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Coloproctology

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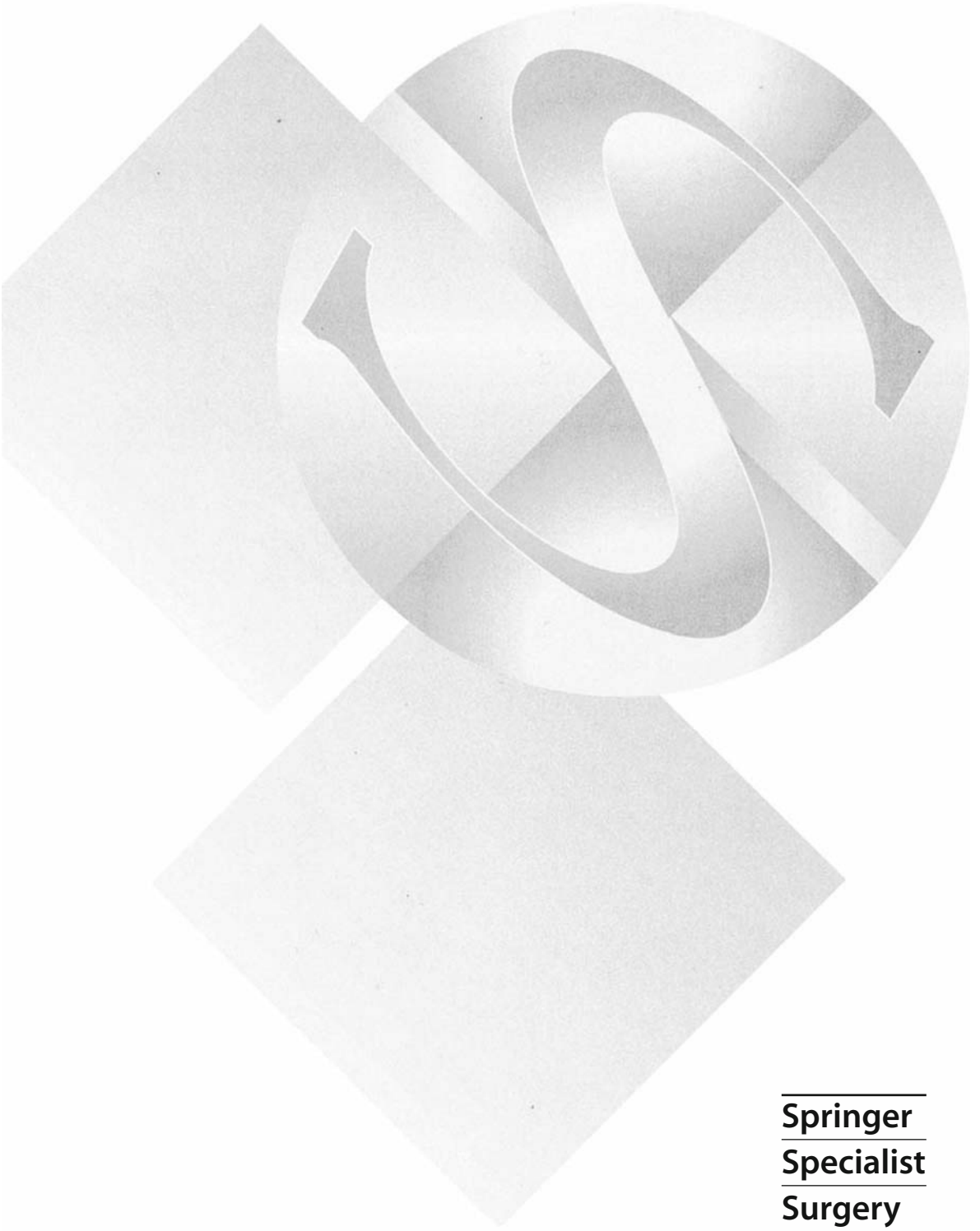

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Coloproctology

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This is dedicated to my parents whose undying support and encouragement provides me with all the direction one could ever need in life...

Andrew P. Zbar

This book is dedicated with love to my two wonderful sons Wesley and Trevor. Their patience with my work schedule and my multitasking is both appreciated by me and fundamental to allow books such as this one to be produced. They are the shining stars in my life.

Steven D. Wexner

Foreword

A request by colleagues to write a foreword to their book is always a compliment and honor. Forewords are often requested by authors who are not well-known but this is certainly not the case for this book as Drs. Andrew Zbar and Steven Wexner are skilled and accomplished authors in their own right and are eminently qualified to edit a book of this nature. The task therefore falls on describing the merits of the contents of the book and perhaps highlighting some of its most prominent attributes.

In this Specialist Surgery Series, Drs. Zbar and Wexner set out to address some of the most difficult and controversial problems as well as new areas of development facing practitioners of colorectal surgery. They selected contributors who are expert in the discipline of colorectal surgery and whom they believed would discuss these subjects with up-to-date information relevant to the practicing surgeon. Their goal was accomplished as the authors of each chapter met face on the challenging disorders affecting the lower GI tract and provided for the reader a better understanding of the disease process and management options. For example, the book starts off with a chapter providing an extensive review of the genetics of colorectal cancer – an area of exploding knowledge and one in which I believe holds the future in the early diagnosis and detection of colorectal cancer and if I may be so bold as to predict, holds the key to the future treatment of the disease. Subsequent chapters deal with the management of advanced cancer from the point of view of the propriety of chemotherapy, radiotherapy, and operation. An issue of growing importance is the role quality of life should play. The idea is reinforced that quality of life trials should be performed to provide better information for both patients and doctors to permit better preoperative assessment in recommending informed management for patients. Other difficult management issues described include revisional pouch surgery, fecal incontinence, new approaches to perianal Crohn's disease and complex anal fistula and rectovaginal and rectourethral fistula. The book ends on a strong note with a chapter on the changing paradigm in the treatment of sigmoid diverticulitis. This is an especially important chapter because of the frequency of the disease seen in clinical practice and the excellent review of this subject.

The reader should find this book a welcome reference source and a reliable guide to the sound practice of colorectal surgery.

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Preface

Coloproctology has been a burgeoning field for surgeons over the last two decades. It now represents an eclectic array of subspecialties for those specifically interested in colorectal genetics, neoplasia, inflammatory bowel disease, and functional bowel disorders. This textbook aims to bring together numerous international experts to incorporate the current management and investigation of these important areas for colorectal practitioners and trainees. In this book, the reader will find up-to-date approaches toward a myriad of challenging areas including genetic testing in hereditary and familial cancer, the role and outcome of multivisceral resections in rectal cancer, and the recommended management of presacral tumors and recurrent rectal carcinoma. These discussions are allied with an update on chemotherapy and immunotherapy trials in colorectal cancer, new approaches to radiotherapeutic delivery, and important quality of life issues that affect overall postoperative outcomes. Additional chapters include the specialized areas of inflammatory bowel disease management, including revisional pouch surgery and perianal Crohn's disease.

Functional bowel disorders represent a particularly difficult group of referred patients for which there has been a radical change in management through the introduction of a sometimes confusing array of new diagnostic and therapeutic modalities. Patients who may benefit from this spectrum of evaluation and management include those individuals with fecal incontinence, poor postoperative functional outcomes, and evacuatory difficulty. Two perhaps more commonly seen but nonetheless challenging areas included in the text are updates on complex anal fistula management, including the very difficult to treat rectovaginal and rectourethral fistulas, and the current status of the diagnosis and treatment of complicated sigmoid diverticular disease. It is hoped that this textbook will be a practical guide for patient assessment and will provide both the practising surgeon and the surgical trainee with formulaic and rational pathways for specialized patient care.

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Genetic Approaches to Colorectal Cancer

Raul D. Bernabe, Ronghua Zhao,
and Marcia R. Cruz-Correa

Introduction

Colorectal cancer (CRC) is a significant public health problem throughout the world affecting over one million individuals every year. CRC is the third most common cancer in the U.S. and the second leading cause of cancer deaths in North America, accounting for approximately 150,000 new cases and 60,000 deaths annually. There are three major forms of colorectal cancer: sporadic (85% of cases), familial (10–30%), and hereditary (less than 10%). CRC develops from apparently normal mucosa into a benign precursor stage, the premalignant polyp, and can progress to invasive disease. There are three major molecular mechanisms identified in the pathogenesis of colorectal cancer: chromosomal instability, microsatellite instability, and aberrant methylation. The classic tumor suppressor pathway, also known as the chromosomal instability pathway (CIN), is present in approximately 70–85% of CRC cases. This traditional pathway is characterized by a mutation in the APC gene, mutation of K-ras, loss of 18q, and deletion of 17p which contains the tumor suppressor gene p53. In contrast, the microsatellite instability (MSI) or mutator pathway affects approximately 15–20% of all CRC. In the MSI pathway, there exists failure of the mismatch repair system (MMR) to repair DNA following replication. The MMR system is composed of several proteins that create complexes that maintain the fidelity of DNA during replication. Failure of the MMR complex results in detectable differences between tumor and germline DNA in the number of copies found in short repeat DNA sequences called microsatellites, which consist of repeating units of 1–6 base pairs in length. The aberrant methylor pathway refers to abnormal DNA methylation patterns as a way of regulating gene transcription. Methylation of DNA can occur at cytosine bases when cytosine and guanosine occur in a dinucleotide pair, known as CpG islands. Hypermethylation of the CpG islands found within the promoter sequence of the genes will result in transcriptional silencing of the methylated genes. This chapter reviews the recent developments in defining CRC pathways.

Colorectal Cancer Epidemiology

Colorectal cancer (CRC) is a major world public health problem, as reflected by its annual worldwide incidence of over one million (Jemal et al. 2007). CRC shows a similar distribution between the genders, and is responsible for approximately 492,000 deaths worldwide and about 50% of them die within 5 years (Weitz et al. 2005). In North America, CRC is the third most common cancer and the second leading cause of cancer deaths, accounting for approximately 150,000 new cases and 60,000 deaths annually (Imamura and Sobue 2004). Family history, tobacco smoking, alcohol consumption, and obesity have all been identified as risk factors for CRC. Although several genetic syndromes have been identified to be associated with CRC, the most common

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risk factor for CRC is a positive family history of CRC (Lynch and de la Chapelle 2003).

The etiology of CRC is heterogeneous, including environmental and genetic factors. Fortunately, CRC is preventable and highly curable if detected in the early stages of development. There are three major forms of CRC: sporadic (85% of cases), familial (10–30%), and hereditary (less than 10%) (Soreide et al. 2006).

Molecular Biology of Colorectal Cancer

There are three major molecular mechanisms identified in the pathogenesis of CRC: chromosomal instability, microsatellite instability, and aberrant methylation.

Chromosomal Instability (CIN) or Tumor Suppressor Pathway

Approximately 70–85% of CRC develop via the tumor suppressor pathway (Grady 2004). Most colorectal carcinomas are triggered by inactivation of the APC/β-catenin pathway, followed by clonal accumulation of genetic alterations, including activation of proto-oncogenes such as K-*ras* and inactivation of other tumor suppressor genes candidate such as p53, DCC, and SMADs on chromosome 18q, as well as uncharacterized suppressor genes on chromosomes 8p and 1p. These tumors have prominent allelic losses and gains, which reflect extensive cytogenetic abnormalities, and this pathway has been described as the *chromosomal instability pathway* or *Tumor suppressor pathway* (Lynch et al. 1993; Aaltonen et al. 1994; Lynch 1997).

Microsatellite-Instability Pathway or Mutator Pathway

The Mutator pathway occurs in about 15% of sporadic colorectal carcinomas, and is distinguished from the suppressor pathway by extensive nucleotide insertions or deletions in numerous, intrinsically unstable repeated sequences (microsatellites) in tumor DNA with infrequent allelic imbalances and infrequent cytogenetic abnormalities. The alterations are described as high levels of microsatellite instability (MSI-H; also termed DNA replication errors/RER, ubiquitous somatic mutations/USM, or nucleotide instability) (Dietmaier et al. 1997; Boland et al. 1998; Wahlberg et al. 2002; De la Chapelle 2003). This MSI pathway includes the mismatch repair (MMR) genes, whose functions are abolished by germline mutations or promoter hypermethylation (of *hMLH1*). The MMR system is composed of at least seven proteins, hMLH1, hMLH3, hMSH2, hMSH3, hMSH6, hPMS1, hPMS2, which associate with specific partners to form functional heterodimers (Hoeijmakers 2001). During the replication process, the DNA polymerase is susceptible to making errors in the microsatellites; hence, MMR dysfunction results in detectable differences between tumor and normal tissues on germline DNA in the number of copies found in the microsatellites – a phenomenon known as MSI. MSI-H tumors occur frequently in hereditary non-polyposis colorectal cancer (HNPCC) and are present in approximately 15–20% of sporadic CRC cases. The majority of MSI-H CRC tumors are therefore sporadic and result from epigenetic silencing of the h*MLH1* gene (Deng et al. 1999).

Aberrant Methylation Pathway

DNA methylation is a transmissible mechanism of modifying gene expression without changing the underlying DNA sequence. The aberrant methylation patterns produce a growth advantage relative to the surrounding cells (Jackson and Loeg 1998; Tomlinson and Bodmer 1999). Global decreases in 5-methyl-cytosine content have been associated with the formations of several types of malignancies. On the other hand, de novo CpG island methylation is a common event during neoplasia (Feinberg et al. 2004; Issa et al. 1996). In fact, aberrant methylation pattern of numerous genes provides another mechanism that is important in colorectal carcinogenesis (Worthley et al. 2007; Cheng et al. 2008; Issa 2008; Ogino et al. 2009), termed as CpG island methylator phenotype (CIMP). Promoter sequence methylation interrupts the gene expression by directly inhibiting transcription factor binding, and hence accessibility to the transcriptional machinery. Transcriptional silencing results from aberrant methylation of cytosines in the cytosine–guanine rich promoter region of the genes or CpG islands. Furthermore, studies show that in sporadic MSI-H, tumors

appear to be a subset of CIMP tumors, which occur when *hMLH1* happens to be one of the methylated genes (Miyakura et al. 2001). CIMP CRCs rarely present with alterations in the chromosomal CIN, suggesting a separate pathway of colorectal carcinogenesis (Cheng et al. 2008). Moreover, there is mounting evidence for fundamental clinicopathologic differences between CIMP-positive and CIMP-negative tumors. CIMP tumors tend to occur in the proximal colon in older patients, with slight increased prevalence among women, as well as tend to have BRAF and KRAS mutations and fewer *APC* and *p53* mutations (Cheng et al. 2008). CIMP-positive CRC tumors generally have a poorer prognosis (Issa 2004).

There are two main methylation marker panels to help identify CIMP CRC. Depending on the markers used, 24–51% of all CRC are CIMP-positive (Toyota et al. 1999; Toyota and Issa 1999; Samowitz et al. 2005). The most common panel includes the analysis of the promoter regions of the genes h*MLH1* (Weisenberger et al. 2006), $p16^{CDK4A}$ (Lee et al. 2004; Goel et al. 2007), *MINT 1, 2, 3* (Toyota et al. 1999; Shen et al. 2007), *APC* (Esteller et al. 2001a, b), *RASSF1A* (Wagner et al. 2002; Lee et al. 2004), *CDH1* (Lee et al. 2004), *TIMP-3* (Lee et al. 2004; Goel et al. 2007), *DAPK* (Anacleto et al. 2005), *MGMT* (Anacleto et al. 2005; Paz et al. 2003; Lee et al. 2004), and *COX*-2 (Toyota et al. 2000).

The general perception of methylation of discrete CpG islands followed by transcriptional silencing of the genes has been accepted for many years. However, recently Frigola et al. (2006) demonstrated epigenetic silencing in a large 4-Mb domain of the chromosomal region 2q14 in CRC. This phenomenon was termed as long-range epigenetic silencing (LRES). DNA methylation in each three enriched CpG island clusters was associated with suppression of the flanking genes, despite the fact that these genes themselves remained unmethylated. Furthermore, this suppression was caused by methylation of histone H3, independent of DNA gene methylation. The hypermethylation at LRES may influence the long-range suppression of the neighboring genes by modifications in the histones, followed by the resultant chromatin alterations (Frigola et al. 2006). Moreover, Hitchins et al. (2007) described LRES at 3p22 in MSI-sporadic CRCs that display *hMLH1* promoter hypermethylation. Studies show that LRES regions are associated with transcriptional silencing of the genes related to carcinogenesis, *hMLH1*, *EN1* (Wnt pathway), *GL12* (tumor suppressor), *DLEC1*, and *CTDPL* (tumor suppressor) (Frigola et al. 2006; Hitchins et al. 2007). All the data suggest a possible connection between MSI, CIMP, and LRES in the development of CRC.

Hereditary Genetic Syndromes

Several hereditary syndromes caused by specific germline mutations have been characterized, accounting for 5–6% of all CRC patients. These include familial adenomatous polyposis (FAP), HNPCC, MYH-Polyposis (MAP), Peutz–Jeghers syndrome, and juvenile polyposis. Genetic testing is available for the diagnosis of the major inherited syndromes of colon cancer. When used appropriately, genetic testing may assist in the diagnosis, surveillance, and management of both the patients and their families. The two most prevalent forms of hereditary genetic syndromes will be hereby reviewed.

Hereditary Non-Polyposis Colon Cancer

HNPCC, also known as Lynch syndrome, is a clinically heterogeneous disease that has historically been diagnosed based on family-history criteria (Amsterdam and Bethesda) as well as pathologic criteria (Rodriguez-Bigas 1997; Vasen et al. 1999; Umar et al. 2004). HNPCC is characterized by increased risk of early onset CRC and other extracolonic cancers, including those of the endometrium, ovary, stomach, small intestine, hepatobiliary tract, ureter, and brain (Lynch et al. 1993; Lynch and Smyrk 1996). Two-thirds of the colon cancers are found in the proximal colon (Lynch and Smyrk 1996; Lynch and de la Chapelle 2003). The lifetime risk for colon cancer in HNPCC subjects is approximately 80% with the average age of colon cancer diagnosis approaching 45 years of age (De la Chapelle 2004). There is a significant excess of synchronous and metachoronous CRC, with close to 30% chance of having a second primary CRC within 10 years of surgical resection for the initial CRC. When compared with nonfamilial CRC, tumors tend to be poorly differentiated, with an excess of mucoid and signet-cell features, and

contain a significant excess of tumor infiltrating lymphocytes within the tumor (Lynch et al. 2006). There appears to be an accelerated carcinogenesis process, and tiny adenomas may emerge into a carcinoma within 2–3 years, when compared with the 8–10 year interval in the general population. Two other cancer predisposition syndromes share the genetic and clinical features with HNPCC: Muir–Torre syndrome (Entius et al. 2000) is characterized by HNPCC-associated cancers as well as skin-gland neoplasms and Turcot's syndrome (Hamilton et al. 1995; Miyaki et al. 1997) is characterized by CRCs and glioblastomas (Lucci-Cordisco et al. 2003).

HNPCC is an autosomal dominant disease. The majority of HNPCC cases, and a proportion of cases not fitting these criteria, can be accounted for by mutations in one of the several genes involved in DNA mismatch repair (MMR). In cases with defective MMR, approximately 90% have alterations in one of the three of the MMR genes, *hMLH1*, *hMSH2*, or *hMSH6*, with a smaller proportion attributable to mutations in other MMR genes (Lynch et al. 2006). Mutations in *hMLH1*, *hMSH2*, or *hMSH6* generally will lead to MSI tumor phenotype, and it was the discovery of this phenotype that led to the original discovery that MMR genes are the causative defect in HNPCC.

Molecular Genetics of HNPCC

HNPCC is caused by a mutation in any one of MMR genes. The mismatch repair genes include: *hMSH2* on chromosome 2p16, *hMLH1* on chromosome 3p21, *hPMS1* on chromosome 2q31, *hPMS2* on chromosome 7q11, and *hMSH6* on chromosome 2p16 and *hMSH3*. Germline mutations of *hMSH2* and *hMLH1* account for more than 95% of the mutations identified in the HNPCC patients (Liu et al. 1996). There are certain racial and ethnic genotype variations. For instance, in North America, there is a similar frequency in h*MLH1* and h*MSH2* mutations, while in other countries such as Korea, Finland, Spain, and China, most mutations are found in h*MLH1* (Liu et al. 1994). In addition, a genotype–phenotype correlation has also been reported. Among individuals with an h*MSH2* mutation, there is an increased risk of extracolonic cancers by the age of 60 years, when compared with those with h*MLH1* mutation. Similarly, gender differences among individuals with the same mutations have been reported. For instance, CRC risk is increased among males with h*MSH2* mutations, when compared with females (96 vs. 39%) (Lin et al. 1998). These genotype–phenotype differences may have important implications on screening, surveillance, and diagnostic strategies used for the affected HNPCC individuals.

The MMR proteins function to maintain fidelity of DNA during replication by correction of nucleotide base mispairs, which is the result of DNA-polymerase mistakes. As a consequence of MMR gene mutations, the cell loses its ability to repair DNA base–base mismatches, resulting in the accumulation of simple repetitive sequences of DNA microsatellites (stretches of DNA in which a short sequence of 1–6 nucleotides is repeated several times) throughout the genome; these sequences have variable lengths due to insertion or deletion mutations. A typical mononucleotide repeat microsatellite might be a contiguous area of 13 adenines. This phenomenon, called MSI, is found in 90% of HNPCC-related CRC, in contrast to only 15–20% of sporadic CRC (Lin et al. 1998). In HNPCC-related CRC, MSI is the result of mutational inactivation of one of the mismatch repair genes, while in sporadic CRC, MSI arises through somatic epigenetic biallelic methylation of the promoter sequences of h*MLH1* gene (De la Chapelle 2003). Patients whose colorectal tumors exhibit MSI have improved survival (Halling et al. 1999) and better response to chemotherapy than those whose tumors do not express MSI (i.e., are microsatellite stable) (Elsaleh et al. 2000).

Diagnosis of HNPCC

Clinical Diagnosis. The lack of characteristic pathognomonic phenotype markers makes the diagnosis of HNPCC particularly demanding. Most often, diagnosis relies on correlating the clinical characteristics of HNPCC to the family history. Those families that fulfill the Amsterdam Criteria I can be easily classified as HNPCC kindreds (Table 1.1) (Vasen et al. 1991). However, the diagnosis of HNPCC should also be considered in less classic phenotypes that include extracolonic HNPCC-associated cancers (endometrial, small bowel, ureter, or renal pelvis) and the Amsterdam Criteria II

Table 1.1. Amsterdam criteria (international collaborative group) for the diagnosis of hereditary nonpolyposis colorectal cancer

Amsterdam criteria I (Vasen et al. 1991)	Amsterdam criteria II (Vasen et al. 1999)
3 or more relatives with CRC, 1 of whom is a first-degree relative of the other two; FAP should be excluded	3 or more relatives with verified HNPCC-associated cancer (CRC, endometrial, small bowel, ureter, or renal pelvis), 1 of whom is a first-degree relative of the other two; FAP should be excluded
CRC involving at least two generations	CRC involving at least two generations
1 or more CRC patients diagnosed before the age of 50	1 or more CRC patients diagnosed before the age of 50

Table 1.2. Revised Bethesda guidelines for testing of colorectal tumors for microsatellite instability (MSI) (Umar et al. 2004)

Individuals diagnosed with colorectal cancer at age <50 years
Individuals with two HNPCC-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers, regardless of age
Individuals with colorectal cancer with the MSI-H histology diagnosed before 60 years
Individuals with colorectal cancer and ≥1 first-degree relatives diagnosed with colorectal cancer or other HNPCC-related tumor; one of the cancers diagnosed at <50 years (or adenoma diagnosed at <40 years)
Individuals with colorectal cancer and ≥2 first- or second-degree relatives diagnosed with colorectal cancer or other HNPCC-related tumor, regardless of age

[a]Endometrial, ovarian, gastric, hepatobiliary, small bowel, or transitional cell carcinoma of the renal pelvis or ureter.

(Table 1.1) (Vasen et al. 1999). The Bethesda guidelines were developed to aid in the decision process regarding genetic testing for individuals with cancer in families that do not fulfill the Amsterdam criteria (Rodriguez-Bigas 1997). The Bethesda guidelines were recently revised to identify patients who are at risk for hereditary cancer, including colonic and extracolonic cancers, and to identify h*MSH2* and h*MLH1* germline-mutation carriers in patients with cancers who might or might not fulfill the Amsterdam II criteria (Table 1.2).

