elective surgery: organ transplant patient, immunosuppression, diabetes, and chronic organ dysfunction (lung, kidney, liver).

Acute noncomplicated diverticulitis requires oral antibiotic treatment for 7–10 days after diagnosis (Table 2.1). The treatment must cover the gastrointestinal flora of Gram-negative and anaerobe bacteria, especially *E. coli* and *B. fragilis*. There is no evidence to support dietary changes for patients selected for outpatient management.

Acute complicated diverticulitis requires inpatient treatment. Antibiotic treatment should be given intravenously (Table 2.2), and in addition to this complication-specific treatment as well as pain management is necessary:

- Frank perforation—emergency surgery (see below)
- Microperforation—no additional treatment needed

Table 2.1 Oral antibiotic treatment regimens suitable for outpatient treatment of acute uncomplicated diverticulitis

Medication	Dosage	Frequency	Duration
1. Amoxicillin + clavulanate	875 + 125 mg	12 hourly	5 days
2. Cephalexin	500 mg	6 hourly	5 days
+ Metronidazole	400 mg	12 hourly	5 days
3. Metronidazole	400 mg	12 hourly	5 days
+ Trimethoprim+ sulfamethoxazole	160 + 800 mg	12 hourly	5 days

(For patients with immediate penicillin hypersensitivity)

Table 2.2 Intravenous antibiotic treatment regimens suitable for inpatient treatment of acute severe or complicated diverticulitis

Medication	Dosage	Frequency	Duration
1. Amoxicillin/ampicillin	1000 mg	6 hourly	3 days
+ Gentamicin	4–7 mg/kg for 1 dose		
(2nd/3rd dose depending on kidney function)			
+ Metronidazole	500 mg	12 hourly	3 days
(Change to regimen 2, 3, or 4 if clinical findings did not improve after 3 days)			
2. Piperacillin + tazobactam	4000 + 500 mg	8 hourly	@
3. Ticarcillin + clavulanate	3000 + 100 mg	6 hourly	@
Choose regimen 2 or 3 for patients with contraindication to gentamicin			
4. Metronidazole	500 mg	12 hourly	@
+ Ceftriaxone or cefotaxime	1000 mg	Daily	
Choose regimen 4 for patients hypersensitive to penicillin			

@Continue treatment until afebrile for 24–48 h

- Abscess—can be seen in up to 50% of patients with acute complicated diverticulitis. Small abscesses (<3 cm) can be treated without intervention; larger abscesses should be drained percutaneously (CT-guided drainage)
- Obstruction—urgent surgery (see below)
- Fistula formation—this can occur between the large bowel and the bladder, vagina, uterus, and other segments of the small/large bowel; (urgent) surgery (see below)

Complicated diverticular disease is best classified using the *Hinchey criteria*:

- Pericolic or mesenteric abscess
- Walled-off pelvic abscess
- Generalized purulent peritonitis
- Generalized fecal peritonitis

Successful nonsurgical treatment of acute uncomplicated as well as complicated diverticulitis requires a *colonoscopy* at approximately 6 weeks after initial presentation (once all symptoms have resolved) to exclude an underlying bowel cancer (unless complete colonoscopy was done within 1 year prior to presentation with

acute diverticulitis). After successful treatment of acute complicated diverticulitis (percutaneous abscess drainage, conservative treatment of small abscess/microabscess), *elective surgery* needs to be planned to avoid the morbidity and mortality associated with a recurrent episode of diverticulitis (incidence up to 40%, mortality of elective vs. emergency surgery 0.3% vs. 4.6%).

Dietary intervention does not prevent recurrent disease after acute diverticulitis, and patients do not need to avoid seeds, corn, and nuts.

2.4 Surgical Management

Most patients presenting with complications of diverticular disease can be treated conservatively, but approximately 15% will require surgery.

Emergency surgery is required with free perforation and subsequent fecal peritonitis. This condition is associated with a mortality rate of up to 25%.