MSI testing. MSI is found in the CRC DNA of individuals with MMR gene mutations. MSI testing of the tumor serves as a screening test for HNPCC, and should be the first step in the genetic evaluation of families suspected to be affected by HNPCC. According to the MSI criteria, tumor DNA is classified as microsatellite unstable (MSI-high or -low) or as microsatellite stable (MSS). Individuals with MSI-H tumors should undergo testing for mutation of the *hMSH2* and *hMLH1* genes. However, those individuals with MSI-low or MSS tumors are unlikely to harbor germline mismatch repair gene mutations, and further genetic work-up is deferred. While germline mutations in the MMR gene are generally the cause of MSI-H tumors in HNPCC, somatic mutations account for the small fraction of sporadic CRC with MSI phenotype (Shitoh et al. 2000; Jass et al. 2002). The National Cancer Institute (NCI) has recommended a panel of five markers, known as Bethesda (or NCI-panel) markers, which include two mononucleotides, BAT25 and BAT26, and three dinucleotide repeat loci, D2S123, D5S346, and D17S250 on chromosome 4q12, 2p21–22, 1p13.1, 2p16, 3p21, 5q21–22, and 17q11.2–12, respectively. Tumors with no instability in any of the markers are considered to be MSS, while tumors with two or more altered markers are considered to be MSI-H (Umar et al. 2004; Jenkins et al. 2007).

Immunohistochemistry. Immunohistochemistry (IHC) has recently been proposed as an inexpensive alternative for identifying MSI-positive tumors. IHC can identify loss of *hMLH1* and *hMSH2* protein products, and has shown a direct correlation with 100% specificity to MSI-H tumors and 96.7% for MSS tumors. This technique may be used as a first step to characterize the tumor as MSI or MSS, before genetic testing of the MMR genes. The options of MSI testing or IHC may be equivalent, but the precise algorithm may need to be done in accordance with the local practice and recommendations (Pinol et al. 2005). A strong correlation can be seen between MMR gene mutation and loss of staining of the corresponding protein using IHC, and this, along with an assessment of family history, has been recommended as a starting point for diagnosing HNPCC (Lindor et al. 2002), although it should be noted that not all MMR mutations lead to a loss of protein expression (Wahlberg et al. 2002).

Mismatch repair gene testing. MMR gene testing is indicated for: (1) confirmation in patients

whose tumors express MSI-H, (2) affected patients in families meeting any of the first three Bethesda Criteria, and (3) presymptomatic testing in adults at risk for HNPCC. At present, commercial analysis is only available for mutations in *hMSH2* and *hMLH1*. Once a mutation is found in an affected family member, genetic testing of at-risk relatives provides true positive or negative results. However, if the mutation is not identified in the affected family member, no further testing is performed among at-risk relatives because negative results are uncertain. In this setting, a negative result may be a false-negative result owing to the inability of the test to identify mutations even if present, or mutations in other known or unknown MMR genes (Giardiello et al. 2001; Cruz-Correa and Giardiello 2002).

In patients in whom tumor tissue is not available for initial MSI analysis (Levin 1999), germline testing might be considered in any of the following conditions: (1) individuals with cancer in families that meet the Amsterdam criteria, (2) individuals with two HNPCC-related cancers, including synchronous and metachronous CRCs or associated extracolonic cancers, and (3) individuals with CRC and a first-degree relative with CRC and/or a colorectal adenoma (one of the cancers diagnosed at the age of <50 years, and the adenoma diagnosed at the age of <40 years) (Giardiello et al. 2001).

The appropriate algorithm for HNPCC testing includes: (1) the Amsterdam I/II criteria; (2) Bethesda criteria; (3) tumor testing for MSI or the absence of hMSH2 or hMLH1 by IHC; and (4) genetic testing of the main HNPCC genes. If individuals are found to have disease-related mutations, they are confirmed to have HNPCC (Fig. 1.1). This stepwise approach for genetic testing in HNPCC, including a screening test (Amsterdam I/II and Bethesda criteria), followed by tumor phenotype (MSI and IHC) and subsequent genotype (mismatch repair gene testing) allows confirmation of the diagnosis or the presymptomatic testing in adults at risk for HNPCC (Giardiello et al. 2001).

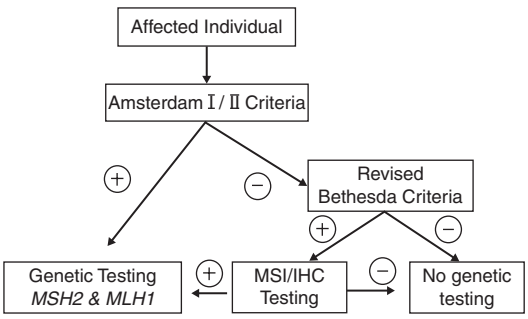

Figure 1.1. Stepwise approach for genetic testing in affected individuals from families with suspected HNPCC.

Genetic Counseling for HNPCC

Recommendations for the rational use of genetic tests have been published by several organizations (American Society of Clinical Oncology 1996; Levin 1999; Lynch 2008). The American Society of Clinical Oncology (ASCO) recommends that practitioners must ensure that the patient or guardian has given informed consent. Experts advise that written informed consent should be obtained on test-specific forms that include information about: the purpose of the test, description of the test, meaning of a positive and negative test, and the implications of a positive and negative test. In addition, ASCO advocates that practitioners include pre- and posttest genetic counseling about the possible risks and benefits of early detection of cancer and of prevention modalities with presumed but unproven efficacy for individuals at the highest risk for cancer. Genetic counseling addresses concerns seen in gene mutation positive subjects (including anger, denial, worry about social stigmata, fear of loss of insurability) and those concerns seen in gene mutation negative patients including the survival guilt (guilt over escaping an illness that has afflicted other family members) (Rosen et al. 2007; Lynch 2008). As a general rule, genetic testing should be offered when: (1) the person has a strong family history of cancer or early age of onset of the disease, (2) the test can be adequately interpreted, and (3) the results will influence the medical management of the patient or family member.

Familial Adenomatous Polyposis

FAP was the first CRC-predisposing condition for which a causative gene at chromosome 5, *APC* (*Adenomatous Polyposis Coli*), was identified (Kinzler et al. 1991). FAP is an autosomal dominantly inherited syndrome that arises from a germline mutation of the *APC* gene. FAP is

clinically characterized by the occurrence of hundreds to thousands of adenomas throughout the colon at an early age (Cruz-Correa and Giardiello 2003). This disorder is estimated to affect one in 10,000 individuals, and has nearly 100% penetrance (Giardiello and Offerhaus 1995) with an equal gender distribution. Such polyps typically emerge during the second decade of life, but have been noted to occur until the age of 40. The defining feature of FAP is the development of multiple adenomatous large bowel polyps that inevitably progress to colorectal carcinoma. In an unscreened person with FAP, the average age at diagnosis of polyposis ranges from 34.5 to 43 years, while the average age of CRC diagnosis is 39 years (Giardiello and Offerhaus 1995). FAP has been classified according to the polyp number into certain subgroups: sparse (polyp number between 100 and 500), profuse (>2,0001995), and attenuated (10–100). FAP is also known by other terminologies including familial polyposis (patients without extracolonic manifestations) or Gardner's syndrome (patients with extracolonic manifestations). Other variants of FAP include Crail's syndrome, previously termed Turcot's syndrome, defined as typical FAP together with central nervous system malignancies (medulloblastoma), and attenuated familial adenomatous polyposis colon cancer (AFAP). The clinical characteristics of AFAP include oligopolyposis (fewer than 100 colorectal adenomas at presentation) and a delayed onset of CRC occurring on an average of 12 years later than in classic FAP (Giardiello and Offerhaus ; Lynch et al. 1995).

In addition to multiple colonic polyps, patients with FAP can develop a variety of extracolonic tumors, including malignancies of the upper gastrointestinal tract (duodenal, periampullary but very rarely the jejunum), thyroid, pancreas (Giardiello et al. 1991), biliary tree and brain (Laken et al. 1999), and hepatoblastomas. FAP patients can develop a variety of extracolonic manifestations, including extracolonic polyps (fundic gland polyps and adenomas of the small intestine), desmoid tumors, cutaneous lesions (lipomas, fibromas, epidermal cysts), odontomas, osteomas, pigmented ocular fundic lesions (POFLs), adrenal adenomas, and nasopharyngeal angiofibroma (Giardiello et al. 1993a-c, 1997b). Improved surveillance and prophylactic surgery have led to a reduction in mortality owing to CRC in FAP patients. However, ampullary carcinoma and desmoids continue to represent major causes of FAP-related death (Cruz-Correa and Giardiello 2003).

Molecular Genetics in FAP

FAP is caused by germline mutations of the *APC* gene on chromosome 5q21–22 (Hamilton et al. 1995). *APC* is a large gene encoding a protein of 2,843 amino acids in its common isoform (Laurent-Puig et al. 1998). The *APC* gene containing exon 15 is the largest coding region (6.5 kb). *APC* is a tumor-suppressor gene that has been implicated in a number of cell processes including transcription regulation, cell adhesion, apoptosis, and in maintaining the fidelity of chromosomal segregation (Bienz 2002; Nathke 2004).

Over 300 different disease-causing mutations of the *APC* gene have been reported in FAP. Approximately 30% of the 800 described mutations on *APC* can be found at codons 1061 and 1309 in the 5′ region of exon 15, a region known as the mutation cluster region and comprising 20% of the entire gene (Laken et al. 1997; Laurent-Puig et al. 1998). The majority of the remaining mutations are spread between codons 200 and 1600, with only a few mutations occurring outside this region. Approximately 90% of the *APC* mutations found in FAP are frameshift or nonsense mutations that lead to an inactive truncated protein product.

Genotype–phenotype correlations have been observed in FAP. Classic FAP with severe polyposis (greater than 5,000 polyps) is generally associated with mutations between codons 169 and 1600, while increased 5′ and 3′ APC mutations result in attenuated FAP (De la Chapelle 2004). Congenital hypertrophy of the retinal pigment epithelium (CHRPE) seen in some FAP patients is usually associated with mutations in codons 463–1444 (Bodmer et al. 1987; Giardiello et al. 1997a, b), whereas Gardner's syndrome involving severe desmoids, osteomas, epidermoid cysts, and upper gastrointestinal polyps, is generally associated with *APC* mutations in codons 1445 and 1578 (Dobbie et al. 1996; Giardiello et al. 1997a). No consistent genotype correlation has been found for duodenal polyposis. Saurin and his coinvestigators reported that patients with mutations in codons 279–1309 of the *APC* gene had a higher duodenal polyp Spigelman

score when compared with those with other mutations (Saurin et al. 2002). However, other investigators have not identified an association between the site of germline mutation and the presence of duodenal polyps (Friedl et al. 2001; Groves et al. 2002). Considerable phenotypic variability may occur even among individuals and families with identical genotypic mutations (Soravia et al. 1998a, b). Missense mutations in *APC* have been described. A specific missense mutation in *APC* (I1307K) is seen in persons of Ashkenazi Jewish descent (Laken et al. 1997). While this missense mutation does not appear to have any effect on APC function, carriers do have an increased risk of CRC, but not polyposis or other extra colonic manifestations of FAP.

MYH-Associated Polyposis (MAP). Some patients with multiple colorectal adenomas (generally 10–1,000 polyps) but no identifiable *APC* gene mutation have been shown to harbor homozygous or compound heterozygous germline mutations in the *MYH* gene, located on chromosome 1p33–34 (Al-Tassan et al. 2002; Croitoru et al. 2004). These mutations may be missense or nonsense, the latter yielding protein truncation. Two common mutations, *MYH* Tyr165Cys (Y165C) and Gly382Asp (G382D), have been reported (Sieber et al. 2003; Gismondi et al. 2004). MYH-Associate Polyposis (MAP) is transmitted in an autosomal recessive inheritance pattern and is clinically undistinguishable from FAP presenting with multiple colorectal adenomas but a negative APC gene mutation. Clinical findings of an increased number of polyps may trigger suspicion of either MAP or attenuated FAP; however, the number of polyps is extremely variable and may be very low in about 25% of patients (Jo and Chung 2005). MAP is defined as involving biallelic inactivation of *MYH*, although some data suggest that even monoallelic *MYH* mutations may be associated with an increased risk of colorectal cancer, and perhaps, other epithelial tumors; however, more recent publications suggest the contrary (Balaguer et al. 2007).

Two *MYH* mutations, Y165C and G382D, account for approximately 80% of the reported *MYH* mutations in Caucasians (Sieber et al. 2003). Mutation of the *MYH* gene may explain a proportion of patients with the appearance of FAP or AFAP in whom no *APC* gene mutation can be identified. As *MYH* mutations are present in up to 1% of the predominantly Caucasian populations, and as the founder mutations are present in other ethnic groups, it is very likely that proving an increased cancer risk caused by *MYH* mutations will have immediate clinical relevance with respect to tailored CRC screening and risk-modification strategies.

Diagnosis of FAP

Genetic Testing. The screening test of choice is genetic testing for the *APC* gene mutation. First-degree relatives of FAP patients should undergo screening for FAP between 10 and 12 years of age (Giardiello et al. 2001). The *APC* gene mutation responsible for the disorder in the pedigree can be identified in 80–90% of FAP families. Genetic counseling is an essential part of genetic testing. Genetic counseling should include patient education, screening and management recommendations, possible consequences of genetic testing, and written informed consent for APC gene testing obtained from the patient and/or parents (Giardiello et al. 2001). Consequently, it is often prudent to refer relevant families to a regional high-risk colon cancer program for evaluation, where trained personnel are available to perform genetic testing and pedigree research.

Endoscopic Screening. Once the disease-causing mutation is identified in an individual affected with FAP, other family members can be tested, and endoscopic surveillance should be directed only at those who test positive for the mutation. If the pedigree mutation is not found or if informative genetic testing cannot be done, all first-degree family members should undergo endoscopic screening (Giardiello et al. 2001; Cruz-Correa and Giardiello 2003). Current screening recommendations include yearly sigmoidoscopy starting from the age of 12 years, reducing screening frequency with each subsequent decade up to the age of 50 years (every 2 years after 25 years, every 3 years after 35 years), after which screening should conform to the guidelines for average-risk persons. Regarding upper gastrointestinal screening in patients affected with FAP, most authorities recommend upper endoscopy (with biopsy and brushing) of the stomach, duodenum, and periampullary region with front- and/or side-viewing endoscopes starting at 25 years of age in asymptomatic FAP patients (Table 1.3) (Giardiello et al. 2001).

Table 1.3. Screening/surveillance guidelines in FAP patients (Cruz-Correa and Giardiello 2003)

At-risk individuals	Genotyping
	APC gene mutation (+), flexible sigmoidoscopy annually starting at age 12 years
	APC gene mutation (−), flexible sigmoidoscopy age 25 years
	If genotyping not available
	Flexible sigmoidoscopy annually starting age 12 years, then every 2 years starting age 25 years, then every 3 years starting age 35 years, then as per the guidelines for average risk individuals starting at age 50 years
Affected individuals	Upper GI tract surveillance every 3–5 years, and annually if upper tract polyps
	If retained rectum or J-pouch, flexible sigmoidoscopy every 6 months or 1–2 years, respectively
	Annual physical exam and routine blood tests

Genetic Counseling for FAP

Mutation screening can identify *APC* sequence changes in up to 95% of patients presenting with classical FAP. Approximately 75% of families show vertical transmission of the disease among generation (indicating autosomal dominant inheritance), while the majority of the remaining pedigrees have a single affected patient. In *APC*-related families, first-degree relatives are at 50% risk of having inherited the mutant gene. Heterozygous individuals virtually have a 100% chance of developing phenotypic manifestations.

First-degree relatives of FAP patients should undergo screening for FAP, starting between the age of 10 and 12 years. The screening test of choice is genetic testing for the *APC* gene mutation. Indications for *APC* gene testing include: >100 colorectal adenomas, first-degree relatives of patients with FAP, ≥20 cumulative colorectal adenomas, and first-degree relatives of patients with AFAP. The *APC* gene mutation responsible for the disorder in the pedigree can be identified in more than 90% of the FAP families. In cases where *APC* mutations are not identified in subjects with moderate numbers of adenomas (10–1,000), *MYH* analysis is carried out (Riegert-Johnson et al. 2007). Currently, the available commercial genetic testing offers both *APC* and *MYH* genetic testing for individuals with colonic polyposis (Jo and Chung 2005; Kaz and Brentnall 2006).

Genetic counseling is an essential part of genetic testing. Genetic counseling should include patient education, screening and management recommendations, possible consequences of genetic testing, and written informed consent for genetic testing obtained from the patient and/or parents. Consequently, it may be prudent to refer relevant families to a regional high-risk colon cancer program for initial evaluation, where trained personnel are available to perform genetic testing and pedigree research.

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2

Multivisceral Resection in Rectal Cancer

Martin R. Weiser and Mark Y. Sun

Introduction

The treatment of locally advanced rectal cancer (T3/4 or N1/2) is challenging and requires a multidisciplinary approach including diagnostic radiology, medical oncology, pathology, radiation therapy, and surgery. Unlike many solid tumors, locally advanced or locally invasive rectal cancer is not necessarily unresectable (Lopez 2001). Indeed, over the past 30 years, it has been shown that a significant percentage of even large colorectal tumors remain localized and do not metastasize; therefore, en-bloc resection with clear margins can lead to cure (Lopez 2001; Gebhardt et al. 1999; Nakafusa et al. 2004; Lehnert et al. 2002; Klaassen et al. 2004; Govindarajan et al. 2006). In a study by Spratt and Spjut involving examination of more than 1,000 colorectal tumors, two-thirds of the large or locally invasive tumors had reportedly not metastasized to even locoregional lymph nodes (Spratt and Spjut 1970). However, it is important to recognize that up to 15% of rectal cancer tumors will be adherent to or invasive into adjacent pelvic organs. Since the surgeon cannot easily differentiate a malignant fistula from an inflammatory adhesion (Gebhardt et al. 1999), and because separation of a malignant fistula can lead to local tumor dissemination and recurrence, multivisceral resection should be considered. Advanced planning, with strict adherence to the principles of surgical oncology, is necessary when treating these difficult cases.

Although multivisceral resection, compared with standard resection, can improve outcome of advanced lesions, these are complex procedures associated with increased morbidity and even perioperative mortality (Birkmeyer et al. 2003, 2007). It is critical to anticipate the need for assistance in order to mobilize a large, multidisciplinary surgical team, which may include colorectal, urologic, gynecologic, orthopedic, neurosurgical, and plastic surgeons. In addition, it is important to recogn ize the need for perioperative care including radiologists, intensivists, and specialized nurses as well as occupational and physical therapists (Madoff 2006). Multivisceral pelvic resections are a challenge not only for surgeons, but also for the patient and the healthcare system. For these reasons, it is both rational and necessary to treat such advanced lesions at specialty centers (Madoff 2006).

This chapter provides a general overview of the role of multivisceral resection during treatment, as well as strategies and guidelines to be used when approaching patients with locally advanced rectal cancer.

Preoperative Procedures

Staging and Imaging

Proper staging of rectal cancer is imperative, not only in planning the proper operation, but also

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in selecting those patients who will benefit from neoadjuvant treatment. Early in the workup process, it is important to differentiate, those patients who have early rectal cancers and can be treated with immediate surgery from those with locally advanced tumors that may require chemoradiation prior to resection (Klaassen et al. 2004). It is also necessary to identify those patients who already have distant metastases, in order to avoid any unnecessary and potentially morbid treatment.

Physical Examination

Although many consider modern imaging modalities to be the most effective means of tumor staging, the importance of a proper physical examination and digital rectal exam cannot be overlooked. An experienced surgeon may gain valuable information regarding the extent of the tumor, as well as its fixation to adjacent organs and the bony pelvis. This information can also help guide the radiation oncologist in determining the necessity of preoperative chemoradiation. A thorough pelvic exam may be the simplest, most direct method of determining the feasibility of a sphincter-sparing operation or the necessity of multivisceral resection. Complete colonoscopy should be done to rule out the possibility of synchronous primary tumors (Lopez 2001).

Radiologic Imaging

Contrast-enhanced computed tomography (CT) scanning remains the most commonly utilized imaging modality for assessing the extent of tumor and the presence of metastases. Although CT scans can provide an approximate idea of tumor size, it is often difficult to accurately differentiate tumor margins from surrounding viscera. Since obtaining adequate circumferential resection margins is paramount to a curative resection, CT scanning may not always be adequate in patients with locally advanced tumors. In the setting of T3 or T4 lesions, magnetic resonance imaging (MRI) may provide a better assessment of pelvic involvement and the potential need for multivisceral resection. Several published studies have compared CT with MRI in predicting extrarectal involvement. One study found that MRI, although demonstrating only moderate accuracy in predicting tumor stage, provided a consistent and highly accurate prediction of the circumferential resection margin compared with final histologic findings (Beets-Tan et al. 2001). Other studies have shown that in the setting of T3 and T4 lesions, possible invasion of the mesorectal fascia was better predicted by MRI, with a sensitivity of 80%, a specificity of 84%, and a negative predictive value of 96% (Klaassen et al. 2004; Mathur et al. 2003).

Endorectal ultrasound (EUS) is another imaging tool that may be used to assess the local extent of rectal tumors. Early and mobile transmural bowel lesions can be accurately gauged by EUS (Lopez 2001). However, in the setting of locally advanced tumors, EUS is less accurate (Klaassen et al. 2004). EUS tends to understage larger lesions due to limited resolution (Siddiqui et al. 2006). Also the accuracy of EUS, as for all imaging modalities, in staging of rectal cancer is markedly reduced after radiation therapy as a result of postradiation edema, inflammation, necrosis, and fibrosis. Studies have indicated that the accuracy of EUS in assessing T-stage after radiation is only 50%, with a 40% rate of overstaging (Siqqiqui et al. 2006). See Fig. 2.1 for examples of all three imaging modalities in the same patient.

Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) is a newer imaging modality that is becoming more valuable in the preoperative staging of locally advanced rectal cancer. FDG-PET is a powerful, noninvasive tool for imaging tumor metabolic activity and can be used to assess changes in tumor glucose metabolism (Cascini et al. 2006). Identifying nodal disease remains a challenge for all imaging modalities. A prospective study of 104 patients by Llamas-Elvira et al. compared FDG-PET and conventional CT. FDG-PET was vastly superior in identifying metastatic disease, showing a sensitivity of 89% vs. 44% for CT. FDG-PET revealed previously unknown metastatic disease in 19% of patients, changed staging in 13%, and modified the scope of surgery in an additional 12% (Llamas-Elvira et al. 2007). However, both FDG-PET and CT demonstrated poor sensitivity in detecting regional lymph nodes (21% and 25%, respectively). Another potential use of FDG-PET is identifying recurrent disease. EUS, CT, and MRI are poor at differentiating viable tumor from scar or inflammatory tissue. FDG-PET appears to have a role in differentiating scar from viable tumor (Cascini et al. 2006).

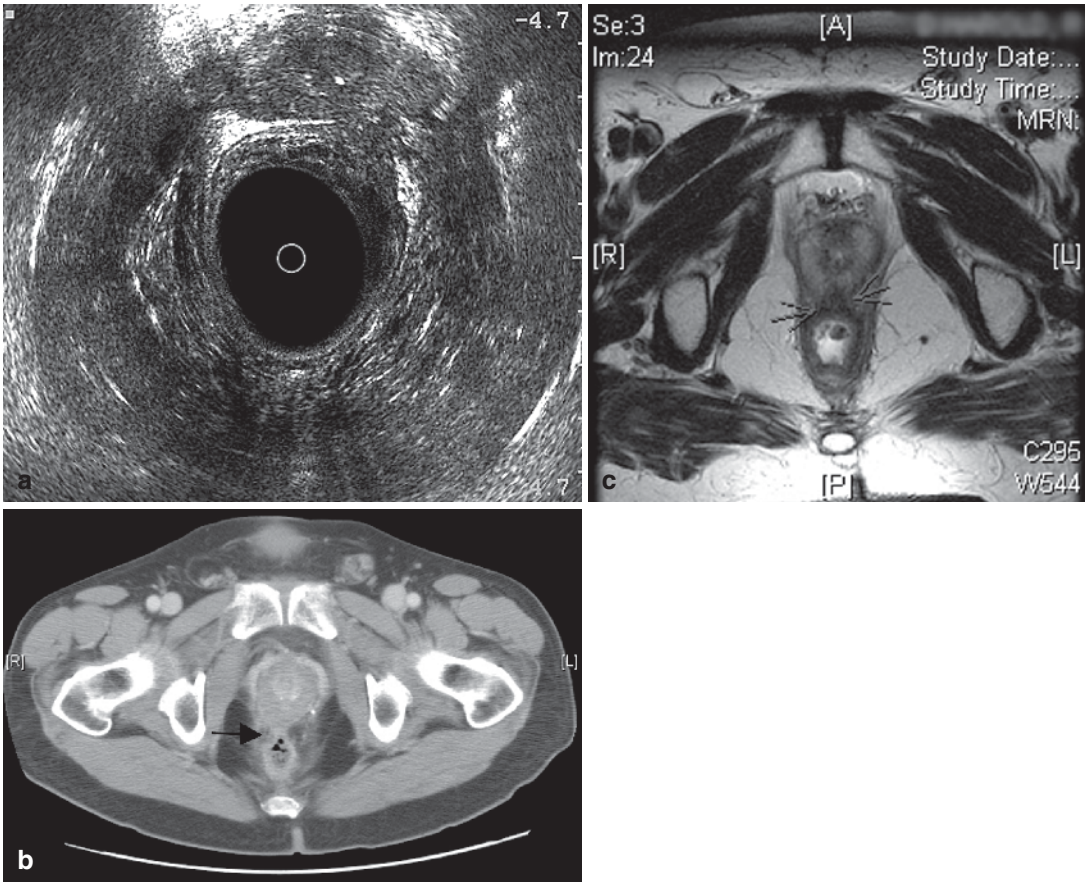

Figure 2.1. A comparison of EUS (**a**), CT (**b**), and MRI (**c**) in a patient who has rectal cancer with prostate invasion.

Although no single imaging modality yet exists that can accurately and consistently stage locally advanced rectal cancers, technology is quickly evolving. Newer imaging tools such as PET-CT may soon be changing the way we stage these difficult cases (Gearhart et al. 2006).

Neo-Adjuvant Therapy

The single most important factor in the cure of rectal cancer remains complete excision of the tumor, with negative macroscopic and microscopic margins. Multimodality therapy is often the best method for achieving this goal.

Over the last two decades, the introduction of adjuvant and neoadjuvant therapy has helped to decrease local recurrence rates and improve long-term survival rates. Postoperative chemoradiation has been found to improve survival. In a landmark randomized trial conducted by the North Central Cancer group, chemotherapy was shown to enhance the efficacy of pelvic radiation (Krook et al. 1991). The National Institutes of Health Consensus Development Conference on Adjuvant Therapy for Patients With Colon and Rectum Cancer resulted in a National Cancer Institute Consensus Statement released in 1990, which recommended that adjuvant therapy, combining chemotherapy and radiotherapy, should be used to improve local control and survival in Stage II and Stage III patients ([No Authors Listed]1990).

With preoperative radiation therapy, potential tumor downsizing may help ensure an R0 resection and may downstage the tumor so that a sphincter-preserving procedure may be undertaken and postoperative quality of life improved. The Colorectal Cancer Collaborative

Group published a meta-analysis in 2001 combining the data from 22 randomized trials and comparing the results of preoperative radiotherapy, postoperative radiotherapy, and no radiotherapy for rectal cancer ([No Authors Listed] 2001). They found that the yearly risk of local recurrence was 46% lower in those who had preoperative treatment than in those who had surgery alone, and 37% lower in those who had postoperative treatment than in those who had surgery alone. They also demonstrated that fewer patients treated with preoperative radiotherapy died of rectal cancer than those treated with surgery alone (45% vs. 50%, respectively) (Krook et al. 1991).

Although preoperative radiotherapy and postoperative chemoradiation have become the standard of care for advanced rectal cancers, chemotherapeutic regimens as well as use of preoperative chemotherapy vary among institutions. A recent study by Bosset et al. investigated the potential benefits of preoperative vs. postoperative chemotherapy. The study enrolled 1,011 patients, divided into four treatment groups as follows: (1) preoperative radiotherapy alone; (2) preoperative chemoradiotherapy; (3) preoperative radiotherapy and postoperative chemotherapy; (4) preoperative chemoradiotherapy and postoperative chemoradiotherapy. They found no significant difference in overall survival between the groups receiving chemotherapy preoperatively or postoperatively. The combined 5-year survival rate was 62.5%. Although overall survival rates were not altered, local recurrence rate were. The 5-year cumulative incidence rate for local recurrence varied from 7.6 to 9.6% in those receiving chemotherapy, and was 17.1% in those receiving radiotherapy alone (Bosset et al. 2006). These findings corroborated those of the German Rectal Cancer Study Group, which assessed preoperative vs. postoperative chemotherapy in patients with T3 or T4 disease. In that study, overall survival was not affected by preoperative vs. postoperative radiotherapy; however, local recurrence rates were significantly decreased in the group receiving preoperative treatment (6% vs. 13%) (Sauer et al. 2004).

Intraoperative Procedures

The goal of any cancer operation is an R0 resection. Positive margins, particularly grossly positive margins, greatly increase the risk of local recurrence, and few patients benefit from such incomplete resections (Madoff 2006). Meticulous and thorough preoperative assessment of the patient will hopefully provide the surgeon with adequate information for a successful procedure.

Surgical Treatment

Lateral Invasion

As Klaassen and colleagues have shown, total mesorectal excision (TME) can still be performed after neoadjuvant treatment, when tumor extends in the direction of the radial margin; however, if tumor penetrates the mesorectal fascia and invades surrounding pelvic structures, en-bloc resection of the pelvic autonomic nerve plexus should be attempted in a plane lateral to the nerves. Direct extension into the pelvic wall, including the iliac vessels, necessitates resection lateral to the internal iliac as well as ligation of the gluteal vessels and the ventral branches of S2–S4 (Klaassen et al. 2004).

Posterior Invasion

Invasion into the sacrum, requiring an abdominosacral resection, is more often seen in recurrent cases than in advanced primary cases (Klaassen et al. 2004). The idea of an abdominosacral resection was advanced in the early 1980s by Wanebo and Marcove (1981). The major problems they found with these resections were: (1) the technical considerations of extensive surgery; (2) potential for iatrogenic sequelae such as neurologic defects involving bladder, bowel, and sexual functioning; (3) potential musculoskeletal defects as a result of instability caused by high sacral resection [21]. Some believe that the major morbidity and decrease in quality of life (QOL) associated with abdominosacral resection are mainly due to the high amputation of the sacrum, as resections are extended to the sacral promontory or sciatic notch. Moriya et al. concluded that a less extensive sacral amputation led to acceptable QOL, with similar survival rates (61% at 3 years and 46% at 5 years). Although the survival rates quoted by Moriya et al. were slightly higher than others in the published literature, local rerecurrence and lung metastasis occurred in more than 90% of the patients in their series

(Moriya 2006). Surgery may still be an option in these settings, but the low patient survival rate must be weighed carefully alongside the high morbidity of this procedure.

Anterior Invasion

Klaassen et al. demonstrated that in extensive resection for rectal cancer, the presence of a dedicated urology team is critical in preoperative evaluation of the urinary system as well as postresection reconstruction. When the ureter is involved unilaterally, it can be resected en-bloc and repaired with a psoas hitch procedure (Klaassen et al. 2004). In the setting of tumor involving the base or trigone of bladder or prostate, total pelvic exenteration (TPE) with resection of the bladder, lower ureters, and internal genital organs may be required. As Vermaas et al. have noted, since its introduction in 1948, TPE has been viewed as a very difficult procedure associated with poor QOL and considerable morbidity and mortality (Vermaas et al. 2007). Over the years, however, technique, technology, and experience have improved to the point where TPE may now provide a good chance of survival as well as adequate QOL. Vermaas and colleagues found 5-year local control and overall survival rates of 88% and 52%, respectively, in patients with primary advanced rectal cancer. In patients with recurrent rectal cancer, 3-year local control and survival rates were 60% and 32%, respectively (Vermaas et al. 2007). Ike et al. reported a 5-year survival rate of 66% in patients with T3 lesions, and 39% in those with T4 lesions (Ike et al. 2003). Although morbidity rates vary greatly, depending on the study (anywhere from 13 to 75%), the high chance of a potential cure makes TPE a viable option for carefully selected patients (Vermaas et al. 2007; Ike et al. 2003). Male patients with lesions involving the prostate and seminal ve sicles may benefit from total or partial prostatectomy and/or seminal vesiculectomy in addition to resection of the primary lesion. A study by Poggio et al. performed at Memorial Sloan-Kettering Cancer Center found a 2-year local and distant recurrence rate of 83% and 70%, respectively, and a 5-year overall survival rate of 49% in this population of patients (Poggio et al. 2007).

In female patients, anterior invasion of the tumor may be simpler to deal with since the uterus creates a barrier to the urinary system. Klaassen et al. point out that vaginal invasion

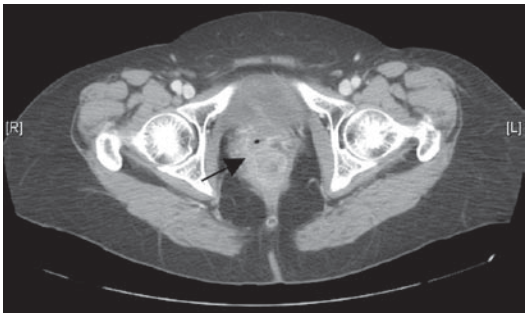

Figure 2.2. A patient with rectal cancer involving the posterior vagina.

necessitates resection of the involved vagina and its paracolpium, with subsequent reconstruction (Fig. 2.2) (Klaassen et al. 2004). This anatomic "barrier" may be why women are four times more likely to receive multivisceral resection than men (Govindarajan et al. 2006). Unfortunately, some surgeons may be reluctant to perform a more aggressive resection in men for fear of the potential morbidity associated with a complex genitourinary resection – thus leaving the patient with an incomplete resection and a high likelihood of recurrence (Lopez 2001).

Pelvic Reconstruction

Reconstruction of the pelvis after an extensive resection constitutes another facet of treatment for these patients. As Madoff has stated, the major goals of reconstruction are simple: to optimize healing, to avoid complications, and if possible, to restore function (Madoff 2006). In most cases, a rectal anastomosis is not possible, and the surgeon must confront a large, irradiated pelvic space prone to wound healing complications. Usually, an omental pedicle graft can be used to fill the pelvis, but some patients may benefit from more complex reconstruction such as a vertical rectus abdominus myocutaneous flap (Madoff 2006; Klaassen et al. 2004; Bell et al. 2005). If a cystectomy is performed, options for urinary diversion include the traditional ileal conduit or an orthotopic bladder substitution. Large vaginal defects may also be reconstructed with a rectus abdominus flap (Bell et al. 2005), or a neovagina may be created; however, at this point in time little is known about the long-term anatomical and functional results of this type of reconstruction (Madoff 2006).

Intraoperative Decisions

Although accurate anticipation of the exact degree of tumor invasion and total scope of the planned resection is ideal, intraoperative surprises cannot always be avoided. In these instances surgical expertise and proper intraoperative decision-making become crucial. On entering the abdomen, a thorough search for distant metastases should be performed, as the presence of metastasis would preclude an en-bloc resection. Additionally, tumor adherence to adjacent organs may represent either malignant invasion or simply inflammatory adhesions. Every effort must be made to avoid finger fracture of adhesions leading to tumor dissemination and the possibility of an incomplete resection. The reported incidence of histologically proven malignant adhesions is 49–84% (Nelson et al. 2001). If it is not possible to reliably differentiate a malignant adhesion from an inflammatory adhesion, en-bloc resection should be performed.

Intraoperative Radiation Therapy (IORT)

Substantial progress has been made in recent years in the experimental, technical, and clinical application of intraoperative radiotherapy (IORT) as a treatment modality for various cancers. A major goal of all radiation oncologists is to increase the dose delivered to the tumor relative to that delivered to the normal adjacent tissues. As Willett and colleagues have noted, this has led to the use of field-shaping techniques with multileaf collimation, multiple field techniques, and intensity-modulated radiation therapy, as well as intracavitary and interstitial brachytherapy (Willet et al. 2007). Two alternative but complementary IORT techniques have evolved using this philosophy of achieving higher effective doses of irradiation in the tumor: intraoperative electron radiation (IOERT) and high-dose rate brachytherapy (HDR-IORT). Delivery of radiation during surgery means that normal tissues can actually be moved aside or physically shielded. Additionally, because the tumor can be visualized, it is possible to more accurately define areas at risk for tumor involvement (Willet et al. 2007).

Since IORT is not widely practiced, no randomized trials have been conducted to evaluate its impact on survival; however, experiences from single large institution studies indicate that IORT may positively influence local control and survival (Willet et al. 2007). In a study performed at the Massachusetts General Hospital, Nakfoor et al. assessed 101 patients with locally advanced primary rectal cancer who underwent preoperative radiation and IOERT. They found that patients undergoing margin-negative (R0) resection had a 5-year local control rate of 89% and a disease-specific survival of 63%. Patients with microscopically involved margins had a local recurrence rate of 68%; and those with gross disease had a local recurrence rate of 57% (Nakfoor et al. 1998). A similar study at the Mayo clinic found an improvement in local control and survival with the addition of IOERT. Five-year overall survival was reportedly 46%, and 3-year overall survival improved from 24 to 55% (Gunderson et al. 1997). In another study at Memorial Sloan-Kettering Cancer Center, Alektiar et al. investigated the effects of HDR-IORT in the management of locally recurrent colorectal cancer (Fig. 2.3). In a series of 74 patients, the 5-year local control rate was reportedly 39%, with a distant metastasis disease-free rate of 39%. Overall 5-year survival was 36% in those patients with R0 resections (Alektiar et al. 2000). Although further studies are needed to justify the routine use of IORT, preliminary studies are encouraging, and use of IORT should be considered in select cases.

Morbidity of Multivisceral Resection

As expected, the morbidity of multivisceral resections is higher than that of standard resections owing to the increased complexity inherent in these procedures, as well as increased blood loss. Morbidity rates vary widely depending on the source, but Lopez quotes a general morbidity rate of 30% in extended resections (Lopez 2001). Poggio et al. found that patients undergoing partial or total prostatectomy had a 79% chance of erectile dysfunction and those undergoing seminal vesiculectomy alone had a 43% chance of erectile dysfunction. In their series of pelvic exenterations, Gannon et al. found an overall complication rate of 43%, with a third of those being major complications

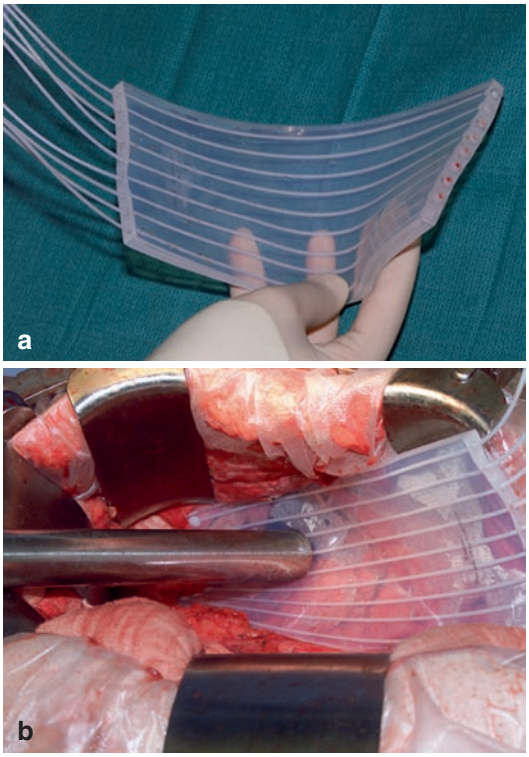

Figure 2.3. HDR-IORT HAM-setup used at Memorial Sloan-Kettering Cancer Center. (Photo courtesy of Dr. Karyn Goodman)

(enterocutaneous fistula, respiratory failure with pneumonia, urinary conduit leaks) requiring a hospital stay >20 days (Gannon et al. 2007).

With a 5-year postoperative survival rate approaching 50%, multivisceral resections warrant more consideration. With thorough preoperative planning, meticulous intraoperative technique, and wide anatomic resection, multivisceral surgeries may result in cure, which should remain our chief objective. The most important factor in preventing local recurrence is obtaining a tumor-free resection margin, as patients rarely benefit from an incomplete resection. However, as Lopez points out, multivisceral resections are not standardized procedures, and not all surgeons should attempt them. The best course for a surgeon unwilling or unable to perform extensive multivisceral resection in the setting of unexpected intraoperative findings is to seek immediate consultation with a more experienced colleague, or else to close the abdomen and refer the patient to a specialty center with significant expertise in this type of complex surgery. This is far better than compromising patient care by performing an incomplete operation (Lopez 2001).

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3

Colonic Stenting

Thomas M. Raymond and Mike C. Parker

Introduction

Self-expanding metal stents (SEMS) are used to treat benign and malignant luminal obstruction of the gastrointestinal tract. Their use was first described in animals in 1985 (Wright et al. 1985). In humans, initially they were used to relieve obstruction of biliary, hepatic, and upper gastrointestinal lesions, but with advancing technology and the introduction of flexible stents with a larger lumen, they are now used in the treatment of colonic obstruction as first described by Dohmoto (1991).

Between 10 and 30% of patients with primary colonic cancer present with obstruction (Deans et al. 1994), 70% of which are in the left colon (Fan et al. 2006; Phillips et al. 1985; Setti et al. 2001; Tekkis et al. 2004). Obstructing cancers (either primary colorectal or extrinsic compression due to pelvic malignancy) are often advanced at the time of presentation with only 50% undergoing potentially curative surgery.

Conventionally, patients are treated by surgical intervention with resection or palliative colostomy. Emergency surgery is associated with high rates of morbidity (40–50%), mortality (15–40%) (Tekkis et al. 2003, 2004; Leitman et al. 1992; Buechter et al. 1988; Mulcahy et al. 1996), and stoma formation (Martinez-Santos et al. 2002), all of which are significantly higher than in an elective setting (Ohman 1982; Fielding and Wells 1974; Runkel et al. 1991, 1998). Following surgical resection, 60% of patients with a stoma will never be reversed (Mauro et al. 2000). Stoma formation has serious implications regarding quality of life and may also be a burden to caregivers and health providers (Karadag et al. 2003).

Various nonsurgical treatments have been tried including balloon dilatation, laser photoablation, and electrocoagulation, but their effectiveness is limited by complications, the need for repeated treatments, and cost (Zollikofer et al. 2000).

Colorectal stents are an addition to the armamentarium in the palliative treatment of colorectal obstruction, thus avoiding surgery and the creation of a stoma (Law et al. 2000; Liberman et al. 2000; Turegano-Fuentes et al. 1998) and facilitate decompression as a bridge to surgery in resectable tumors, converting an emergency procedure into an elective procedure. The benefits include reduced morbidity, mortality, and stoma rates and time for preoperative radiological staging, multidisciplinary meeting discussion, medical optimization, and neo-adjuvant therapy as required. They are contraindicated in very low rectal strictures, ischemia, perforation, or when there are multiple levels of obstruction.

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SEMS: Types

SEMS are expandable metal tubes usually of mesh design made from steel or Nitinol (a nickel and titanium alloy with shape memory). They are advanced to the site of obstruction in the collapsed state where following deployment they expand radially to their maximum diameter under their own force, thereby achieving patency. They differ in luminal diameter, length, and radial expansile force, which allow selection of the most suitable stent for the procedure. The stent becomes incorporated into the tumor and surrounding tissue providing anchorage of the stent, which prevents migration.

Placement

A retrograde radiographic contrast study or contrast CT should be obtained prior to stent placement to assess the anatomy, length of stricture, and degree of obstruction and to exclude other levels of obstruction that would negate the effect of stenting a single site.

Preparation with one to two cleansing enemas prior to the procedure should be considered to ensure that the distal colon is clear. The patient is placed initially in the lateral decubitus position and standard intravenous conscious sedation is usually administered but is not absolutely necessary.

The stent is either placed under fluoroscopic guidance (shorter delivery system but wide diameter stent) or it is passed through an endoscope (longer delivery system and smaller diameter stent) or a combination of the two.

The stent is placed to allow a 1–2-cm protrusion at either end of the stricture, which may require a second or rarely third stent to be deployed for long strictures. Decompression occurs with the passage of flatus and stool through the stent and is often immediate. Radial expansion of the stent may be augmented with balloon dilatation, although this is rarely necessary and risks the considerable increase in perforation rate.

Radiological Placement

The lesion is located fluoroscopically using a water-soluble contrast medium. The stricture is passed using a guidewire (see Fig. 3.1) over which the stent is inserted into the obstructing lesion prior to release (see Fig. 3.2). Rarely, this may require balloon dilatation to aid expansion.

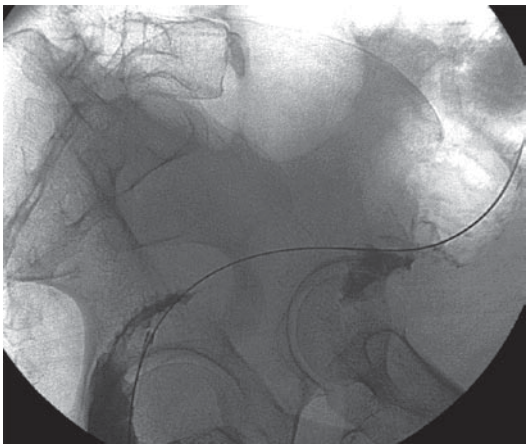

Figure 3.1. Colonic stricture traversed by guidewire (Courtesy of Farhan Ahmad).

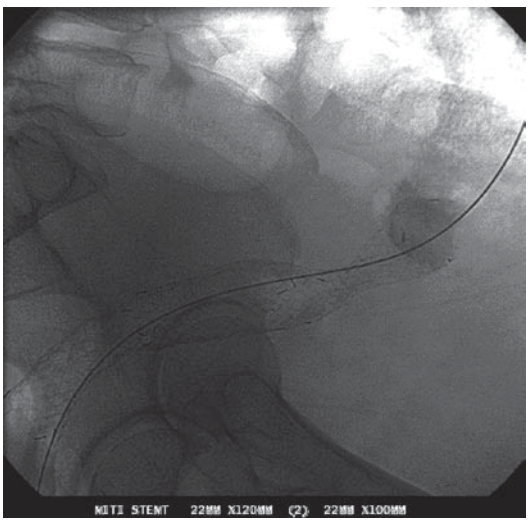

Figure 3.2. Stent deployed over guidewire (Courtesy of Farhan Ahmad).

Endoscopic/Fluoroscopic Placement

The distal end of the obstructing lesion is visualized endoscopically at which point a biopsy may be taken. The length and configuration of the stenosis is demonstrated fluoroscopically by injection of water-soluble contrast media. The guidewire is then passed through the stenosis and the stent delivery system inserted through the scope. The stent is positioned at the level of the stenosis and released under both endoscopic and radiological vision.

Efficacy

Stenting is technically successful with passage of the guidewire and appropriate placement of the stent in a median of 96.2% (66.6–100%) of patients. Clinical success with colonic decompression and resolution of obstructive symptoms within 72 h occurs in 92% (46–100%) of patients (Watt et al. 2007). There is little difference in the technical and clinical success rates when compared with the indication for stenting (palliative vs. bridge to surgery) or the underlying cause of obstruction (primary or recurrent colorectal and urogenital) (Watt et al. 2007; Khot et al. 2002).

The mean time between stenting and surgery in the bridge to surgery group is 7 days (2–12 days) (Watt et al. 2007) with 80% proceeding to single-stage surgical resection (Sebastian et al. 2004) and only 30% requiring a stoma (Martinez-Santos et al. 2002).

For palliative patients, the median duration of patency is over 100 days (68–288 days). For studies reporting patency rates, the median at the end of follow-up (or time of death) is 100% (53–100%) (Watt et al. 2007). Re-intervention is required following 20% of palliative stent placements (0–100%) and includes unplanned surgery, placement of second or subsequent stents, or interventions to maintain patency (laser ablation, colonic irrigation).

Patients undergoing palliative stenting have fewer admissions to the intensive care unit, fewer stomas, and a reduction in the median hospital stay when compared with patients undergoing palliative surgery (Law et al. 2003). However, there is no significant difference when comparing the median survival (Dohmoto 1991; Khot et al. 2002).