Urgent surgery (within the same admission) must be considered for patients presenting with failure of medical treatment, obstruction, abscess formation (Fig. 2.4) not responding to conservative treatment (CT-guided drainage, antibiotic medication), and fistula formation causing urosepsis/pyelonephritis.

Elective surgery should be performed on patients with fistula formation (if not considered for urgent surgery) and on patients with chronic smoldering diverticulitis (initial response to medical treatment followed by recurrent pain, change in bowel habits, and per rectal bleeding). Also patients after successful conservative management of complicated diverticulitis should be prepared for elective resection (preoperative colonoscopy and physiological optimization). Urgent and elective surgeries both have a mortality of up to 5%.

The decision whether or not to operate on a patient suffering from recurrent diverticulitis should be influenced by the following considerations:

- More than 40% of patients after successful nonoperative management of acute diverticulitis are at risk to develop recurrent diverticulitis
- Prior uncomplicated episodes of acute diverticulitis do not predict a higher incidence or higher severity of recurrent diverticulitis
- Complications and colostomy rates are not affected by the number of previous episodes of acute diverticulitis
- More episodes of diverticulitis are not associated with a higher rate of conversion from laparoscopic to open surgery
- The mortality rate of emergency surgery is significantly higher than the mortality rate of elective surgery (0.3% vs. 4.6%)
- Patients with persistent symptoms at 6–8 weeks after onset of symptoms may suffer from chronic smoldering diverticulitis and should be considered for surgery
- Availability of emergency services to patients in case of recurrent disease (travel plans, remote living)
- Immunocompromised patients often require emergency surgery when presenting with a second attack due to atypical and/or late presentation

2.4.1 Surgical Technique

The choice of surgical approach depends on patient factors as well as surgeon factors. The aim of surgery is to remove the affected segment of the bowel. This can be achieved with open as well as laparoscopic surgery. Depending on the patient's presentation, surgery can be performed in a single-stage (resection and primary anastomosis, no diverting stoma), two-stage (resection \pm anastomosis, diverting stoma/end-colostomy), or even three-stage (drainage of abscess/peritonitis, resection + anastomosis, diverting stoma) approach.

Single-stage surgery should be limited to the few patients where the bowel is well-perfused and non-edematous and the anastomosis is tension-free. Most patients require a *two-stage* approach with or without (Hartmann's operation) primary anastomosis. When deciding to perform a Hartmann's procedure, it is important to consider that only half of these patients will have a colostomy closure after recovering from the initial surgery. *Three-stage* surgery may be necessary in patients with colonic perforation due to diverticular disease.

In *unstable patients* unfit for definite surgery, a damage control procedure with limited bowel resection and end-colostomy should be favored.

Laparoscopic surgery has several advantages including lower rates of wound infection, blood transfusion, postoperative ileus, hospital stay, and incisional hernia. More significant complications (leakage, stricture, bowel laceration, bowel obstruction, abscess formation) have been reported to be independent of surgical approach (laparoscopic or open surgery).

Surgery for diverticular disease can be expected to cure the patient; nonetheless up to 10% of patients require repeat surgery for recurrent complicated diverticular disease. Up to 25% of patients suffer from persistent pain similar to the symptoms reported prior to surgery.

2.5 When to Transfer

Nonoperative management of complicated diverticular disease may require CT-guided abscess drainage. If this cannot be offered, a transfer to a center with interventional radiology support must be offered. Emergency surgery may require postoperative care in high-dependency or intensive care units. If this cannot be provided and the patient can still be transferred, this should be considered prior to surgical intervention.

Recommended Reading

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UpToDate®: Acute colonic diverticulitis: Medical Management.

UpToDate®: Acute colonic diverticulitis: Surgical Management.

UpToDate®: Colonic diverticulosis and diverticular disease: epidemiology, risk factors, and pathogenesis.