Safety

For all colorectal stents, the median rate of migration is 10% (0–50%) with similar rates when used for palliation (Watt et al. 2007). Bridge-to-surgery patients have fewer reported cases of migration because of the shorter time they remain in situ. If migration occurs, no intervention is required in over 50% of patients. The remainder may require stent removal with no further intervention, stent re-insertion, or surgery.

Minor bleeding occurs in 5% of patients although significant bleeding requiring transfusion has been reported (Diazz et al. 1999; Miyayama et al. 2000).

Perforation caused by either the guidewire or stent occurs in 4% (0–83%) of cases irrespective of the indication and may be increased to 10% by balloon dilatation of the stricture prior to stent insertion (Khot et al. 2002; Sebastain et al. 2004). Most require surgical intervention although 30% may be managed conservatively.

Re-obstruction occurs in 12% (1–92%) of patients due to tumor overgrowth or ingrowth, migration, and fecal impaction and occurs from 48 h to 480 days post procedure. Modes of treatment include laser photo-ablation, restenting, or colonic irrigation.

Other reported complications include stent fracture, anal/abdominal pain, fistulation, incontinence, and tenesmus, particularly in patients with distally placed stents. These are relatively rare and are usually well tolerated by patients.

Overall mortality is less than 1% and is usually related to perforation at the time of stenting. It is significantly lower than after emergency surgery ($p < 0.001$) at 30 days postoperatively although overall survival at 3 or 5 years does not differ significantly (Saida et al. 2003).

Covered Vs. Uncovered Stents

There are only minor differences in reported technical and clinical success and perforation rates between covered and uncovered stents in the trials comparing their use. Covered stents appear to resist tumor in-growth reflected in the lower re-obstruction rates when compared with uncovered stents, although they may be more prone to migration (Watt et al. 2007).

Costs

The cost of palliative stenting may be half that of a surgically decompressed patient. When used as a bridge to surgery, the cost of SEMS followed by emergency surgery is lower in overall cost than emergency surgery.

These savings are due mainly to a shorter hospital stay, and also to fewer surgical procedures, less operating room time, reduced time in intensive care, and reduction in stoma consumables (Osman et al. 2000; Binkert et al. 1998; Jost et al. 2004; Targownik et al. 2004).

Discussion

Colonic obstruction is a common problem with high rates of morbidity, mortality, and stoma formation. SEMS provide a timely and cost-effective treatment modality at the high levels of technical and clinical success and low rates of serious complication. It is effective as a means of palliation (avoiding a stoma) and as a bridge to surgery providing decompression and time before elective resection when higher rates of primary anastomosis and a reduced stoma rate may be achieved with reductions in hospital stay. This view should be balanced against some studies that have prematurely closed trials of surgical vs. nonsurgical therapies using SEMS-type stents because of some serious adverse events, particularly perforations in "permanent" stent cases over time either at the proximal end of the stent or in patients undergoing chemotherapy (van Hooft et al. 2006, 2008). Despite these reservations, recent studies have shown a reduction in median hospital stay in stented patients for incurable cases with a limited requirement for subsequent surgery (Faragher et al. 2008), clinical success for patients with extrinsic obstruction (Shin et al. 2008), proximal cancers (Repici et al. 2007), and in selected benign strictures (Dafnis 2007). The utilization of stenting as a bridge to surgery does not prevent subsequent laparoscopic resection (Stipa et al. 2008) and appears to be cost-effective when compared with emergency surgery in terms of quality-adjusted months of life benefit secondary to reduced acute procedural mortality and derivative stoma costs (Govindarajan et al. 2007). These effects are offset in differing series dependent on stent-related complications (perforation, technical failure, and migration) and overall operative anesthetic risk.

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4

Chemotherapy Trials for Colorectal Cancer in Advanced Disease: What's the Current Hypothesis?

Ashok D. Nikapota, Mark Harrison, and Rob Glynne-Jones

Introduction

Colorectal cancer is one of the commonest solid tumors, and is responsible for considerable clinical morbidity and mortality. Between 25% and 30% of patients are found to have metastatic disease at the time of diagnosis, and a further 30–40% may subsequently develop metastases. Systemic chemotherapy can control the disease, provide substantial symptom palliation, and prolong survival, but the median survival in studies, until recently, has almost invariably remained less than 24 months (Saunders and Iveson 2006). Early data from the 1980s suggested that chemotherapy should be initiated early to maintain the quality of life (QOL) (Nordic Gastrointestinal Tumour adjuvant Therapy Group 1992; Acland et al. 2005). Current chemotherapy is more complex and associated with greater toxicity, but is changing the patterns of the disease (Sundermeyer et al. 2005).

Some sites of metastatic disease, i.e., bone (Hotta et al. 2006; Heras et al. 2007) and ovary (Goere et al. 2008) appear to respond less favorably to systemic chemotherapy. With the introduction of numerous new agents, the overall survival (OS) in metastatic colorectal cancer (MCRC) patients has nearly doubled during the past 10 years. Yet, the reason for some patients responding to chemotherapy and others failing to do so still remains poorly understood, although some authors have identified groups of patients with a poor outcome in terms of both toxicity and efficacy based on clinical, biochemical, and molecular factors (Kohne 2002; Sorbye et al. 2007; Braun et al. 2008; Sargent et al. 2009).

Since the early 1980s, fluororopyrimidine 5-Fluorouracil (5FU) alone, and more recently, in the 1990s, combinations of cytotoxic chemotherapy using oxaliplatin or irinotecan, have represented the mainstay of treatment for patients with advanced MCRC. There have also been more subtle developments in these chemotherapeutic treatment options.

Chemotherapy can facilitate liver resection (Delaunoit et al. 2005). Clinical response has once again become an increasingly important endpoint, because surgical resection of metastatic disease can be achieved in 33–56% of the cases (Pozzo et al. 2008). Liver resection, if performed, appears to be compatible with long-term survival (Adam et al. 2001), and can be facilitated with the biologicals even after subsequent lines of treatment (Adam et al. 2007). Hence, recently, three drug combinations (Falcone et al. 2008) have been employed. In addition, a number of molecularly targeted agents have been integrated into chemotherapy regimens to further improve response rates or extend progression-free (PFS)

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and OS, albeit with varying success (Hurwitz et al. 2004; Van Cutsem et al. 2008; Tol et al. 2009; Folprecht et al. 2008).

Many different strategies are possible, i.e., the sequential use of cytotoxic chemotherapy starting with a single agent; using two or three drug combinations up-front; treating to progression with or without a maintenance component, or employing a stop-and-go strategy; and integrating the biologicals either up-front or as maintenance. The aim of this chapter is to review the published and ongoing studies in MCRC and discuss these various strategies of treatment.

5-Fluorouracil

For 50 years, the cornerstone of treatment has been 5FU, which has offered modest activity with clinical response rates in the range of 10–20%, and median survival reported in the range of 6–8 months. The addition of leucovorin to 5-FU in advanced disease was shown to improve response rates, with no improvement in OS (Poon et al. 1989; Anon 1992). Different schedules provoked substantially different toxicity profiles (Buroker et al. 1994). Since then, various treatment schedules have been championed by different investigators, including bolus 5FU, prolonged venous infusional 5FU, or 5-FU/LV combinations using different schedules (Mayo regimen, Roswell Park regimen and de Gramont regimen). Meta-analyses initially confirmed a higher response rate with the addition of leucovorin (meta-analysis 1992), and when updated, a small OS advantage (11.7 vs. 10.5 months, $p < 0.004$) (The Meta-Analysis Group in Cancer 2004). Subsequently, the use of infusional 5FU was demonstrated to be more effective and less toxic than bolus administration – particularly in terms of both hematological toxicity and diarrhea (Lokich et al. 1989; De Gramont et al. 1997) (Table 4.1).

Capecitabine

The introduction of the oral 5-FU prodrug capecitabine has simplified the administration of fluropyrimidine chemotherapy in colorectal cancer. The bolus and infusional 5-FU regimes can have a considerable impact on a patient's QOL, requiring regular hospital visits or indwelling lines (PICC or Hickman) with the associated risks and complications. The majority of colorectal cancer patients

Table 4.1. Studies comparing single-agent 5FU against combinations with Irinotecan or Oxaliplatin

Study	N	RR (%)		PFS/TTP, months		OS, months	
		5-FU	Combination therapy	5-FU	Combination therapy	5-FU	Combination therapy
Oxaliplatin studies							
Giacchetti 2000	200	16	53 $p < 0.001$	6.1	8.7 $P = 0.048$	19.9	19.4 NS
De Gramont et al. 2000	420	22	51 $P = 0.0001$	6.2	9.0 $P = 0.0003$	14.7	16.2 $P = 0.12$
Porschen et al. 2007	242	23	48 $p < 0.0001$	5.2	7.8 $P = 001$	16.1	19.7, $P = 0.19$
Irinotecan studies							
Saltz et al. 2000	683	21	39 $p < 0.001$	4.3	7.0 $P = 0.004$	12.6	14.8 $P = 0.04$
Douillard et al. 2000	387	31	49 $p < 0.001$	4.4	6.7 $p < 0.001$	14.1	17.4 $P = 0.031$
Kohne et al. 2005	430	34	62 $p < 0.0001$	6.4	8.5 $p < 0.0001$	16.9	20.1 $P = 0.2779$

RR = response rate, *PFS* = progression-free survival, *TT P* = time to progression, *OS* = overall survival, *NS* = non-significant.

appear to prefer oral chemotherapy, provided there is equal efficacy to IV bolus 5-FU/FA (Liu et al. 1997; Borner et al. 2002). The preference appears based on improved tolerability and greater convenience, as oral medication can be taken at home and avoids the need for intravenous access (Twelves et al. 2006). Oral medication does pose different challenges in terms of over and under compliance, and a greater risk of drug interactions. In addition, unexpected toxicity can sometimes be observed when capecitabine is administered after prolonged treatment with 5FU and leucovorin, which possibly reflects persisting intracellular folate repletion (Hennig et al. 2008). Different populations may also have widely different pharmacogenomics. Patients in the USA appear to have a worse toxic effect profile for capecitabine than those in other countries – even when adjusted for age, gender and creatinine clearance (Haller et al. 2008). There are many potential explanations for this (Midgely and Kerr 2009).

However, trials suggest that the oral fluoropyrimidines capecitabine, UFT and S1, are all probably more or less equivalent to regimens of 5FU. Capecitabine is now regularly used both as a single agent and in combination chemotherapy regimes as a substitute to intravenous 5-FU owing to ease of administration and patient convenience. The side effect profile differs from 5-FU, with palmar plantar erythema and diarrhea being the more predominant feature.

Randomized phase III trials have been performed in the advanced setting, which compared capecitabine (Hoff et al. 2001; Van Cutsem et al. 2001) with bolus 5FU/leucovorin. A combined analysis of both trials using 1,207 patients (Van Cutsem et al. 2004), demonstrated a statistically significant superior response rate with capecitabine when compared with 5-FU/LV (26% vs 17%, $P < 0.0002$). This finding was consistent even in patient subgroups with poor prognostic indicators.

In contrast, the two randomized studies of UFT were performed at a similar time (Carmichael et al. 2002; Douillard et al. 2002). Both studies produced a rather disappointing response rate for UFT, but secondary endpoints of PFS and OS were again not significantly different. In the first of these studies (Carmichael et al. 2002), the overall response rate among all the patients was 10.5% (20 of 190 patients) in the UFT/LV treatment arm and 9.0% (17 of 190 patients) in the 5-FU/LV-treatment arm. The poor results of the 5-FU/LV-control arm may be owing to the fact that the treatment was delivered with a 5-week rather than a more conventional 4-week schedule. Hence, there was no statistically significant difference in response rate between the two treatment arms ($P = 0.593$). In the second study (Douillard et al. 2002), the overall response rate was also similar between the treatment arms (UFT/LV, 11.7%; 5-FU/LV, 14.5%, $P = 0.232$).

Irinotecan

Initial studies of the addition of irinotecan to 5FU/leucovorin (IFL regimen) caused excitement because they were associated with considerable toxicity, but clearly resulted in improved efficacy. The response rate almost doubled with IFL from 21% to 39% ($p < 0.001$). PFS improved from 4.3 to 7.0 months ($P = 0.004$) and OS from 12.6 to 14.8 months ($P = 0.04$) (Saltz et al. 2000). However, concern regarding unacceptable toxicity with the combination of bolus 5FU and irinotecan (Rothenberg et al. 2001) has led to the more widespread use of infusional regimes in preference to bolus even in the USA. Bi-monthly de Gramont and modified de Gramont regimens of folinic acid and 5FU employ an infusional administration of 5FU (FOLFIRI). This regimen has caused little neutropenia and has a low risk of severe gastrointestinal toxicity. This favorable tolerability has enabled oncologists to add other cytotoxic agents without anxieties regarding life-threatening and overlapping toxicity.

Irinotecan administered in combination with infusional 5-FU and leucovorin led to an increase, similar to IFL, in terms of response rate from 22% to 35% ($P = 0.005$) (Douillard et al. 2000). This study also demonstrated a longer time to treatment failure and a modest OS advantage (17.4 vs. 14.2 months, respectively, $P = 0.031$). A further randomized phase III study using the German weekly infusional 5FU/leucovorin regimen (AIO) with or without irinotecan also demonstrated a similar improvement in the outcome. Response rate increased from 31% to 54% ($p < 0.0001$) (Kohne et al. 2005). This study also demonstrated a longer time to treatment failure as well as an OS advantage (16.9 vs. 20.1 months, respectively, which did not reach statistical significance).

Other schedules have been tested in randomized trials. The Nordic schedule of 5FU/folinic

acid has been commonly used. A recent study aimed to compare their schedule combined with irinotecan or the more common FOLFIRI regimen in patients with metastatic colorectal cancer (Glimelius et al. 2008). The Nordic regimen was associated with more neutropenia and alopecia, and although fewer responses were seen in the Nordic schedule (35% vs. 49%), both PFS and OS were quite similar. Most of the researchers would now accept that FOLFIRI is an effective and well-tolerated regimen, which often forms the control arm in biological studies.

Oxaliplatin

In a randomized phase III study, the combination of oxaliplatin with leucovorin and infusional 5-FU (LV5FU2) in the treatment of advanced colorectal cancer showed an increase in response (50.7% vs. 22.3%, $P = 0.0001$) and PFS, when compared with LV5FU2 alone (9 vs. 6.2 months, $P = 0.0003$) with acceptable toxicity and no deterioration in QOL (De Gramont et al. 2000). The combination regime (FOLFOX) was associated with both an increased neutropenia rate and neurosensory toxicity. The small difference in OS of 16.2 vs. 14.7 months did not reach statistical significance. However, with only 420 patients being randomized, the trial was probably not powered to do so. Also, the influence of crossover diluted the effects on OS as in other studies, because the control arm was able to receive salvage therapy.

The intergroup N9741 trial had randomized three groups – FOLFOX4 and an arm without 5FU, containing both irinotecan and oxaliplatin (IROX) and the irinotecan containing control arm of IFL (Goldberg et al. 2004). This study helped to establish FOLFOX 4 as a standard first-line therapy because of the higher response rate when compared with IFL (45% vs. 31%, p 0.002). TTP also improved (8.7 vs. 6.9 months, $P = 0.0001$) along with median OS (19.5 months vs. 14.8 months, $P = 0.0001$). This advantage was achieved with a much lower incidence of gastrointestinal toxicity and febrile neutopenia (Goldberg et al. 2004). Also, the problem of cumulative peripheral sensory neuropathy was also highlighted.

A meta-analysis (Cassidy et al. 2008a) has shown that capecitabine is at least as effective as 5-FU as systemic therapy for metastatic colorectal cancer. For this reason, both oxaliplatin (Cassidy et al. 2004) and irinotecan have been integrated into such regimens and have more recently have been integrated into the oral fluoropyrimidine capecitabine regimens (Porschen et al. 2007; Seymour 2007a). A phase III randomized study on MCRC found that treatment with the combination of capecitabine plus oxaliplatin was associated with a lower risk of neutropenic sepsis, but a higher risk of G3/G4 diarrhea and hand-foot syndrome than FOLFOX-4 (Cassidy et al. 2008b).

What Is the Optimal Sequence of Cytotoxics?

With the current availability of three chemotherapeutic agents, studies are now focused on the sequencing of these drugs in metastatic colon cancer to determine the superiority of a particular regimen. The GERCOR phase III study evaluated the use of folinic acid, 5- FU and irinotecan (FOLFIRI) and folinic acid, 5-FU, and oxaliplatin (FOLFOX6) in advanced colorectal cancer (Tournigand et al. 2004). This study investigated the two sequences: FOLFIRI followed by FOLFOX6, and FOLFOX6 followed by FOLFIRI. The primary endpoint was TTP from the start of first-line treatment to the time that progression was documented after second-line treatment. Response rates were very similar for initial FOLFIRI (56%) and initial FOLFOX (54%). The median survival was 21.5 months in 109 patients allocated to arm A vs. 20.6 months in 111 patients allocated to arm B ($P = 0.99$). In first-line therapy, FOLFIRI achieved 8.5 months median PFS, vs. FOLFOX6, which achieved 8.0 months median PFS ($P = 0.26$). The median second PFS was 14.2 months for initial FOLFIRI vs. 10.9 in arm B for initial FOLFOX ($P = 0.64$). The incidence of G3/G4 diarrhea was almost identical with 14% in both the arms, but myelosuppression was higher with initial FOLFOX. Therefore, both the sequences achieved a prolonged survival with no significant difference between the two, other than the toxicity profile. It is important to recognize that 21 of 111 patients (19%) in Arm B were downstaged sufficiently to undergo liver resection when compared with only 8 of 109 patients in Arm B (7.3%). Based on the results of this study, initial treatment with FOLFOX is accepted as the most

appropriate regimen for downstaging potentially resectable liver metastases.

This data is supported by an Italian trial (Colucci et al. 2005), which randomized 360 patients between FOLFOX and FOLFIRI. In both the arms, the median time to progression (TTP, 7 vs 7 months, respectively), duration of response (9 vs 10 months, respectively), and OS (14 vs 15 months, respectively) were similar, without any statistically significant difference. Both the studies suggest that the main differences between these two first-line combination therapies lies in the toxicity profile.

The combination of capecitabine and oxaliplatin (XELOX) was compared with FOLFOX in a large randomized study (NO16966, which showed similar response rates (46% vs 49%), PFS (8.0 vs 8.5 months), and OS (19.8 vs 19.6 months), respectively (Cassidy et al. 2008b). Others have confirmed similar results (Porschen et al. 2007; Diaz-Rubio et al. 2007; Ducreux et al. 2007). Many of these studies have been assessed in a pooled analysis of six phase II and III trials, which also confirmed their equivalence in terms of PFS and OS, albeit with a statistically lower response rate when capecitabine is partnered with oxaliplatin, when compared with FOLFOX (Arkenau et al. 2008). These studies support the view that XELOX is a valid alternative to FOLFOX.

Kohne (2008) study aimed to demonstrate the benefit of adding a COX2 inhibitor celecoxib to irinotecan fluouropyrimidine regimen and to confirm the non inferiority of capecitabine when compared with 5FU/folinic acid. However, because of eight deaths in the first 85 patients enrolled, the trial was closed. The addition of celecoxib appears to cause unexpected toxicity and is associated with a worse outcome, and hence, should not be added to first-line regimen.

Is Response Rate Important?

Despite dramatic recent advances in the treatment of advanced disease, which include the incorporation of oxaliplatin and irinotecan into the first-line regimens, triplets of chemotherapy (FOLFOXIRI), and the more recently selected integrated use of targeted monoclonal antibodies, the 5-year survival rates from chemotherapy for patients with advanced colorectal cancer remain less than 10% (Goldberg et al. 2007). For patients with colorectal liver metastases, liver resection offers the only realistic hope for cure in terms of a 30% 5-year survival. However, relapse after resection will occur in almost 75% of the patients. Recurrence occurs predominantly within the first 2 years after surgery, and is located in the liver in approximately 50% of the cases (Fong et al. 1997, 1999).

Only approximately 15% of patients who develop MCRC have disease confined to the liver, which is considered resectable. A retrospective study originally highlighted the role of preoperative, neoadjuvant chemotherapy in the treatment of colorectal cancer patients with unresectable metastases and reported a resection rate of 16% (53/330 patients) and a 5-year survival rate after resection of 40% (Bismuth et al. 1996; Adam et al. 2001). There has been a growing acceptance (even by NICE in the UK) that combination chemotherapy regimens using 5-fluorouracil/folinic acid (5-FU/FA) in combination with either oxaliplatin or irinotecan can facilitate the down-sizing of colorectal liver metastases and render initially unresectable metastases, resectable. Presumably, preoperative chemotherapy potentially allows surgery on tumors that have become smaller in response to chemotherapy.

Hence, perioperative chemotherapy in patients with metastases confined to the liver is now used in three defined treatment settings; the preoperative setting can be used to render initially unresectable metastases resectable; alternatively, neoadjuvant chemotherapy can be used in already resectable patients prior to and/or following surgery as an adjuvant to reduce the substantial risk of further recurrence.

Until recently, the classic contraindications for resection of CRC liver metastases have been: > four metastases, disease outside the liver, metastatic nodes in the porta hepatis, a potential resection margin of < 1 cm, the presence of co-morbid disease, and an incomplete resection. Although, the number and size of metastases are important, when considering liver resection, the volume of the remaining liver after resection is considered critical. Strategies such as portal vein embolisation can result in hypertrophy of the remaining liver, and increase the normal liver reserve enabling more extensive liver resections (Azoulay et al. 2000), although its role and benefit is as yet unproven. However, these limitations for resectability are being rapidly modified in the face of technical

advances in surgery and more active chemotherapy. Resection is only likely to be contraindicated when it is impossible to clear all the metastases or in the presence of coeliac and para-aortic lymph nodes.

Folprecht's analysis is pivotal to our current management of patients with liver metastases (Folprecht et al. 2005). He examined all published and presented trials as well as retrospective studies, which reported objective response rates and the rates of resection of initially unresectable liver metastases. His analysis was based on only a few studies of selected patients, i.e., those patients with disease confined to the liver, but comprised data from over 2,900 patients. He demonstrated that in both unselected and selected patients, both response rate and the delivery of preoperative chemotherapy strongly correlated with resectability. The higher the response rate, the more liver resections were achieved. This hypothesis supports a treatment approach, which delivers the most active regimen particularly in potentially curable (i.e. selected) patients. The duration of neoadjuvant chemotherapy in this setting depends on the quality and speed of response. Treating until best response may not be advisable, as liver lesions disappear, and determining the exact location of the tumor at surgery can become problematic. It is therefore currently recommended that patients be treated until the point when their disease becomes resectable.

For this reason, the percentage of patients potentially eligible for curative liver resection is increasing. In addition, long-term survival rates for patients with initially unresectable metastases treated with neoadjuvant chemotherapy and then brought to surgery are similar to those of patients whose metastases were considered to be resectable.

In an Italian phase III study from the GONO Group in patients with unresectable metastatic disease, the triplet combination of cytotoxic agents FOLFOXIRI was associated with a higher response rate 60% vs. 34% ($p < 0.001$) when compared with the more commonly used doublet of FOLFIRI (Falcone et al. 2008). In addition, the R0 resection rate was 15% when compared with only 6% with FOLFIRI ($P = 0.033$), leading to a significant improvement in both PFS (9.8 vs. 6.9 months) and OS (23.6 vs. 16.7 months, respectively). More recently, triplet chemotherapy has been even more effective in terms of response rates.

Recently, the results of the multicenter EPOC trial showed that perioperative chemotherapy with FOLFOX4 is safe and compatible with major liver surgery. The study randomized 364 patients with histologically proven colorectal cancer and up to four liver metastases, to either six cycles of FOLFOX4 before and six cycles after surgery or to surgery alone (Nordlinger 2008). The study showed that only 12 patients (6.9%) patients progressed on FOLFOX chemotherapy. Some of these may have been more accurately described as stable disease, because 8/12 remained resectable. In eligible patients, the PFS improved by 8.1%, from 28.1% to 36.2% ($P = 0.041$), and in patients who actually underwent resection by 9.2%, from 33.2% to 42.4% ($P = 0.025$). However, the improvement in PFS with chemotherapy appears during the first 2 years, but afterwards, the curves remain parallel.

In 2008, a multidisciplinary team discussion became an essential part of the management of a patient with potentially resectable liver metastases. There is a small but growing subset of patients with initially unresectable liver disease, who can now be rendered eligible for resection. This group is likely to increase in the future with the successful integration of both the triplets of chemotherapy (FOLFOXIRI) and the new molecular targeted drugs, bevacizumab and cetuximab, with appropriate selection into the neoadjuvant setting. In a small study of 18 patients (Falcone GI ASCO 2008 –abstract 363; Masi et al. 2008), the clinical RR with FOLFOXIRI and bevacizumab was even higher at 87% with 13% achieving stable disease, and no patients progressed. Toxicity was acceptable with G3/4 neutropenia (23%) and diarrhea (12%).

The future is likely to challenge our ideas regarding surgery as a curative or debulking manevre, as a single operation with the aim of macroscopic clearance may represent a lack of vision.

Grothey and Sargent carried out a pooled analysis of 11 large published phase III trials of advanced colorectal cancer for which data on exposure to all three drugs (5-FU, irinotecan, and oxaliplatin) were available (Grothey et al. 2004). This analysis included 5,768 patients and showed that the percentage of patients receiving all the three drugs in the course of their treatment correlated significantly with the OS for that arm. The conclusion from this study was that access to all the three active agents was

more important than the use of irinotecan- or oxaliplatin-based combination therapy upfront. This analysis has been updated (Grothey and Sargent 2005). However, it was also shown that patients who receive combination chemotherapy first-line have a greater chance of receiving all three active agents.

However, first-line combination chemotherapy with all possible options delivered simultaneously is not necessarily the best approach for all patients with metastatic disease. Median time to progression is only extended by 2–3 months when doublet combinations are used in preference to a single agent. Also, some patients logically will not benefit from oxaliplatin or irinotecan. Several phase III studies in the new millennium have shown that for some patients, a sequential approach can be as effective (Seymour et al.2007a, b; Cunningham et al. 2009; Koopman et al. 2007; Bouche et al. 2007) (Table 4.2).

All the abovementioned trials comprised a selected population who had not received any prior chemotherapy for metastatic disease, where patients who had resectable or potentially resectable liver metastases were unlikely to be entered. All the trials used 5FU or capecitabine, oxaliplatin, and irinotecan in a planned sequential strategy. However, no anti-EGFR or anti-VEGF antibodies were used. OS was either the primary or secondary endpoint. There is a suggestion that patients with poor performance status (PS = 2) and abnormal liver function tests may be compromised in terms of OS if they fail to respond to single agent.

In the LIFE trial (Cunningham et al. 2009), the addition of oxaliplatin significantly improved the response rates (54.1 vs. 29.8%, $p < 0.0001$) and extended median PFS (7.9 vs. 5.9 months, $p < 0.0001$). However, the study failed to demonstrate an OS benefit from the addition of oxaliplatin (15.9 vs. 15.2 months).

The largest of these trials, Fluorouracil, Oxaliplatin, CPT-11 Usage Study (FOCUS) assessed whether combination chemotherapy with irinotecan or oxaliplatin was superior to standard sequential chemotherapy (Seymour et al.2007a). The study used a complicated design to determine if combination chemotherapy is best utilized as first-line therapy or as planned second-line following progression on first-line single agent chemotherapy with OS as the primary endpoint (Seymour et al. 2007a). The FOCUS trial recruited 2,135 patients. A small non-significant improvement in OS was observed when combination chemotherapy was given as first or second line. However, no improvement in

Table 4.2.

Study	Number	Median age	% of patients PS = 2	First-line	Median survival (months) Single agent vs combination
FOCUS (Seymour et al. 2007a)	2135	64	9	Multiple options 5FU/ FOLFOX/FOLFIRI	15.1 vs 15.9
FOCUS 2 (Seymour et al. 2007b)	460	75	29	Reduced dose 5FU vs capecitabine and FOLFOX or XELOX	NS
LIFE (Cunningham et al. 2009)	725	62	6	FOLFOX or PVI 5FU + Oxaliplatin vs. 5FU followed by irinotecan	15.2 vs 15.9
CAIRO (Koopman et al. 2007)	803	63	4	Capiri then Capeox	16.3 vs 17.4
FFCD (Bouche et al. 2007)	410	69	16	LV5FU2 followed by FOLFOX6 (arm A) to FOLFOX6 followed by FOLFIRI (arm B)	17 vs 16

NS = not stated.

OS was seen when combination chemotherapy was given as first line as opposed to progression after single-agent chemotherapy (Seymour et al. 2007a). Only 20% of patients had access to all the three agents (5FU, irinotecan, and oxaliplatin).

A recent hypothesis-generating study from the FOCUS trial suggested that it might be possible to predict patients who are likely to benefit from sequential treatment using immunohistochemistry of topoisomerase-1 (Topo1) (Braun et al. 2008). These authors also concluded that Topo1 immunohistochemistry identified subpopulations that did or did not benefit from irinotecan, and possibly also from oxaliplatin. Topo1, as the molecular target of SN38 (active agent of irinotecan), is a plausible predictive marker for irinotecan sensitivity, but previous studies of palliative chemotherapy have failed to confirm this link until the results of the UK FOCUS trial.

They also showed an association between Topo1 and Thymidylate Synthase (TS). Higher Topo1 correlated with higher TS ($p < 0.001$). Low Topo1 expression, like low TS expression, appears to be a good prognostic factor in patients receiving FU alone. Patients with low levels of Topo 1 fared well with first-line FU, but did not benefit from an additional drug in terms of PFS, and obtained no survival benefit from first-line combination chemotherapy. With increasing levels of Topo1, the outcome with just FU alone became worse, but adding a second drug improved the survival for the highest expressing patients.

However, similar predictive value for patients treated with FU and oxaliplatin makes the relationship between Topo1 levels and the drug's mechanism of action less dependent on the SN38 pathway and less clear, overall. The predictive value of Topo1 may reflect other differences in tumor biology, such as proliferative rate or a lowered apoptotic threshold, which perhaps determine sensitivity in favor of more intense combinations of various chemotherapeutic agents rather than the specific combination with irinotecan.

Continuous vs. Intermittent Therapy

A UK study (CR06B) randomized 354 patients who either responded or had stable disease on LV5FU2, PVI 5FU, or single-agent, raltitrexed, either continuing with therapy until progression or intermittent 3-monthly chemotherapy (Maughan et al. 2003). The intermittent arm experienced less serious toxicity. There was no difference in OS. At that time, this study attracted little attention. However, the controversy between continuous and intermittent treatment has gained ground with the increasing diversity of treatment options, the wish to preserve overall QOL, and the recognition of cumulative neurotoxicity from oxaliplatin. All question the issue of the optimal duration of chemotherapy. Neuromodulatory agents such as xaliproden have failed to show meaningful clinical benefit in preventing oxaliplatin-induced neurotoxicity. Perhaps, planned treatment "holidays" can allow patients to recover from the physical and psychological side effects of their chemotherapy, provided efficacy is not compromised. In France, at the same time, modifications to the FOLFOX4 regimen by increasing the dose of oxaliplatin appeared to increase the response rate (Maindrault-Goebel et al. 2000). This more active regimen (FOLFOX 7) was then tested in the OPTIMOX study, and compared with the more traditional FOLFOX 4 (Tournigand et al. 2004).

The phase III trial OPTIMOX-1 showed that induction (FOLFOX) followed by maintenance chemotherapy (infusional 5-FU/LV, no oxaliplatin) and subsequent reintroduction of FOLFOX is a feasible strategy. The stop-and-go strategy used in an OPTIMOX1 fashion, does not compromise efficacy, and reduces the incidence of grade 3/4 neurotoxicity compared with continuous FOLFOX, until disease progression or unacceptable toxicity (Tournigand et al. 2006). Giving patients a break from oxaliplatin during the maintenance phase, with a planned reintroduction at a future point, allows the maximum benefit from oxaliplatin therapy, and at the same time provides improved QOL for patients.

The OPTIMOX concept was taken a step further by addressing whether complete chemotherapy-free intervals (CFIs) instead of maintenance might provide the same overall treatment results in the OPTIMOX-2 study (Maindrault-Goebel et al. 2007). Continuation of treatment with a maintenance protocol resulted in longer PFS, compared with pausing treatment altogether (8.3 vs 6.7 months, $P = 0.009$). Duration of disease control (DDC) was almost identical in both the arms (12. vs 11.7 months, P = NS). However, DDC is not a validated endpoint in randomized

clinical trials as a surrogate for survival, and hence, its relevance for clinical practice is not yet established. Survival is now observed, and patients who continued on maintenance therapy had a median OS of 26 vs. 19 months in the "stop and go arm" ($P = 0.5$). The results, although not statistically significant, suggest inferior survival in patients who had chemotherapy-free intervals.

In the OPTIMOX-2 study, unsurprisingly, the duration of the interval without chemotherapy appeared to depend on the clinical prognostic factors. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 2, elevated levels of lactate dehydrogenase (LDH), raised alkaline phosphatase > 3 × upper limit of normal (ULN), and two or more sites of metastatic disease, had an interval of only 4.6 months, compared with 8.0 months in patients with more favorable prognostic factors.

Three biological agents have now entered clinical practice in colorectal cancer, namely, cetuximab, panitumumab, and bevacizumab. Cetuximab is a chimeric monoclonal antibody against the extracellular domain of the epidermal growth factor receptor (EGFR); Panitumumab is a fully humanized IgG2 monoclonal antibody against human EGFR; and bevacizumab is an anti-angiogenesis agent, which targets the vascular epidermal growth factor (VEGF).

CR06B and OPTIMOX-2 confirm that intervals without chemotherapy may be appropriate for some patients, especially those with favorable, i.e., non-aggressive tumor biology. However, the results are not reliably transferable into current clinical practice, because they were conducted when treatment options were more limited before the introduction of biologic therapies, such as bevacizumab and cetuximab. Now that many patients are expected to live longer than 2 years after diagnosis of metastatic disease, should treatment be continued with the same intensity until progressive disease? The advantage of biologics could lie in their use as maintenance therapy after the induction of response with conventional chemotherapy. This approach is being tested in ongoing clinical trials such as the COIN and DREAM studies.

The original design for DREAM-OPTIMOX3 study used FOLFOX7, bevacizumab, and erlotinib as first-line therapy for patients with MCRC, and then randomized patients to receive bevacizumab with or without erlotinib during a CFI. The study has been redesigned after finding the combination too toxic. The phase II study showed an 86% grade 3/4 toxicity rate, which meant patients dropped out of the study before progressive disease (Tournigand et al. 2007). The most common toxicity was diarrhea, which probably relates to erlotinib. In addition, the response rate at only 34% was disappointing, and appeared lower than anticipated with FOLFOX and bevacizumab alone. It proved impossible to deliver more than six cycles of combination chemotherapy. Patients now receive the combination of bevacizumab and erlotinib as maintenance after six cycles of either FOLFOX7 or XELOX4 and bevacizumab (NCT00265824).

A similar study from the Spanish Cooperative Group for Gastrointestinal Tumour Therapy is currently comparing XELOX plus bevacizumab until disease progression or toxicity with XELOX plus bevacizumab for six cycles followed by bevacizumab alone until disease progression (NCT00335595).

Other recent trials have focused on oral fluoropyrimidine vs. infusional 5FU in combination with oxaliplatin (TREE 1 and TREE 2 trials); sequential vs. combination treatments; continuous vs. intermittent chemotherapy; and the integration of novel targeted agents. Significant progress has been made with the integration of novel biological agents, specifically the anti-EGFR antibody, cetuximab and panitunimab, and the anti-VEGF (Bevacizumab). As a result, the median survival for patients with metastatic disease has increased from 13.7 to 23 months. With the continued development of new biological agents, treatment outcomes are likely to continue improving. We will deal with these topics, each in turn focussing on trials performed in 2006/7 and ongoing trials at the time of writing in 2008.

An alternative approach has been developed, in which rather than combining three cytotoxic drugs, one of these targeted biological agents is added to combinations of cytotoxics to avoid overlapping toxicity. Hence, numerous studies have investigated the addition of bevacizumab, cetuximab, panitumumab, or oral tyrosine kinases to combinations of a fluoropyrimidine and irinotecan or a fluoropyrimidine and oxaliplatin in first- or second-line strategies. These biologicals have also been tested as a single

agent in second- and third-line treatments. The results of these studies suggest that both cetuximab and bevacizumab appear to enhance the benefits of cytotoxic chemotherapy. Cetuximab and panitumumab (but not bevacizumab) also have some modest activity as single agents. The results of other phase III studies are awaited.

Bevacizumab

The growth of primary tumors, as well as metastatic disease, requires an intact and expanding vasculature. Therefore, VEGF, which is one of the most important angiogenic growth factors and known to regulate angiogenesis, represents an attractive target for chemotherapy. Several therapeutic approaches have been taken to inhibit VEGF signaling, which include inhibition of VEGF/VEGF receptor interactions by targeting either the VEGF ligand with antibodies or soluble chimeric receptors, or by direct inhibition of the VEGF receptor associated tyrosine kinase activity by small molecule inhibitors. Bevacizumab is a recombinant humanized monoclonal antibody, targeted against all splice variants and post-translationally modified forms of VEGF-A. It binds to and prevents VEGF-A from interacting with their target VEGF receptors.

In addition, solid tumors commonly manifest an elevated interstitial fluid pressure (IFP) and regions of hypoxia when compared with normal tissues, which contribute to a decreased transcapillary transport, and leads to the poor delivery of cytotoxic drugs. This observation appears relevant to angiogenesis inhibitors, which have been shown to normalize the vasculature and reduce IFP, and may thereby increase the tumor uptake of chemotherapeutic agents (Huang and Chen 2008). In addition, data from a clinical study in locally advanced rectal cancer demonstrated that tumor IFP was lowered by the use of the anti-VEGF monoclonal antibody bevacizumab (Willett et al. 2004). Two pivotal studies have shown the potential utility of these two approaches in colorectal cancer (Willet et al. 2004; Kabbinavar et al. 2003).

Proof of principle was obtained from the randomized phase II AVF0780 trial, which evaluated the safety and efficacy of two dose levels of bevacizumab in MCRC. The doses in the bevacizumab arms were 5 mg/kg or 10 mg/kg. The two treatment arms that included bevacizumab at doses of 5 mg/kg and 10 mg/kg resulted in higher response rates (40% and 24%), a longer median time to progression (9 and 7.2 months), and median survival (21.5 and 16.1 months) when compared with 5-FU and LV alone (17%, 5.2 and 13.6 months respectively). The 5mg/kg arm suggested a higher clinical efficacy, and therefore, this dose level has been continued in further studies. This study did highlight the lack of specificity of bevacizumab, and raised some important safety considerations. It was shown that bevacizumab therapy is associated with an increased incidence of thromboembolic complications, hypertension, proteinuria, and bleeding complications with epistaxis, headache, fever, and rash.

There are a number of other trials evaluating the use of bevacizumab in the treatment of colorectal cancer in the neo-adjuvant and metastatic setting (see table). This section will discuss the trials currently in progress in the neo-adjuvant and metastatic setting. Bevacizumab is effective in first-line with all regimens of chemotherapy. It has been proven to be safe in the wider community setting (BRiTE) (Grothey et al. 2008a) and in the post-marketing BEAT study (Berry et al. 2008). In addition, retrospective analyses show that surgery with curative intent can be performed in about 20% of the patients. Bevacizumab is also active in the second-line setting, but not in the third line.

The randomized phase III AVF 2107 trial evaluated the addition of bevacuzimab to Irinotecan and 5FU/LV chemotherapy or 5FU/LV chemotherapy alone (Hurwitz et al. 2004). As the first phase III trial to show an improvement in OS using a biological agent in the first-line treatment of MCRC, this trial confirmed the value of anti-angiogenic agents. There was an improvement in PFS (10.6 vs 6.2 months, HR, 0.54) and OS (20.3 vs 15.6 months, HR, 0.66).

The addition of bevacuzimab to oxaliplatin-based combination chemotherapy was studied in the XELOX-1 trial. This trial initially compared capecitabine plus oxaliplatin with FOLFOX, and showed the non-inferiority of capecitabine. The study was amended to test the addition of bevacizumab to these agents. The combined analysis of XELOX and FOLFOX with or without bevacizumab showed an improvement in PFS for the addition of the antiangiogenic agent, 9.4 vs. 8.1 months (HR 0.83, $p < 0.0001$). The median time to progression was

6.9 vs. 6.0 months ($P = 0.003$, HR 0.84) and there was a non-significant trend towards improved OS (21.3 versus. 19.9 months, $P = 0.0769$). The response rates were similar in the two arms, as was the median treatment duration.

In the Xelox-1/NO16966 study where patients were unsuitable for liver resection, the RR was only 38%. Yet, 19.2% of patients with disease in liver only and treated with bevacizumab proceeded to surgery with curative intent, when compared with 12.9% treated with XELOX or FOLFOX alone (Tables 4.3, 4.4 and 4.5).

These results with oxaliplatin and bevacizumab in the first-line therapy are consistent with the results of the prospective phase II TREE 2 study, which followed the TREE I that compared the efficacy of three different oxaliplatin regimens combined with either infusional or bolus 5FU or capecitabine. In the TREE 2 study, these three similar regimens with the addition of bevacizumab were again compared (Hochster et al. 2008). When bevacizumab was added to the standard FOLFOX regimen, a small but significant extension in PFS was observed (8.7 vs. 9.9 months). Again, many have questioned the clinical utility of 1.2 months.

The ML 18405 (AIO Trial 0604) study compared safety and response rate with bevacizumab in combination with capecitabine and oxaliplatin (CapOx/Bev) vs. capecitabine and irinotecan (Capiri/Bev). This randomized phase II study used a primary endpoint of PFS at 6 months, and incorporated secondary endpoints of OS, toxicity, and resectability of liver or lung metastases. The trial protocol had a planned dose reduction in the irinotecan and capecitabine, because the results of previous studies using this combination had raised concerns regarding excess toxicity. Arm A received bevacizumab of 7.5 mg/kg D1 with oxaliplatin (130 mg/m2 D1)/capecitabine (1,000 mg/m2), BID D1–14 (CapeOx/Bev – Arm A), or irinotecan (200 mg/m2 D1)/capecitabine (800 mg/m2 BID D1–14) (CapeIri/Bev – Arm B). The preliminary results were presented at ASCO 2007 showing equivalent toxicity, rather than toxicity in Arm A, and response rates. The primary endpoint of PFS at 6 months was 78% in Arm A and 84% in Arm B; thus, with no significant difference (Schmiegel et al. 2007). More mature results showed that both the regimens are highly active with equivalent tumor response rates of 54% and 55% respectively, and are safe (Reinacher-Schick et al. 2008).

In a neoadjuvant study in liver metastases, xelox and bevacizumab achieved a 70% RR, and an astonishingly high pathological complete response rate of 9% (Gruenberger et al. 2007). This figure is equivalent to the results of studies of 5FU-based chemoradiation in locally advanced rectal cancer. In many studies, signi ficant improvement of OS was observed in histopathological tumor responders after neoadjuvant radiochemotherapy (Rosenberg et al. 2008).

The BICC-2 study demonstrated a significant improvement in OS from 23.1 to 28 months when bevacizumab was added to a standard FOLFIRI regimen (Fuchs et al. 2007, 2008).

Two non-randomized observational phase IV studies (the BriTE and the first BEAT study) included almost 4,000 patients, and support the use of bevacizumab beyond first progression (BBP). Despite the fact that in both the studies, there was a very heterogeneous population with regard to patient selection and treatment regimes, the overall median survival in these studies was 24.5 and 22.7 months. In the BRiTE registry of 1,953 patients, the median survival was more than 30 months when bevacizumab was continued beyond first progression of the disease (Grothey et al. 2008). Amongst the patients with first disease progression, 34.8% received cetuximab and 53.8% received BBP. In a multivariate analysis, BBP and exposure to any second-line agent were independently associated with an increased OS (both $p < 0.0001$).

The CALGB trial 80203 examined whether the addition of cetuximab to both the standard chemotherapy regimens (FOLFOX or FOLFIRI) could further increase their antitumor activity in this setting (Venook et al. 2006) – using the so-called "dealers choice" selection of cytotoxic partner. The primary endpoint of the study was OS and secondary endpoints included response rate, PFS, and toxicity. Initially designed as a phase III trial with a planned accrual of 2,200 patients, this study experienced the same problem as BICC-C, TREE, and OPTIMOX-2, i.e., with the availability of bevacizumab to patients, the trial design with randomization to a non-biologics-containing arm became unfeasible.

The trial enrolled 238 patients on four different treatment arms (FOLFOX or FOLFIRI, each $\pm$ cetuximab), but it is not a 2×2 factorial randomized phase II trial. With a median follow-up of 16 months, the addition of cetuximab appears to increase the activity of both FOLFOX and

Table 4.3. Recent and current first line trials with bevacizumab

Trial name	Indication	Phase	Stage	Randomization	Primary endpoint	Number of Pts
ASSO-LM1	Neoadjuvant – metastatic	I/II	IV	XELOX + bev 5 cycles followed by surgery and then 6 cycles of XELOX + bev	Resectability	40
MO 18725 – R Adam	Metastatic – Neo adjuvant	II	IV	FOLFOXIRI + bev vs FOLFOX + bev followed by surgery	Rate of surgical complications	80
MO 19286 (AVEX)	Metastatic – 1st line		IV	Capecitabine + /– bev	PFS	430
ML 18513 MAX	Metastatic – 1st line	II/III	IV	Capecitabine vs Capecitabine + bev vs Capecitabine + Mitomycin + bev	PFS	450
CONcePT	Metastatic – 1st Line	IV	IV	mFOLFOX7 + bev (int Oxaliplatin) vs mFOLFOX7 + bev (cont Oxaliplatin)	TTF	532
ML 18735 (CAIRO 2)	Metastatic – 1st line	IV	IV	Capecitabine + Oxali + Bev vs Capecitabine + Oxali + Bev + Cetuximab	PFS	755
MO 18420 DREAM	Metastatic – 1st line	III	IV	XELOX 2 + bev vs mFOLFOX7 + bev followed by maintenance bev + /– tarceva	PFS	640
ML 18605	Metastatic – 1st line		IV	XELOX + bev until progression vs XELOX + bev 6 cycles and then bev to progression	PFS	470
ML 20907 (CAIRO 3)	Metastatic – 1st line	IV	IV	XELOX + bev randomized to observation vs Capecitabine + bev until progression	PFS	800
ML 18405	Metastatic – 1st line	II/III	IV	XELOX + bev vs XELIRI + bev	PFS	240
CALGB 80405	Metastatic 1st line	III	IV	FOLFOX or FOLFIRI + bev vs FOLFOX or FOLFIRI + cetuximab vs FOLFOX or FOLFIRI + bev + cetuximab	PFS	2,289
ML 18357	Metastatic – 1st line	II	IV	XELIRI + bev vs FOLFIRI + bev	PFS	150
Spanish TTD	Metastatic – 1st line	III	IV	Capecitabine, Oxaliplatin and bevacizumab followed by maintenance bevacizumab alone or in combination with oxaliplatin and capecitabine	PFS	470

Table 4.4. Second-line trials

Trial Name	Indication	Phase	No of Pts	Primary endpoint	Randomization	No of pts
E3200	Metastatic– 2nd line/refractory	III	829	OS	FOLFOX4 with or without bevacizumab or bevacizumab alone	828
ML 18417	Metastatic– 2nd line	IV	580	PFS	AIO-Iri/FOLFIRI/CAPIRI/ XELIRI +/– bev vs FUFOX/FOLFOX/ CAPOX/XELOX +/– bev	580

FOLFIRI, with statistically higher response rates for the cetuximab-containing arms when compared with the chemotherapy doublets alone (52% vs 38%, $P = 0.029$). As the study was closed prematurely, it is not powered for statistical analysis of PFS and OS.

The preliminary results of CALGB 80203 with the E3200 (Saltz et al. 2008) and the BOND-2 (Saltz et al. 2007) studies validated the design of the ongoing Intergroup trial CALGB/SWOG 80405, which aims to randomize 2,289 patients to bevacizumab or cetuximab or bevacizumab + cetuximab added to a chemotherapy backbone of FOLFOX or FOLFIRI (dealer's choice). However, this study has also been forced to restrict eligibility to patients expressing WT Kras.

The E3200 study evaluated the use of bevacizumab in the treatment of MCRC (Saltz et al. 2008).The patients were previously treated with a fluoropyrimidine and irinotecan. The patients were randomized into one of the three treatment groups: FOLFOX4 with or without bevacizumab or bevacizumab alone. The median duration of survival for the group treated with FOLFOX4 and bevacizumab was 12.9 months when compared with 10.8 months for the group treated with FOLFOX4 alone (HR 0.75, P = 0.001), and 10.2 months for those treated with bevacizumab alone. In addition, the median PFS and response rates were significant higher in the group treated with FOLFOX4 and bevacizumab (Giantonio et al. 2007).