Gastroenteropancreatic Neuroendocrine Tumours

3

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3.1 Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are rare neoplasms and represent a heterogeneous group of tumors. These tumors can arise from neuroendocrine cells throughout the body and were formerly referred to as gastrointestinal carcinoids (a term introduced by Oberndorfer more than 100 years ago) and islet cell tumors of the pancreas. Functional tumors produce peptides and hormones and cause characteristic symptoms (including diarrhea and/or flush in carcinoid syndrome, hypoglycaemia in insulinoma, gastrointestinal ulcers in Zollinger-Ellison syndrome). Non-functional tumors lack characteristic symptoms and become clinically apparent due to tumor mass effects (i.e. jaundice, abdominal pain).

Using criteria established by the WHO in 2010, neuroendocrine tumors are classified into well-differentiated neuroendocrine tumors (NET) and poorly differentiated neuroendocrine carcinomas (NEC). Grading (G1–G3) is defined on the basis of mitotic count and/or Ki67 staining. The classification system is well established and predicts the biological behaviour of the tumor with high probability (Fig. 3.1).

Due to their rarity, incidence data on GEP-NETs are difficult to obtain and are mainly based on national cancer registries and small retrospective analyses. Nonetheless incidence is rising, which might be due to improved understanding of the disease and superior imaging modalities. The incidence rate varies between

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Fig. 3.1 Grading classification according to the WHO (HPF mitotic counts per 10 high power fields)

Grading	Ki-67 index	Mitotic rate
G1	≤ 2 %	< 2 / 10 HPF
G2	3 – 20 %	2 - 20 / 10 HPF
G3	> 20 %	> 20 / 10 HPF

studies and is about 1.3–3.5/100,000 per year. The mean age at initial diagnosis is dependent on the primary tumor and peaks in the late 50s; however, appendiceal NETs may arise at the age of 40–50 years. Prognosis is determined by the presence of distant metastases and particularly by the proliferative activity/grading. NETs occurring in the small intestine are the most prevalent, with an annual incidence of 0.67–0.81/100,000 per year representing approximately 35% of all cases. The second most common GEP-NET arises from the appendix with a yearly incidence of 0.15–0.6/100,000 and is usually diagnosed incidentally during appendectomy. Pancreatic NETs are subdivided into functional and non-functional and have an incidence of 0.1–0.3/100,000 per year.

Due to the complexity of GEP-NETs, patients should be treated by an experienced multidisciplinary team. The only chance of cure is complete tumor resection. Nonetheless, even tumor debulking may be beneficial if >90% of the tumour burden can be removed. A surgical approach may also be recommended for relief of tumor-related symptoms in stage IV patients.

3.2 Diagnosis

3.2.1 Imaging Modalities

Cross-sectional imaging using CT or MRI is the cornerstone of initial staging to rule out locoregional or distant metastases. The modalities should follow modern protocols with contrast media, which is adapted to the investigated organ (i.e. MRI with liver-specific contrast agent and various sequences including DWI and T2 to detect liver metastases). GEP-NETs are best detected in the arterial phase of a triple-phase CT scan, and the hyperenhancement of the primary tumor as well as of liver metastases with intravenous contrast agent is characteristic for GEP-NETs.

Most GEP-NETs express somatostatin receptors on their surface, commonly type 2. As a consequence a PET/CT scan specifically targeting the somatostatin receptor (i.e. ⁶⁸Gallium-DOTA-TATE, ⁶⁸Gallium-DOTA-TOC) shows very high sensitivity. Detection of functional somatostatin receptor expression facilitates the therapeutic use of peptide receptor radionuclide treatment in NET G1/G2 tumours. In contrast, most poorly differentiated NECs lose somatostatin receptor expression; thus ¹⁸fluorodeoxyglucose PET/CT is the preferred diagnostic imaging procedure. Somatostatin receptor-targeted radionuclide therapy is not feasible in NECs.