The SWOG 0600 study (iBET) is investigating the use of irinotecan and cetuximab with or without bevacizumab in the treatment of patients with MCRC, who have progressed during first-line therapy. The study questions whether there is any benefit associated with continuation of bevacizumab following disease progression after first-line therapy. The additional aim is to assess whether 5mg/kg or 10 mg/kg is the more appropriate dose of bevacizumab in the second-line setting.

Also, there is evidence from several studies that secondary resection of liver metastases after combination chemotherapy and bevacizumab is feasible and safe (Cassidy et al. 2008; Gruenberger et al. 2007). Evidence from the BEAT study in MCRC examined the effect of bevacizumab on surgery. The percentage of wound healing complications was 1.3%, bleeding was 3.4%, and GI perforation was 1.8%, respectively. The BRITE study and the ARIES study showed similar results. However, the data suggests that the interval to surgery should be 6 weeks from the last administration of bevacizumab (two half lives of

Table 4.5. Results of first-line trials

Trial Name	Indication	Phase	No	Randomization	ORR	ORR	PFS	PFS	OS	OS
					+bev		+bev		+bev	
Hurwitz et al. 2004	Metastatic – 1st line	III	813	IFL vs 5FU/LV +/– bev	45%	35%	10.6m	6.2m	20.3m	15.6m
NO16966	Metastatic 1st line	III	1401	XELOX +/– bev vs FOLFOX +/– bev	48% 47%	48% 47%	9.4m	8.0m	21.6m 21m	19m 18.9m

bevacizumab). In the BEAT observational study, 215 of 1,914 enrolled patients were eligible for surgery of initially inoperable metastatic disease, with a potential for cure. Among them, 170 achieved an R0 resection. Such patients who received bevacizumab and chemotherapy and then underwent surgical resection had a higher chance of surviving for 2 years (82% vs. 44%).

The CONcePT Trial (Grothey et al. 2008b, ASCO 4010)

Using first-line chemotherapy with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) + bevacizumab for MCRC, the CONcePT trial aimed to further examine the Stop-and-Go strategy developed by the French Oncology Research Group (GERCOR). The second aim was to prevent the neurotoxicity of oxaliplatin with a calcium and magnesium (Ca^{2+}–Mg^{2+}) infusion. Preliminary results suggested a smaller response rate in the two arms of patients treated with FOLFOX-bevacizumab plus Ca^{2+} –Mg^{2+}. For this reason, the administration of Ca^{2+} Mg^{2+} was stopped half way through the trial.

With respect to all the trials together, there is strong evidence that the addition of bevacizumab is useful in first line and on progression. There is a suggestion that the quality of response may be better, and we are beginning to see significant number of pathological complete responses in metastaic disease. In a neoadjuvant study by Gruneberg, the pCR rate in resected liver metastases was 9% (Grunenberg 2008). Others have suggested that in practical terms, the NO16966 is a negative trial, and questioned the clinical meaningfulness of the addition of bevacizumab in a broad patient population treated with effective chemotherapy (Booth 2008). With so many active agents when compared with the limited scope in the 1990s, efforts in research have focussed on identifying optimal combinations, optimal sequencing, the optimal induction therapy, treating to progression or allowing cytotoxic-free intervals, and the timing of the re-introduction of chemotherapy. Several recent reviews (Kelly and Goldberg 2005; Zuckerman and Clark 2008; O'Neil and Goldberg 2008) have partially addressed these complex issues.

These authors feel that the evidence of all the abovementioned trials both in terms of the different response rates and the duration issue of bevacizumab suggest that there is more benefit from the combination of bevacizumab and irinotecan than bevaizumab and oxaliplatin.

Cetuximab

The EGFR is a member of the Erb-B family of proteins, and is also known as Erb-B1 or HER-1 receptor. In addition, there are Erb-B2 (HER-2), HER-3, and HER-4. These receptors are a part of a complex and inter-related downstream signaling pathway, which when de-regulated, leads to malignant transformation. EGFR activation also plays a role in resistance to both chemotherapy and radiotherapy. EGFR can be targeted either through the small molecule tyrosine kinase inhibitors (TKIs) or monoclonal antibodies, anti sense nucleotides, ligand toxins, and inhibitors of downstream effects of EGFR signalling pathway. Current established therapeutic options are limited to monoclonal antibodies and TKIs in colorectal cancer. Surprisingly, monoclonals and TKIs have rarely been used in combination, perhaps because they may confer unacceptable toxicity (Spigel et al. 2006; Tournigand et al. 2007).

These monoclonal antibodies, such as cetuximab, function by binding to the extra cellular domain and leading to competitive inhibition of ligand binding, which then prevents the dimerization and activation of the receptor and inhibits the downstream signaling pathway. Binding of the antibody also stimulates the cell to internalize and degrade the receptor. Current monoclonal antibodies in clinical use include cetuximab and panitumumab. The mechanism or action of these monoclonal antibodies appear to involve cell cycle arrest at G1, promotion of pro-apoptopic factors, and decreased levels of anti apoptopic factors inhibition of angiogenesis. Cetuximab is usually delivered on a weekly basis, but recent data suggests that this interval can be extended to 2 weeks (Tabernero et al. 2008).

It is now recognized that EGFR testing is probably irrelevant (Chung et al. 2005). No correlation has been found between the degree of EGFR expression and clinical outcome in trials utilizing cetuximab (Lenz et al. 2005). A recently reported phase II study with cetuximab, in which 346 patients with EGFR-positive MCRC

were treated with the agent, also failed to identify a relationship between the levels of EGFR and outcome (Lenz et al. 2006). However, because patients lacking any EGFR expression were not eligible to be enrolled, the question cannot be answered definitively. It is difficult to explain how a tumor with perhaps less than 1% of cells expressing low levels of EGFR has the same likelihood of response to an agent that supposedly only targets that population, than a tumor where 90% of the cells express high levels of the target. Tumors are heterogeneous with regard to expression of the EGFR, and there may be differences in EGFR expression observed between primary tumors and corresponding liver metastases (Scartozzi et al. 2004).

In contrast, interest has centered on K-ras status. K-ras mutations appear constitutively to activate the signalling pathways and stimulate cell proliferation (Bos 1989). In addition, an acne-like rash, which is a characteristic side effect of EGFR-targeted agents, including cetuximab, correlates with response (Van Cutsem et al. 2004). A class effect of all the anti-EGFR agents appears to be a macular, popular, and pustular rash, which seems dose-dependent and affects 30–60% of patients. The distribution is mainly on the upper part of the body, face, neck, trunk, and upper torso. The rash usually is visible within 2–3 weeks of starting therapy. The presence and severity of this rash has already been demonstrated to predict both response and survival in patients with colon cancer (Saltz et al. 2003). The EVEREST study investigated the value of tailoring patient's cetuximab dose to the biological correlate of a skin rash. They aimed to increase doses after 14 days until a skin rash is observed and then continue at the dose, which achieves a rash, to see if this strategy would maximize the efficacy of cetuximab. Preliminary data showed that efficacy could be improved by escalating the dose of cetuximab in patients with only grade 0/1 skin reactions (Tejpar et al. 2008). The response rate in wild-type (wt) K-ras patients rose from 4/19 (21.1%) to 13/28 (46.4%). However, patients with mutant K-ras did not respond even if the dose was escalated. The EVEREST trial has clearly demonstrated that patients with mutant k-ras will not benefit from cetuximab either at standard doses or with dose escalation to toxicity (Tejpar et al. 2008) (Table 4.6).

Results of First-Line Trials

Cetuximab has been used as a single agent in first-line therapy in elderly patients (Pessino et al. 2008). Cetuximab has also been added to a FOLFOX regimen in first-line therapy to increase efficacy. Very high rates of response (81%) were observed in a small phase II study when cetuximab was combined with oxaliplatin (Tabernero et al. 2007). A similar phase II study combining cetuximab and FOLFIRI demonstrated a response rate of 46% (Rougier et al. 2004).

The CALGB trial 80203 examined whether the addition of cetuximab to both standard chemotherapy regimens (FOLFOX or FOLFIRI) could further increase their antitumor activity in this setting (Venook et al. 2006) using the so-called "dealers choice" selection of cytotoxic partner. The primary endpoint of the study was OS and secondary endpoints included response rate, PFS and toxicity. Initially designed as a phase III trial with a planned accrual of 2,200 patients, this study experienced the same problem as BICC-C, TREE, and OPTIMOX-2, i.e., with the availability of bevacizumab to patients, the trial design with randomization to a non-biologics-containing arm became unfeasible. The trial enrolled 238 patients on four different treatment arms (FOLFOX or FOLFIRI, each ± cetuximab), but it is not a 2×2 factorial randomized phase II trial. With a median follow-up of 16 months, the addition of cetuximab appears to increase the activity of both FOLFOX and FOLFIRI, with statistically higher response rates for the cetuximab-containing arms compared with the chemotherapy doublets alone (52% vs 38%, $P = 0.029$). As the study was closed prematurely, it is not powered for statistical analysis of PFS and OS.

Table 4.6. Results of first-line trials

Trial Name	Indication	Phase	No	Randomization	ORR	ORR	PFS	PFS	OS	OS
CRYSTAL	Metastatic – 1st line	III	1217	FOLFIRI +/– cet	45%	35%	10.6m	6.2m	20.3m	15.6m

The CRYSTAL study showed that patients with metastatic colorectal cancer had a significantly better clinical response, a significant improvement in PFS, and a higher rate of curative resections for liver metastases when cetuximab was added to first-line FOLFIRI (Van Cutsem et al. 2008). Archived samples from 587 of the 1,198 patients recruited into the CRYSTAL trial were re-evaluated to examine whether their tumors showed wild type (wt) or mutant K-ras expression.

When the 540 K-ras evaluable tumor samples were tested for mutations in codon 12 and 13, this was detected in 192/540 samples, i.e., 36% of the population under study. One-year PFS rates were 25% and 43% in patients with wt K-ras tumors, when FOLFIRI was compared with FOLFIRI plus cetuximab, respectively. Median PFS improved from 8.7 to 9.9 months (hazard ratio 0.68 and $P = 0.017$). The objective clinical response rate was 43.2% vs. 59.3% ($P = 0.0025$). Thus, there was a favorable effect in wt K-ras patients, which was not seen in those patients who expressed mutant K-ras.

An updated report (Van Cutsem et al. 2008) showed a response rate of 77% for wt K-ras tumors confined to the liver.

In the randomized phase II OPUS trial (Bokemeyer et al. 2009), which examined FOLFOX vs. FOLFOX plus cetuximab, the overall response increased from 36% to 46% with the addition of cetuximab. Patients with wt K-ras tumors had a significantly increased response rate (ORR 61% vs. 37%; $P = 0.011$), increased PFS, and a decreased risk of progression (HR 0.57; $P = 0.0163$). In the K-ras mutant population, patients who received cetuximab had a worse RR, and PFS – raising the possibility of a negative interaction in this group of patients.

COIN is a three-arm trial comparing continuous oxaliplatin and fluoropyrimidine-based chemotherapy with or without cetuximab, and a third arm of intermittent chemotherapy alone in the first-line treatment of advanced colorectal cancer. In the first two arms, treatment is given until progression, cumulative toxicity, or patient choice; in the intermittent arm, chemotherapy is stopped at 12 weeks in stable/responding patients and reintroduced following progression off treatment. The primary endpoint is OS. The trial has concluded recruitment with over 2,400 patients. Preliminary safety data (Maughan et al. 2007) showed fatigue, skin rash, and diarrhea, which were an issue particularly for patients receiving capecitabine. The COIN trial which will collect many tumor samples before and after treatment may help us to identify predictive markers of response.

COIN-B (COIN-Biological) is a multicenter, randomized Phase II trial of two research arms to complement the questions asked in the main UK COIN Trial.

The trial aims to randomize 136 patients between intermittent chemotherapy with continuous cetuximab and intermittent chemotherapy with intermittent cetuximab in first line treatment of metastatic colorectal cancer. The chemotherapy regimen combines oxaliplatin, 5-fluorouracil and folinic acid (OxMdG) repeated every 2 weeks as used in the FOCUS trial. Cetuximab is also administered at an initial loading dose of 400 mg/m2 followed by a weekly maintenance infusion of 250 mg/m2. The trial aims to clarify how biological therapy with cetuximab might be best added to chemotherapy, and whether intermittent cetuximab and chemotherapy is feasible. Other secondary outcome measures include the safety of cetuximab reintroduction (with regard to risk of allergic reactions), the proportion of patients achieving disease control (CR + PR + SD) at 24 weeks, OS, progression-free survival, response rates at 12, 24, and 36 weeks, and toxicity.

The ongoing CALGB 80405 compares FOLFOX plus cetuximab with FOLFOX plus bevacizumab with and without cetuximab (see above) for first-line MCRC, which was recently amended to include only patients with wt *K-ras* tumors (Table 4.7).

Second-Line Trials

Early phase II trials (Saltz et al. 2001, 2004) showed that cetuximab is active when added to irinotecan, in patients who have previously been refractory to, or have progressed after irinotecan chemotherapy either in combination or as a single agent, respectively. Partial responses were observed in 9–12% of patients, and a further 30% achieved stable disease. However, most patients who progressed showed evidence of treatment failure after only 6 weeks of therapy.

The BOND trial was performed in 329 such irinotecan refractory patients. The design randomized between cetuximab and cetuximab plus

Table 4.7. Current trials with cetuximab

Trial Name	No of Pts	Indication	Phase	Selection	Randomization	Primary endpoint
CRYSTAL	1,217	Metastatic – 1st line	III	EGFR expressing	FOLFIRI vs FOLFIRI + Cetuximab	PFS
EPIC	1,300	Metastatic – 2nd line	III	EGFR expressing	Irinotecan vs irinotecan + cetuximab	OS
OPUS	337	Metastatic 1st line	Randomized II	EGFR expressing	FOLFOX vs FOLFOX + Cetuximab	PFS
CAIRO 2 – should be moved to next table	755	Metastatic – 1st line	III		Capecitabine + Oxali + Bev vs Capecitabine + Oxali + Bev + Cetuximab	PFS
EVEREST	99	Metastatic – 2nd line	IV	EGFR expressing	Dose escalating study of cetuximab + Irinotecan	RR
CALGB 80405	2,289	Metastatic 1st line	III		FOLFOX or FOLFIRI + bev vs FOLFOX or FOLFIRI + cetuximab vs FOLFOX or FOLFIRI + bev + cetuximab	PFS
EORTC – BOS – should be moved to next table	100	Neoadjuvant – Resectable liver metastatic disease	Randomized II		Cetuximab, Leucovorin, Oxaliplatin and Flurourcail +/– bevacizumab	RR
NEW EPOC	340	Neoadjuvant – resectable liver metastatic disease	III	Restricted to Kras WT	OxMdG or CAPOX +/– cetuximab	PFS

irinotecan, in a 1:2 randomization (Cunningham et al. 2004). This study showed a significantly higher response rate for the combination of cetuximab and irinotecan over cetuximab alone – 22.9% vs. 10%, respectively, and a longer time to progression. The median OS was 8.6 months in the combination arm and 6.9 months in the cetuximab alone arm.

Cetuximab was generally well tolerated and did not significantly increase the frequency or severity of irinotecan-associated adverse events. This study also supported a correlation between response, survival, and severity of the rash.

The acneiform rash (grade 3/4 12%) appears to be expressed maximally after 3 weeks of treatment, and then often improves on further therapy. Hypersensitivity reactions are observed outside the US, but have been recorded in about 4.7% (2.2% grade 3/4) of patients. Fatigue is a major issue with cetuximab. However, side effects are very low when compared with standard cytotoxic chemotherapy. The study concluded that cetuximab as a single agent is effective in heavily pretreated MCRC patients, and that cetuximab in combination with irinotecan appears to overcome previous resistance to irinotecan.

More mature data regarding the role of irinotecan and cetuximab in irinotecan refractory patients have been recently reported in a multicenter international phase IV study (MABEL) with 1,461 patients (Wilke et al. 2008), 64% of whom had already received two or more chemotherapy lines. The study recruited patients from a large number of centers, to reflect the real-world more closely, rather than academic use of cetuximab and irinotecan treatment. Eligibility criteria required patients to have metastatic disease where tumor expressed EGFR. In 1123 evaluable patients, the subjective overall response rate was 20.1%, and the 12-week overall PFS rate was 61% (CI 58–64%). The median survival for the combination was 9.2 months (8.7–9.9) with grade 3/4 adverse events being diarrhea (20%), neutropenia (10%), asthenia (6%), and skin toxicity (including acne-like rash) (19%). Hypersensitivity reactions occurred in 1.5% of the patients (Wilke et al. 2008). The BOND and MABEL studies confirm the effectiveness of cetuximab in combination with irinotecan in the treatment of patients with MCRC, whose disease has failed prior irinotecan-based therapy.

However, more recently, it has been demonstrated that patients who have mutant-type K-ras are extremely unlikely to have any response to cetuximab or panitunimab (Lievre et al. 2008; Amado et al. 2008). There is a highly consistent message that the K-ras status can predict response to cetuximab and enhance PFS.

The EPIC second-line phase III study aimed to determine whether the addition of cetuximab to irinotecan prolongs survival in patients with MCRC previously treated with fluoropyrimidine and oxaliplatin (Sobrero et al. 2008). This study randomized 1,298 patients with EGFR-expressing MCRC who had failed or progressed on first-line fluoropyrimidine and oxaliplatin treatment failure to cetuximab (400 mg/m^2 day 1 followed by 250 mg/m^2 weekly) plus irinotecan (350 mg/m^2 every 3 weeks) or irinotecan alone. Primary endpoint was OS and secondary endpoints included PFS, response rate (RR), and QOL. Health-related QOL was determined using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire, version 3.0.

The study failed to deliver its primary endpoint as median OS was not significantly different between the treatments, i.e., 10.7 months for the combination of cetuximab and irinotecan and 10.0 months for patients receiving irinotecan alone. The failure to improve OS may reflect the fact that a large number of patients in the irinotecan arm received crossover cetuximab and irinotecan post study. However, the combination did significantly improve PFS (median, 4.0 vs 2.6 months, $p < 0.0001$) and RR (16.4% vs 4.2%, $p > 0.0001$). Interestingly, this is one of the vey few studies, which shows a significant improvement in global QOL ($P = 0.047$). Several functional scales were improved in patients who received the combination therapy, including pain, nausea, and insomnia. One surprising finding was that fewer patients reported diarrhea on the QOL assessment, although diarrhea was actually more common with the combination on the safety assessment. Clearly, there can be a major disparity in the side effects reported by physicians and patients.

Panitumumab

Panitumumab (formally known as ABX-EGF) is a fully humanized IgG2 monoclonal antibody against human EGFR. Panitumumab binds to a different epitope on EGFR, is more powerful,

and has a longer half life – and hence, can be administered weekly, 2 weekly, or 3 weekly, allowing flexibility in designing different schedules integrating into chemotherapy and radiotherapy. The humanized characteristic may avoid hypersensitivity reactions, and may also not act on antibody dependent cell cytotoxicity (ADCC) – which could be an additional tumor mechanism of action.

Recognized toxicity is similar to cetuximab in terms of an acneform rash, diarrhea, conjunctivitis, and hypomagnesemia. Phase II studies have explored its use in combination with irinotecan in first-line treatment (Berlin et al. 2007).

Response rates in phase II studies of panitumimab monotherapy following progression on irinotecan and oxaliplatin are in the region of 10% and stable disease in 38%, with the duration of response of 5.2 months (Hecht et al. 2007).

There are three phase III studies examining panitumumab in first- and second-line treatment. The PRIME (203) multinational phase III study (20050203) randomized 1,183 untreated advanced colorectal cancer patients to FOLFOX with or without panitumumab as a first-line treatment with the main endpoint as PFS (Siena et al. 2008). Patients were randomized to receive either panitumumab of 6 mg/kg plus FOLFOX4 every other week or FOLFOX4 alone. The secondary endpoints were OS, ORR, duration of response, time to progression, and safety. A pooled interim safety analysis of 903 patients (455 patients receiving Panitumumab plus FOLFOX4, 448 patients receiving FOLFOX4 alone) has reported acceptable toxicity but no efficacy outcomes (Siena et al. 2008).

A further randomized, multicenter, phase III study (20050181) evaluated the efficacy and safety of panitumumab in combination with chemotherapy in second-line treatment (Peeters et al. 2008). Patients were allowed one prior chemotherapy regimen for MCRC, and required radiographically documented disease progression while receiving the therapy for ≤ 6 months after receiving the last dose of prior first-line fluoropyrimide-based chemotherapy. Key exclusion criteria included prior irinotecan, anti-EGFR antibody, or EGFR inhibitor treatment. Patients were randomized to receive both panitumumab of 6 mg/kg and FOLFIRI every 2 weeks or FOLFIRI alone. The primary endpoints were PFS and OS, and the secondary endpoints were ORR, duration of response, time to progression, and safety. A pooled interim safety analysis of 1,097 patients (548 Panitumumab plus FOLFIRI, 549 FOLFIRI alone) also reported acceptable toxicity (Peeters et al. 2008), but efficacy data were not reported.

In addition, there is a phase IIIb study – the Panitunimab advanced colorectal cancer evaluation (PACCE) trial (Tol et al. 2009), which is described subsequently.

Studies with Two Targeted Agents Combined

Several studies have attempted to combine biologically targeted agents. The BOND 2 study was initially planned and undertaken when both cetuximab and bevacizumab were still under investigation as potential agents without proven utility in colorectal cancer. Patients who had progressed whilst receiving irinotecan, or within 6 weeks of receiving the last dose of therapy, were eligible. The trial was set out to evaluate both safety and feasibility of administering the two monoclonal antibodies, bevacizumab and cetuximab, concurrently together as a part of a strategy to explore the utility of the drugs both with chemotherapy and on their own as a targeted agent. Although the initial design called for 150 patients to be enrolled, the rapid registration of these antibodies meant that they could be obtained in clinical practice. Recruitment became more difficult, and the statistics were re-calculated for a target accrual of only 35 patients per arm. Eventually, a total of 83 patients were randomized with a median of 3, prior to chemotherapy regimens. In one arm, patients received irinotecan, cetuximab, and bevacizumab (ICB), and in the second arm, patients received cetuximab and bevacizumab without irinotecan (CB). The combination of irinotecan, cetuximab, and bevacizumab showed an improved TTP (7.9 vs 5.6 months), response rate (37% vs 20%), and (after a median follow up of 28 months) OS (14.5 vs 11.4 months) over cetuximab and bevacizumab with a toxicity profile very similar to that described with the single agents alone. This corresponds to a PFS of 4 months for cetuximab and irinotecan, and 1.6 months for cetuximab alone from the BOND study.

Hence, the combination of biologicals is feasible (BOND-2) and appeared effective, but financial considerations constitute a problem.

A small exploratory phase II study of 67 patients assessed mFOLFOX6 in combination with bevacizumab and cetuximab in a first-line treatment setting (Ocean et al. 2007). The endpoints were response rate, PFS, OS, and safety. In the 58 evaluable patients, 32 responded (55%) including three CRs and 29 PRs, and the median PFS was 9.6 months. Despite two treatment-related deaths, the regimen was considered to have an acceptable toxicity profile, to merit further evaluation.

The CAIRO 2 randomized 755 patients in a study, which compared capecitabine and oxaliplatin (CAPOX) plus bevacizumab with and without cetuximab in the first-line metastatic setting (Tol et al. 2009). An interim analysis of the first 400 patients did not raise concerns regarding excessive or unexpected toxicity in the arm containing cetuximab (Tol et al. 2008), although grade 3/4 toxicity was significantly higher in the cetuximab arm (81% vs. 72%) because of the skin effects. When skin toxicity (but not hand-foot syndrome) was excluded, toxicity was similar between the arms. Further data suggested that patients with mutated K-ras had a better outcome after treatment with CAPOX and bevcizumab when compared with other patients, but a worse outcome if cetuximab was added. The addition of cetuximab provided a similar response rate (40.6% vs. 43.9%, $P = 0.44$), a worse PFS (9.8 vs. 10.7 months, $P = 0.019$), and a similar OS (20.3 vs. 20.4 months, $P = 0.21$). This could suggest antagonism between cetuximab and bevacizumab in K-ras mutant patients (Tol et al. 2009).

Panitumumab advanced colorectal cancer evaluation (PACCE) phase III study tested in the first-line setting whether adding panitumumab to either FOLFOX or an irinotecan based regimen plus bevacizumab would extend PFS. Oncologists could choose to use an oxaliplatin- or irinotecan-based regimen. This study stopped early following a pre-planned interim analysis, because of excess toxicity and inferior efficacy in the oxaliplatin arm (Hecht et al. 2009). Response rates were similar at 45% and 46%, respectively. However, the panitumumab arm appeared inferior to the control arm in terms of PFS (10.0 vs. 11.4 months, respectively – HR, 1.27, 95% CI, 1.06–1.52). Median survival was 19.4 and 24.5 months for the panitumumab and control arms, respectively. There was an excess of SAEs (60% vs. 38% in the control arm), with more dose delays and dose reductions, and 27% of patients discontinued the treatment in the panitumumab arm. Patients who received irinotecan were fewer, but also showed worse PFS, more SAEs, and more acute toxicity. There was a significant difference in favor of the control arms regarding PFS and OS. K-ras analyses showed adverse outcomes for the panitumumab arm in both wild-type and mutant groups.

Hence, toxicity was exacerbated and efficacy was reduced by the combination of two antibodies with chemotherapy. This may have impacted on the efficacy by virtue of dose delays, dose reductions, and decreases in dose intensity. Alternative explanations posit cell cycle arrest or modifications of downstream targets required for the activity of bevacizumab. However, these authors found it difficult to correlate these findings with the fact that both cetuximab (Cunningham et al. 2004) and panitunimab has single-agent activity in refractory colorectal cancer (Van Cutsem et al. 2007). Hence, these two studies (CAIRO-2 and PACCE) do not support the use of cetuximab or panitumumab in combination with bevacizumab and irinotecan or oxaliplatin based chemotherapy (Table 4.8).

Neo-Adjuvant (Metastatic)

Novel strategies such as neoadjuvant chemotherapy to shrink liver metastases and inoperable colorectal primary cancers may now be feasible. These strategies may offer the hope of a potential cure to a small minority of patients. There are a number of trials evaluating the safety and efficacy of bevacizumab in the treatment of MCRC with either unresectable or potentially resectable liver disease.

There is a current neo-adjuvant randomized double-blind international phase II study (MO 18725) evaluating the safety and resectability of colorectal cancer liver metastases, following treatment with bevacizumab in combination with fluoropyrimidine-based chemotherapy. Patients are randomized into two arms: one arm receives seven cycles of FOLFOXIRI chemotherapy with bevacizumab every 2 weeks, and the other seven cycles of FOLFOX and bevacizumab. In addition to evaluating the benefit of neoadjuvant bevacizumab, this trial is also investigating the safety and efficacy of FOLFOXIRI vs FOLFOX. The

Table 4.8. Phase II and randomized phase III studies exploring addition of both bevacizumab and cetuximab to combination chemotherapy

TRIAL	No of pts	Indication	Phase	Randomization	Primary endpoint
BOND2	74	Metastatic – Irinotecan refractory	II	Cetuximab/bevacizumab/ Irinotecan vs cetuximab/ bevacizumab	RR and PFS
OCEAN	67	Metastatic – 1st line	II	FOLFOX6 + bevacizumab and cetuximab	RR, PFS and OS
PACCE – should we remove this as it is panmab not cetuximab	1053	Metastatic – 1st line	III	Irinotecan or oxaliplatin based chemotherapy + bevacozumab +/– panitunimab	PFS – this has stopped early due to excess toxicity
CAIRO 2	755	Metastatic – 1st line	III	Capecitabine + Oxali + Bev vs Capecitabine + Oxali + Bev + Cetuximab	PFS
EORTC – BOS	100	Neoadjuvant – Resectable liver metastatic disease	III	Cetuximab, Leucovorin, Oxaliplatin and Flurourcail +/– bevacizumab	RR

primary objective is the rate of surgical complications at 3 months.

The Austrian Society of Surgical Oncology has examined the resectability rate of colorectal liver metastases after neo-adjuvant bevacizumab in potentially resectable metastatic colorectal cancer. In this study, the patients were treated for six cycles of XELOX and five cycles of bevacizumab. Performing surgery 2 weeks after the last capecitabine administration, allows for 5 weeks between the last bevacizumab administration and surgery. Further chemotherapy with six cycles of bevacizumab and XELOX is delivered after surgery. The primary objective in this study is the resectability rate after neo-adjuvant bevacizumab with secondary outcome measures of surgical complications, overall response rate, recurrence-free survival, and OS. They have planned to enroll 40 patients into the study and recruitment commenced on January 2007.

The BOS study is a phase II study from the EORTC, which randomizes patients with liver metastases deemed operable to either a combination of FOLFOX and cetuximab, or to the same combination and bevacizumab. Hence, all patients receive a biological agent and some will receive both cetuximab and bevacizumab. The primary endpoint is response rate (pre-operative response rate) and safety. Secondary outcomes are PFS, pathological resection rate, and OS.

Initially, no assessment of K-ras mutation status was required; hence, in the light of evidence regarding the lack of efficacy in K-ras mutant tumors, the study is currently suspended.

NEW EPOC is a much larger randomized phase III study performed by the NCRI in the UK, which aims to enrol 340 patients. The study randomizes patients with liver metastases deemed operable to either a combination of FOLFOX and FOLFOX plus cetuximab. The primary endpoint is PFS. Secondary endpoints are in terms of toxicity and RR. Assessment of K-ras mutation status is now required.

Although current data suggests that K-ras status can improve patient selection, not by enrichment, but by defining a group that will be resistant to cetuximab or panitunimab. All the abovementioned studies stopped recruitment in the light of the recent K-ras data, and now either mandate K-ras wild-type status as a requirement for randomization or have increased their sample size to account for the loss of power implicit in the knowledge that tumors with mutant K-ras (approximately 40% of patients) will not benefit from an EGFR inhibition such as cetuximab or panitumumab.

The wt K-ras is an imperfect biomarker, because only 30–50% of patients respond to cetuximab, or have improved PFS or OS. Other studies have confirmed the validity of K-ras

wild-type expression (De rook 2008). Using samples from 113 patients, refractory to irinotecan in four clinical trials (EVEREST, BOND, SALVAGE and BABEL) the authors showed that median OS is better in wt K-ras patients (43 vs 27.3 weeks). Also in wt K-ras patients, there was a significantly better OS when compared with all other patients (74.9 vs 30.6 weeks), when a clear clinical response at 6 weeks was observed.

Even better selection may be possible in the future. Colorectal cancer patients with a mutation in BRAF gene will also not benefit from cetuximab or panitumumab (Di Nicolantonio et al. 2008). BRAF mutations may account for a further 10–12% of patients with MCRC. Recent reports (Khambata-Ford et al. 2007; Jacobs et al. 2008 EORTC/AACR) also suggest that the expression of the ligands epiregulin and amphiregulin mRNAs is higher in patients who respond to cetuximab and irinotecan chemotherapy combinations, and is significantly correlated with PFS and OS in patients with K-ras wild-type status ($p < 0.001$). Early data also suggest that loss of PTEN expression (Frattini et al. 2007; Loupakis et al. 2008) and PIK3CA mutations in colorectal cancer (Sartore-Bianchi et al. 2009) may also be associated with a lack of response to cetuximab. Hence, in the future, a much more precise algorithm that can predict response to cetuximab or panitumumab should be available.

The CELIM study included only patients with unresectable disease confined to the liver. Patients were randomized between two different standard first-line chemotherapy regimens of FOLFOX and FOLFIRI, and the same regimen combined with cetuximab (Folprecht et al. 2008 abstract 510). A response rate of 79% in patients with wt K-ras tumors was observed, allowing resection in 43% and complete resection (R0) in 34%. This study confirms the utility of adding cetuximab to standard chemotherapy in wt K-ras tumors to facilitate a potentially curative resection.

In a multi-institution, phase II study of the combination of FOLFOX, bevacizumab and erlotinib as first-line therapy for patients with MCRC, we observed an 86% grade 3/4 toxicity rate, which led to a higher than anticipated drop-out rate before progressive disease (Meyerhardt et al. 2006). The toxic effects and drop-out rate limit any conclusions regarding the efficacy of the regimen. The response rate of 34% appears lower than anticipated with FOLFOX and bevacizumab alone. Even after exclusion of patients who did not remain on trial for at least 2 months, an RR of 48% does not appear appreciably different than such a regimen without erlotinib. Others have also found higher than expected toxic effects with this combination (Spigel et al. 2006).

Few results from clinical trials are available for the treatment with tyrosine kinase inhibitors of EGFR in MCRC patients. The tyrosine kinase inhibitors, gefitinib (IRESSA) and erlotinib (TARCEVA), have shown significant treatment-related toxic effects without a clear message of additional benefit. Gefitinib that received FDA approval for treatment in metastatic or locally advanced non–small-cell lung cancer was given in combination with FOLFOX4 as first-line treatment in patients with MCRC with a PFS of 7.8 months and an OS of 13.9 months; however, gefitinib failed to show a survival benefit in comparison with other first-line regimens. The efficacy of other agents such as vatalanib or sunitinib still needs to be validated in this setting.

Third-Line Studies

Results from numerous phase II and phase III studies have demonstrated an intrinsic activity for cetuximab in the treatment of MCRC when compared with best supportive care.

One study of 346 patients refractory to irinotecan, fluoropyrimidines, or oxaliplatin and EGFR positive patients achieved an RR of 12% with cetuximab monotherapy (Lenz et al. 2006).

In a recent international randomized phase III study in 463 patients with positive EGFR expression, who were refractory to 5FU, oxaliplatin, and irinotecan (Van Cutsem et al. 2007), the best supportive care was compared with the fully humanized mononclonal antibody to EGFR (Panitumumab) of 6 mg/kg every 2 weeks. The primary endpoint was PFS, with secondary endpoints of RR, safety, and OS. A significant improvement in PFS was seen in the panitumumab arm (median 7.3 vs. 8 weeks, $p < 0.0001$, and mean 8.5 vs. 13.8 weeks). After a 12 month minimum follow-up, 22 patients (10%) in the panitumumab arm had an objective response vs. none in the best supportive care (BSC) arm, and 27% had stable disease. Median survival was 6.4 months, but there was no difference between the arms, possibly because crossover

was allowed for panitumumab after documented disease progression.

Patients with mutated K-ras did not respond to panitumumab. In contrast, patients with wt K-ras achieve higher response rates and a longer PFS (Freeman et al. 2008). However, to date, the relevance of K-ras as a biomarker for panitumumab is confined to the monotherapy setting (Peeters et al. 2009).

A retrospective analysis of the NCIC CTG C0–17 study using 394 archived tumor samples (Karapetis et al. 2008) showed that patients with wt K-ras treated with cetuximab plus BSC had a statistically significant increase in OS and PFS when compared with those who received BSC alone [OS 9.5 vs. 4.8 months HR = 0.55 ($P = < 0.001$) and PFS 3.7 vs. 1.9 months HR = 0.40 ($P = < 0.001$)]. In contrast, the 164 patients with mutant K-ras showed no difference in OS or PFS, irrespective of whether they received cetuximab or not (4.5 vs. 4.6 and 1.8 months in both, respectively). The CO-17 Phase III randomized study with no crossover shows that cetuximab alone offers a significant survival benefit over BSC alone ($P = 0.0046$, HR 0.77).

Conclusion

Oncologists have to balance risk vs. benefit, and this is increasingly difficult as the patient population becomes older and begins to demonstrate co-morbidity. This approach will be further refined with advances in pharmacogenomics. Yet, we still have a long way to go from knowing the best first-line option in terms of cytotoxic chemotherapy, the duration of therapy, and whether the patient will be disadvantaged by a complete break from treatment, or should have maintenance chemotherapy. Currently, in addition to conventional cytotoxic drugs, there are numerous targeted agents that impact on the growth factors and their receptors, signal transduction agents, extra cellular factors, i.e., angiogenesis and matrix metalloproteinases, and other miscellaneous biological switches. Many have reached the clinical trial stage. Phase III trials demonstrate a relatively modest effect of cetuximab, bevacizumab, and panitumumab on PFS and OS. Some have questioned whether the benefits of these targeted agents are clinically meaningful, and surprisingly, we appear to have demonstrated antagonistic effects for some combinations. However, another major unresolved question remains on whether maintenance treatment with a biological agent can be effective in preserving a good QOL?

Defining who does and does not benefit from these treatments is partially within our grasp. The identification of predictive markers to anti-angiogenic therapy has proved elusive, but is critical to our understanding of how best to use such treatment. In contrast, there is a very strong suggestion that K-ras mutations may preclude responses to cetuximab and panitumumab. In addition, Braf mutations, PI3K, and PTEN mutations may further clarify resistance. Also, the activated ligands, epiregulin and amphiregulin, may predict response to EGFR inhibitors. If these predictions can be validated in prospective clinical trials, then we are probably taking the first tentative steps towards the oncologists's dream of an individualized selection of therapy and a more rational approach to the use of biologic as well as cytotoxic agents. In this way, it may be possible to maximize the effectiveness and minimize toxicity and still keep costs under control in treating MCRC.

We also have a very strong biological correlate in that patients who do not develop a skin rash are unlikely to benefit from these agents. In contrast, the efficacy of bevacizumab appears to be unrelated to K-ras status, and at the present time, there are no predictive factors for efficacy or resistance, and no biological correlates. In the CONFIRM studies, which used an oral VEGF inhibitor, there appears to be a relationship between response and changes in the diastolic blood pressure.

However, we still have insufficient understanding with respect to the biology of these targeted agents to rationally plan their integration, at the most appropriate time and in the most appropriate combinations. Hopefully, in the future, other specific patterns of disease or genetic and molecular profiles may allow for a more individualized selection of the available drugs and biological agents tailored to each patient.

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5

Current Clinical Trials in Radiotherapy for Rectal Cancer

Aroor Rao and Maher A. Abbas

Work-Up of Patients with Rectal Cancer

Initial evaluation of patients with rectal cancer should include careful history and physical examination. Attention should be given to symptoms specific to rectal cancer, such as spontaneous passage of red blood with or without defecation, bloody mucous discharge, change in bowel habit and stool caliber, constipation, diarrhea, tenesmus, and incomplete emptying. Some patients may present with genitourinary symptoms or pain in the buttocks or perineum. It is important to obtain a personal and family history of colorectal cancer, colonic polyps, or inflammatory bowel disease.

Complete physical examination should include palpation of the abdomen and groin, and digital rectal examination with special attention to the distance from anal verge to distal margin of the lesion, the position and the size of the tumor, and the presence of ulceration and fixation to the surrounding structures. Rigid proctosigmoidoscopy allows for direct visualization of the tumor for biopsy, provides assessment of the degree of luminal obstruction, and confirmation of distance from anal verge. Female patients should undergo a rectovaginal examination especially in the presence of anterior tumors.

A complete colonoscopy is done to rule out synchronous neoplasms. Tattooing the distal margin of the tumor prior to neoadjuvant chemoradiation is helpful in patients with lesions of the very low rectum. Endorectal ultrasound (EUS) is performed to determine the lesion's depth of invasion and to evaluate for regional node metastasis as well as define sphincteric involvement, which may preclude sphincter preservation (Fig. 5.1). Sensitivity and specificity of EUS approaches 94 and 96% for invasion into the muscularis propria, 67 and 78% for lymph nodes positivity (Bipat et al. 2004; Chun et al. 2006; Massari et al. 1998), respectively. Interobserver evaluation of T3 and T4 lesions has been shown to be consistent.

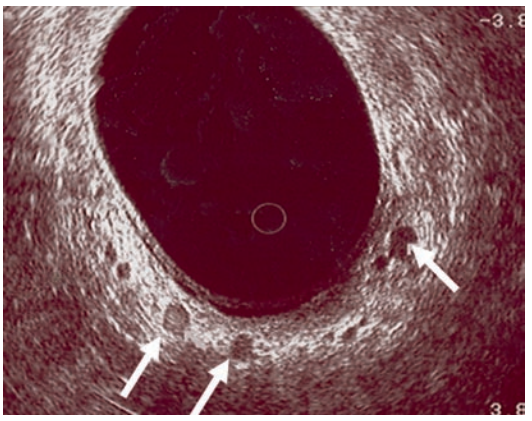

Figure 5.1. Endorectal ultrasound study reveals involved perirectal lymph node (*arrow*).

A. P. Zbar and S. D. Wexner (eds.), *Coloproctology*,
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However, T1 and T2 lesions have shown greater interobserver variation (Burtin et al. 1997). High-resolution pelvic MRI is an alternative to EUS for the evaluation of depth of invasion and extent of circumferential spread. The radial margin can be predicted accurately in approximately 94% of patients undergoing MRI (Brown et al. 2003; Lahaye et al. 2005; MERCURY Study Group 2006). However, MRI evaluation of regional nodal metastasis is less accurate than EUS.

Laboratory tests include carcinoembryonic antigen level (CEA), complete blood count, basic blood chemistry, and liver and renal function tests. Computed tomography (CT) scan of the chest abdomen and pelvis is done to rule out metastatic disease to organs such as liver and lungs. The CT scan is inadequate to evaluate the depth of invasion or small nodal metastasis, but it can demonstrate large involved mesorectal lymph nodes (Fig. 5.2). In addition, it can be useful in delineating the invasion of larger tumors into adjacent organs and/or pelvic side wall involvement (Bipat et al. 2004; Kulinna et al. 2004; Matsuoka et al. 2003; Wolberink et al. 2007). PET/CT is still considered experimental for the initial work-up of rectal cancer, although it is increasingly used for the evaluation of recurrent disease particularly when radiotherapy has been utilized (Siegel et al. 2008).

Staging

The majority of rectal cancers (>90%) are adenocarcinoma. Histologic variations of adenocarcinoma include mucinous tumors in 20% of patients, with 2% being signet ring variant. Squamous cell carcinoma, adenosquamous carcinoma, carcinoid, lymphoma, and leiomyosarcoma are rare. The clinical staging is designated as clinical tumor nodal metastasis (cTNM) and is based on the history and physical findings, imaging, endoscopy, and biopsy and laboratory findings. Pathologic staging is based on examination of the surgical specimen and is designated as pTNM. Use of neoadjuvant therapy frequently results in downstaging. Table 5.1 shows the 2002 American Joint Committee Cancer Tumor Node Metastasis staging system (Greene et al. 2002).

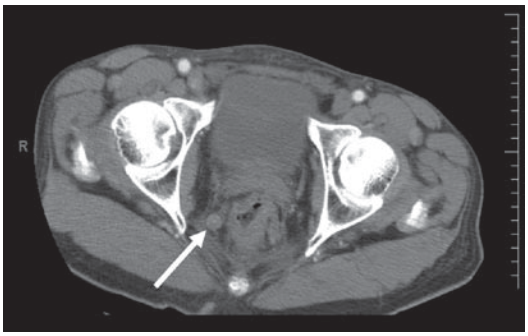

Figure 5.2. CT scan shows rectal mass with adjacent enlarged mesorectal node (*arrow*).

Prognosis

The TNM staging is an important predictor of prognosis in patients with rectal carcinoma. Patients with stage I or II disease are considered as low risk for recurrent disease, while those with stage III disease are high risk. The overall survival and relapse-free survival at 5 years are 76 and 73% for low risk patients and 55 and 48% for high risk patients (Platell and Semmens 2004; Tepper et al. 2002), respectively. Circumferential margin status at the time of resection predicts local recurrence at the anastomosis as well as the risk for distant metastasis. A positive margin following neoadjuvant therapy indicates worse prognosis (Baxter and Garcia-Aguilar 2007; Nagtegaal and Quirke 2008). CEA level greater than 5 ng/mL preoperatively is associated with a higher relapse rate (Yoon et al. 2007; Kim et al. 2006). Patients with poorly differentiated lesions, lymphovascular invasion, and mucinous histologic or signet ring subtype carry worse prognosis. Pelvic nodal metastasis and deep intramural invasion are predictors of locoregional recurrence.

Adjuvant Therapy

Surgical excision remains the primary treatment modality for rectal cancer. Figure 5.3 outlines the treatment algorithm. Early lesions

Table 5.1. Colorectal cancer AJCC, 2002 TNM staging

Primary tumor [T]	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues
T4	Tumor directly invades other organs or structures and/or perforates visceral peritoneum (includes invasion of other segments of colon)
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–3 regional lymph nodes
N2	Metastasis in ≥4 regional lymph nodes
	(Tumor nodules in the pericolonic adipose tissue without evidence of residual lymph node are classified as a regional lymph node metastases)
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
IIA	T3	N0	M0
IIB	T4	N0	M0
IIIA	T1–T2	N1	M0
IIIB	T3–T4	N1	M0
IIIC	Any T	N2	M0
IV	Any T	Any N	M1

From Colon and Rectum. In: Greene et al. 2002.

of mid to low rectum such as carcinoma in situ or T1 tumors (stage 0 or I) with good histologic features (well differentiated, no lymphovascular invasion, or mucinous subtype) can be addressed by local excision and close clinical follow-up as long as a negative margin is achieved at time of resection. Technical considerations for local excision include distance of lesion from anal verge (<8 cm), anterior vs. posterior anatomic location, size of the lesion (<3 cm, <30% of rectal circumference), and patient's body habitus. Adjuvant therapy is recommended for stage II rectal cancer or greater disease.

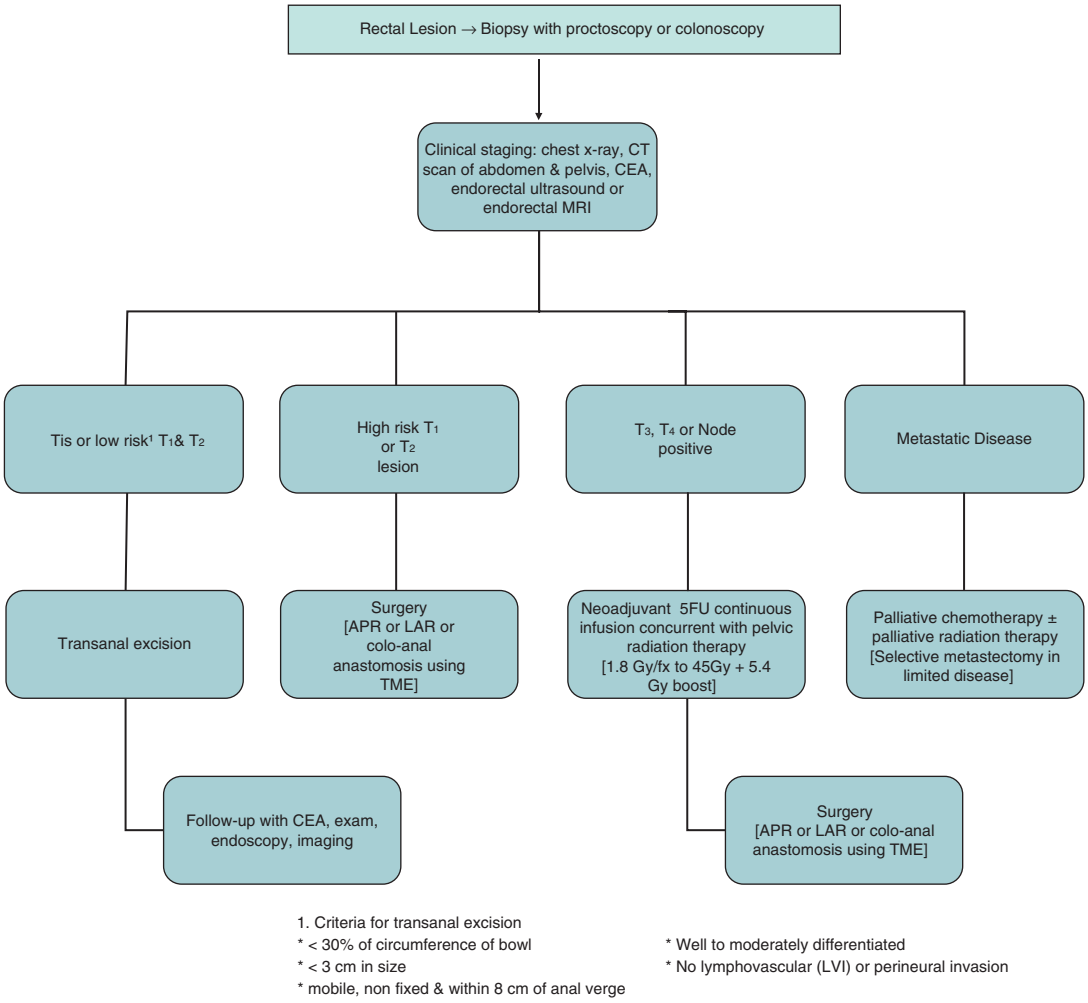

Figure 5.3. Invasive rectal cancer and treatment algorithm.

Adjuvant Postoperative Radiotherapy Without Chemotherapy

This approach was mostly used before 1990. The advantage of adjuvant treatment is accurate pathologic staging of the surgical specimen. The disadvantage of postoperative radiation therapy is increased bowel toxicity, potentially hypoxic post surgical bed, and the use of a larger radiation field in patients who have undergone abdominoperineal resection to include the perineal scar. Two nonrandomized clinical trials from Massachusetts General Hospital and MD Anderson have shown decrease in local failure rates of 4–31% in pT3-4 N0 M0 disease and 8–53% in stage T3-4 N1 M0 disease in patients who received 45–55 Gy postoperatively (Willett et al. 1992; Romsdahl and Withers 1978). There were five randomized trials using postoperative radiation therapy alone in stages pT3 and /or N1-2 rectal cancer (Balslev et al. 1986; Gastrointestinal Tumor Study Group 1985; Arnaud et al. 1997; Medical Research Council Rectal Cancer Working Party 1996; Fisher et al. 1988). None have showed a survival advantage. The NSABP R01 trial showed

local failure of 16% in the irradiated group when compared with 25% in the surgery alone group ($p = 0.06$) (Fisher et al. 1988). In the Medical Research Council Trial, the local failure rate was 21% in the irradiated group when compared with 34% in the surgery alone group (Medical Research Council Rectal Cancer Working Party 1996). In summary, postoperative radiation therapy in patients with rectal carcinoma improves the local pelvic control. However, it has no impact on distant metastasis, disease-free survival, or overall survival. Currently, postoperative adjuvant radiation therapy is considered inadequate.

Intensive Short Course Preoperative Radiotherapy Without Chemotherapy

The Swedish rectal cancer trial randomized 1,168 patients with clinically resectable rectal cancer to receive 25 Gy in five fractions, followed by surgical resection 1 week later vs. surgical excision alone (Fisher et al. 1988; Swedish Rectal Cancer Trial 1997). Patients who received preoperative radiation had lower local recurrence rates (12 vs. 27%, $p < 0.001$) and higher 5-year survival rates (58 vs. 48%, $p = 0.004$). This trial has been criticized for lacking total mesorectal excision (TME) in the surgery alone arm, leading to a high failure rate in surgery alone as well as a moderately high complication rate in Dukes' A cases, who would not normally receive advent preoperative irradiation.

The Dutch CKVO 95-04 trial randomized 1,805 patients with clinically resectable (cT1-3) disease to surgical excision alone using TME or to preoperative radiation (25 Gy in five fractions), followed by TME (Kapiteijn et al. 2001; Gerard et al. 2006). The preoperative radiation significantly reduced local recurrence (8 vs. 2%, $p < 0.001$). However, there was no significant difference in the 2-year survival between the two groups. The 5-year failure rate was higher in the surgery alone group (10.9 vs. 5.6%, $p = <0.001$). The greatest benefit was noted in patients with mid rectal tumors, a negative circumferential margin, and positive lymph nodes. The acute radiation toxicity in this trial included 10% neurotoxicity, 29% perineal wound complications, and 12% postoperative anastomotic leaks. Eighty percent of the patients who developed anastomotic leaks required additional surgical intervention which resulted in an overall 11% mortality. Even though the Dutch CKVO trial did not show survival benefit, the cost-benefit analysis suggested cost benefit in reducing local recurrence.

It is difficult to compare local control and survival results of short intensive preoperative radiation with conventional preoperative chemoradiation therapy, owing to selection bias in favor of series using short-course preoperative radiation. Patients included in conventional preoperative chemoradiation group were patients with T3 and/or N + disease, when compared with cT1-3 disease in short-course preoperative radiation trial.

Preoperative (Neoadjuvant) Chemoradiotherapy

The concurrent use of preoperative radiation therapy with 5 fluorouracil (5-FU) based chemotherapy has gained wide acceptance as the standard adjuvant therapy in the United States. This combined modality treatment has several potential advantages, including improved response to radiotherapy owing to more oxygenated cells, increased chance for complete pathologic resection (R0), increased likelihood of sphincter sparing, and improved patient tolerance owing to a smaller volume irradiated, sparing the small bowel from higher dosage. In theory, chemotherapy can be better delivered owing to better vasculature as well as earlier systemic treatment of occult metastatic disease.

The German Rectal Cancer Study Group evaluated preoperative vs. postoperative chemoradiation therapy (Sauer et al. 2004). In this study, 823 patients with clinical T3/T4 or N + rectal cancer were randomized to two groups. Group I underwent preoperative radiation of 50.4 Gy with concurrent 120 h infusion of 5-FU during weeks 1 and 5 of radiation followed by surgery and four cycles of 5-FU postoperatively. Group II received postoperative chemoradiation with an additional 5.4 Gy boost to the tumor bed. Local failure rates were higher in the postoperative group (13 vs. 6%, $p = 0.006$). Furthermore, group I experienced less toxicity than group II. There was no difference in overall 5-year survival (75 vs. 74%, $p = 0.8$).

The European Organization for Research and Treatment of Cancer EORTC 22921 trial evaluated neoadjuvant chemotherapy and radiation,

as well as the use of adjuvant chemotherapy (Bosset et al. 2006). In this trial, 1,011 patients with T3/T4 rectal cancer were randomized to five treatment groups: preoperative radiation, preoperative chemotherapy, preoperative radiation and chemotherapy, preoperative radiation and chemotherapy followed by postoperative chemotherapy, or preoperative chemotherapy and postoperative chemotherapy. Radiotherapy consisted of fractionated 45 Gy given over 5 weeks. Chemotherapy consisted of 5-FU + Leucovorin (LV) for two cycles of 5 days in the preoperative arms and additional four cycles in the postoperative arms. The 5-year local recurrence rate was low in any arm receiving chemotherapy when compared with the arms receiving radiation alone (8.5 vs. 17%, $p = 0.002$).

The French rectal trial (FFCD 9203) randomized 733 patients with stage T3/T4 NX rectal cancer to preoperative radiation (45 Gy over 5 weeks) with or without 5-FU + LV during the 1st and 5th weeks of radiation (Gerard et al. 2004). All patients were treated with surgery followed by postoperative 5-FU + LV. The 5-year local recurrence rate was lower in the preoperative chemoradiotherapy arm when compared with the radiation alone arm. There was no significant difference in the overall survival and sphincter preservation between the groups.

Postoperative Chemoradiotherapy

The Intergroup INT-0114 trial evaluated 1,695 patients with T3/T4 or N + rectal cancer treated postoperatively with sandwich chemotherapy and radiation, consisting of two cycles of chemotherapy followed by concurrent chemoradiation (45 Gy with a boost to 50.4–54 Gy) and two final cycles of chemotherapy (Tepper et al. 2002). The chemotherapy regimen consisted of bolus 5-FU, 5-FU + LV, 5-FU + Levamisole, and 5-FU + LV + Levamisole. With the different modulation of 5-FU, there was no difference in overall survival, disease-free survival, or local control. The INT-0144 studied postoperative radiotherapy along with bolus 5-FU vs. modulated bolus vs. continuous infusional 5-FU in 1971 patients with T3/T4 or N + rectal cancer (Thomas and Lindblad 1988). Similar to INT-0114, there was no difference in overall survival, disease-free survival, or local failure.

The Gastrointestinal Tumor Study Group (GITSG) GI-7175 randomized 227 patients with Dukes B and C (T3/T4, N0 or N+) rectal cancer to surgery alone vs. postoperative chemotherapy (5-FU/Methyl CCNU [semustine]) vs. postoperative radiation of 40–48 Gy vs. postoperative chemoradiation (40–44 Gy with 5-FU) (Thomas and Lindblad 1988). The results of this study showed a significant improvement in the combined modality treatment over no adjuvant therapy for time to recurrence ($p = 0.005$) and survival ($p = 0.01$). The Intergroup trial INT-86-47-51 showed that continuous 5-FU infusion was superior to bolus 5-FU with less tumor relapse (37 vs. 47%, $p = 0.01$), distant metastasis (31 vs. 40%, $p = 0.03$), and improvement in overall survival (O'Connell et al. 1994). In the NCCTG 79-47-51 trial, patients with T3/T4 or N + disease were randomized to postoperative radiation alone vs. 5-FU based chemoradiation (Krook et al. 1991). During a median follow-up of 7 years, the combined regimen reduced overall recurrence by 34%, local recurrence by 46%, distant metastasis by 37%, cancer deaths by 36%, and overall deaths by 29%. As a result of this trial and the GITSG 7175 trial, the National Cancer Institute (NCI) Consensus Conference concluded in 1990 that combined modality therapy was the standard postoperative adjuvant treatment for patients with T3 and/or N1/N2 disease.

Postoperative Adjuvant Chemotherapy Without Radiation

The 1990 NCI Consensus Conference recommendation for postoperative chemoradiotherapy was based on trials where neither TME technique nor histologic examination of greater than 12 lymph nodes was required. Nissan and associates reported on results in 100 patients with cT2/T3N0 disease who underwent TME alone and had at least 12 nodes examined (Nissan et al. 2006). In the subset of 49 patients with pT3N0 disease, the overall local recurrence rate was 4%. For the total group, local recurrence was significantly higher in those with lymphatic vessel invasion (32 vs. 6%, $p = 0.006$) and elevated (>5.0 ng/mL) preoperative CEA level (21 vs. 0%, $p = 0.004$). Reports from Massachusetts General Hospital and Memorial Sloan-Kettering have identified a favorable subset of patients with pT3N0 disease who, following surgery alone, had 10-year actuarial local recurrence

rates of less than 10% (Willett et al. 1992; Romsdahl and Withers 1978). Leibold and associates treated 121 patients with preoperative chemoradiotherapy and found that the incidence of metastatic disease was higher among the patients who had positive nodes in the proximal pelvis (above L5/S1) when compared with positive nodes elsewhere (Leibold et al. 2008).

These data provide further evidence that patients with upper rectal cancer, who undergo TME, who have at least 12 nodes examined, and who have pT3N0 disease, probably do not require or benefit from chemoradiotherapy and can be treated with postoperative chemotherapy alone. About 3–4% benefit of local control with radiation may not be worth the risk, especially in women of reproductive age. However, the subset of patients with pT3N0 tumors with either adverse pathologic features and/or fewer than 12 lymph nodes in the surgical specimen should still receive postoperative chemoradiotherapy (Willett et al. 1999; Merchant et al. 1999).

Treatment of Locally Advanced Unresectable Rectal Cancer

With the exception of rare "suture line only recurrence," patients with unresectable primary or locally recurrent disease should be considered for chemoradiotherapy (45–50.4 Gy with concurrent 5-FU). The role of surgery depends on the response to preoperative chemoradiation therapy, the possibility of obtaining clear margins, and the patient's willingness to undergo radical surgery. About 50–90% of patients who receive chemoradiation under such circumstances will be able to undergo resection with the possibility of negative margins, depending on the degree of tumor fixation. Still, 24–55% of patients will develop local recurrence. About 10% of patients with locally advanced rectal cancer require pelvic exenteration to obtain negative margins (Law et al. 2004). Tumor invasion into the prostate, the base of bladder, the uterus, or the vagina requires en bloc resection to achieve negative margins. Midline posterior tumors adherent to or invading the distal sacrum may be resectable for cure with an abdominosacral approach. The 5-year survival ranges from 33 to 50%, with significant morbidity and mortality of up to 6% (Law et al. 2004; Sagar et al. 2009).

Intraoperative radiation therapy (IORT) has been used in recurrent and locally advanced rectal cancer. The advantage of IORT is that radiation can be delivered at the time of surgery to the site with highest risk for local failure, while decreasing the dose to the surrounding normal tissues. Similar benefit can be achieved by using brachytherapy with high dose rate technique (HDR). In general, most series have used 10–20 Gy. Nakfoor and colleagues used IORT in 73 patients with locally advanced rectal cancer, where tumor adherence to pelvic structures or residual disease was present at the time of resection (Nakfoor et al. 1998). All the patients also received preoperative radiotherapy mostly with concurrent 5-FU. At 5 years, the local control was associated with the extent of resection. Complete resection and IORT resulted in local control and disease-specific survival of 89 and 63%, respectively, when compared with 65 and 32% for residual disease. The 5-year complication rate was 11%, with the majority of complications being infectious and/or related to poor healing and tissue breakdown. Alektier and associates reported their experience with 74 patients with recurrent rectal cancer, who received intraoperative HDR brachytherapy (10–18 Gy) (Alektier et al. 2000). Less than 50% of the patients received external beam radiotherapy or 5-FU-based chemotherapy. All patients had complete gross resection, but 21 of the 74 patients had microscopic positive margins. The 5-year local control and survival rate were 39 and 23%, respectively.

Radiation Therapy Simulation and Field Arrangement

The patient is planned in the prone position on a belly board to exclude as much of the small bowel as possible. The anal verge, vagina, and perineal scar, if present, are marked with radiopaque markers. The planning CT study is done with the patient in the treatment position to define gross tumor volume (GTV) and the planning target volume (PTV). Oral contrast is given to outline the small bowel. Photons of 10 MV (million electron volt) or higher is used, and we typically use a three pelvis field arrangement (two lateral and a posterior). The rectal field is designed to cover the tumor with margins, presacral and internal iliac nodes (including external iliac nodes for T4 tumors).

The field arrangement for the whole pelvis includes (PA field) borders: superior = L5-S1, inferior = 3 cm below the initial tumor volume or inferior obturator foremen, whichever is most inferior; and lateral = 1.5 cm outside the pelvic inlet. Whole pelvis lateral field borders: posterior = posterior to bony sacrum; anterior = anterior pubis if T4, and mid pubis if T3. Efforts are made to avoid flashing the posterior skin, unless patient's status is post abdominoperineal resection, in which case the perineal scar is included in the field. Corner blocks are used to protect the small bowel. A boost field should include the tumor plus a 2–3 cm margin superior, inferior, lateral, anterior, and posterior margin, to include the sacral hallow (Figs. 5.4–5.7).

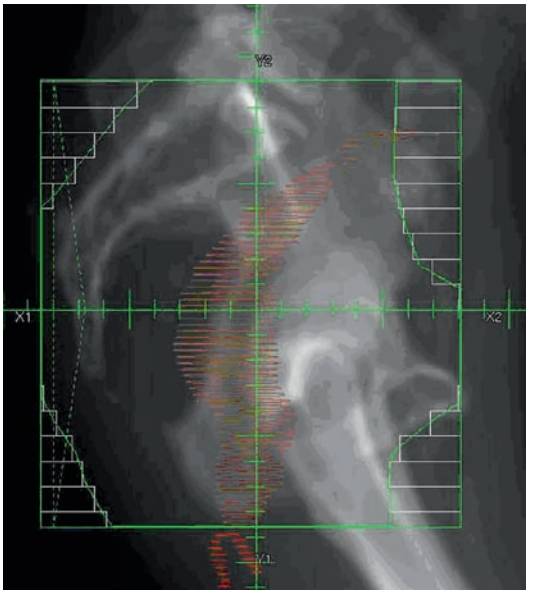

Figure 5.5. Lateral pelvic radiation field. Rectum contoured in *rust* color. Anal verge contoured in *red.*

Current Dose and Fractionation at Kaiser Permanente, Southern California

Our regional radiation rectal clinic at Kaiser Permanente, Los Angeles, provides consultative services and treatment for patients referred from 13 Kaiser Foundation Hospitals. In 2009, our health plan membership in Southern California has exceeded 3 million patients. Treatment of primary rectal carcinoma is uniform and standardized within our organization. Patients with preoperative stage II and III, mid to low rectal carcinoma receive a standard fractionation (1.8 Gy/fraction) for a total of 45 Gy to the whole pelvis, followed by a boost of 5.4 Gy to the boost field outlined above (total of 50.4 Gy). The concurrent chemotherapy consists of continuous 5-FU of 225 mg/m^2 over 24 h, 7 days a week during the entire course of radiation therapy. Oral 5-FU (Zeloda®) is used in some patients.

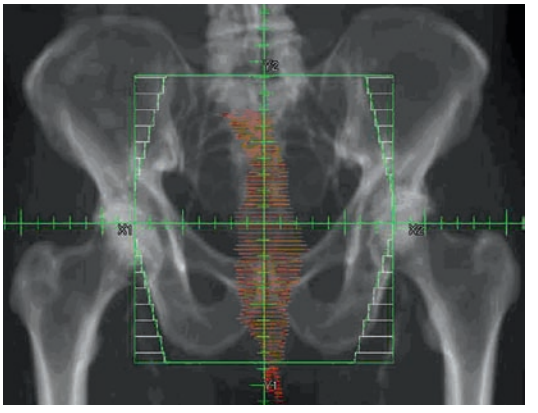

Figure 5.4. Anterior pelvic radiation field. Rectum contoured in *rust* color. Anal verge contoured in *red*.

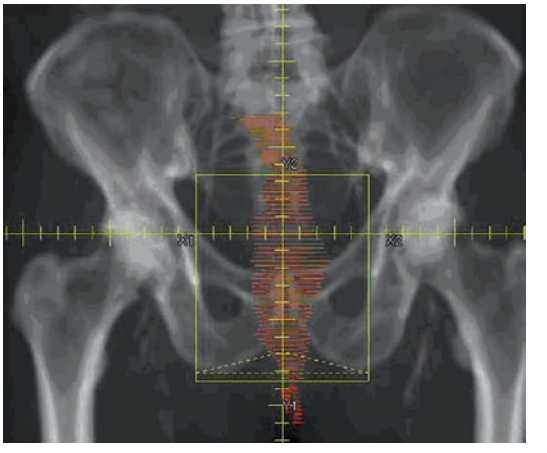

Figure 5.6. Anterior radiation boost field. Rectum contoured in *rust* color. Anal verge contoured in *red.*

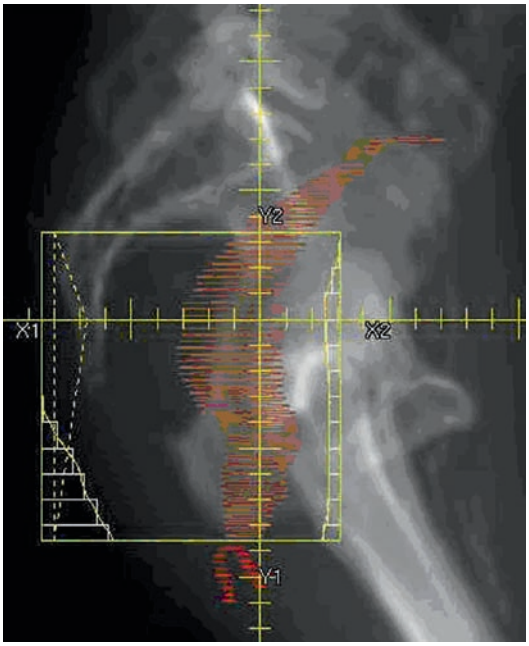

Figure 5.7. Lateral radiation boost field. Rectum contoured in *rust* color. Anal verge contoured in *red.*

Adjuvant postoperative chemoradiotherapy is indicated in patients with T3-4 and/or node-positive disease found in the post operative setting. They receive 5-FU of 500 mg/m^2 IV bolus for 5 days on weeks 1 and 5. This is followed by pelvis radiotherapy of 50 Gy in 5 weeks, along with concurrent continuous 5-FU of 225 mg/m^2 over 24 h, 7 days a week during the entire course of radiation therapy. This is followed by two more course of bolus 5-FU on weeks 10 and 25.

Patients with recurrent disease receive palliative radiotherapy to relieve the symptoms owing to local recurrence and distant metastasis. Symptoms of pain, bleeding, and discharge are effectively palliated with 30 Gy in ten fractions over 2 weeks. However, the obstructive rectal symptom is better palliated with endoscopic stenting.

Acute Side Effects and Complications of Combined Modality Treatment

The acute side effects of combined chemoradiotherapy include diarrhea, dysuria, fatigue, skin irritation, and hematologic toxicity. Severe diarrhea (grade 3 of 4) was reported in 44% of patients treated with 5-FU-based chemoradiotherapy in the INT-0144 trial (Thomas and Lindblad 1988). The incidence of death related to chemoradiotherapy was less than 1% in the GITSG-7175, INT-0114, and NSABP R-02 trials (Tepper et al. 2002; Thomas and Lindblad 1988; Wolmark 2000). The use of IORT is associated with late neuropathy, which appears to increase with doses of 15–20 Gy, and motor changes seen primarily with 20 Gy (Nakfoor et al. 1998).

Chronic Effects of Radiotherapy on Anal and Bowel Functions

Late complications of pelvic radiotherapy include urologic and gastrointestinal changes, such as sexual and urinary dysfunction, bleeding, small bowel obstruction secondary to radiation enteritis, change in bowel habits, diarrhea, stool frequency and fragmentation, urgency, and fecal incontinence (Johnstone et al. 2003; Fischer and Daniels 2006; Gervaz et al. 2001; da Silva et al. 2003; Kollmorgen et al. 1994; Dalhberg et al. 1998; Birnbaum et al. 1994; Van Duijvendijk et al. 2002; Allal et al. 2005). There is accumulating evidence that pelvic irradiation adversely affects anal and bowel functions, which in turn have been shown to seriously impact on quality of life, specifically from a functional standpoint. The deleterious effect of radiotherapy can be divided into two mechanisms: direct and indirect. Direct tissue injury is secondary to damage to normal pelvic structures, such as nerves, pelvic floor and anal musculatures, and bowel. Indirect injury is related to the increased risks of postoperative complications such as septic events and anastomotic leaks which can lead to pelvic fibrosis and/or strictured anastomosis resulting in poor bowel function.

Gervaz and colleagues from the Cleveland Clinic, Florida, evaluated the short-term effect of radiotherapy on anal sphincter function (Gervaz et al. 2001). Quantitative analysis of anal sphincter function was performed in patients with low rectal carcinoma who underwent proctectomy with coloanal anastomosis and diverting loop ileostomy. Prospective anal manometric data were collected at time of diagnosis and prior to ileostomy closure. Comparison was made between patients who received neoadjuvant or

adjuvant chemoradiation vs. those who underwent surgery alone. Prior to ileostomy closure, the irradiated group exhibited significantly lower anal resting pressures. Squeeze pressures were not significantly different between the two groups. From the same institution, Da Silva subsequently reported the morphologic alterations in the internal anal sphincter muscle following radiotherapy (da Silva et al. 2003). Histologic evaluation of abdominoperineal resection specimens was conducted and comparison was made between patients who received radiation prior to operation vs. those who underwent surgery alone. Damage to the myenteric plexus of the internal sphincter muscle with increased intramuscular collagen deposition and fibrosis was noted in the irradiated specimens.

Even in the absence of radiotherapy, bowel dysfunction following low anterior resection or proctectomy with coloanal anastomosis has been well documented, typically consisting of a mixture of increased stool frequency, bowel fragmentation, urgency, and fecal incontinence (Lewis et al. 1995). To mitigate these functional disturbances, several techniques have been advocated including side to end coloanal anastomosis, colosplasty, and neorectal reservoir construction (Hida et al. 1996; Lazorthes et al. 1997a, b; Ho et al. 1996, 2002a, b; Joo et al. 1998; Dehni et al. 1998; Barrier et al. 1999; Machado et al. 2005; Heriot et al. 2006; Hallböök et al. 1997; Fürst et al. 2002, 2003; Park et al. 2005; Z'graggen et al. 2001; Huber et al. 1999; Jiang et al. 2005; Baker 1950; Harris et al. 2001; Heah et al. 2002; Mantyh et al. 2001; Köninger et al. 2004). There is considerable evidence that postoperative radiotherapy leads to an increase in defecation frequency, bowel clustering, detrimental effect on continence along with a deleterious effect on neorectal reservoir compliance, as well as capacity and evacuation pattern (da Silva et al. 2003; Kollmorgen et al. 1994; Dalhberg et al. 1998). These arguments favor preoperative radiotherapy strategies prior to preserve and minimize damage to colorectal or coloanal reconstruction following rectal excision. Other potential advantages to preoperative neoadjuvant chemoradiation include improved tolerance, increased rates of sphincter preservation, diminished small bowel toxicity, reduced locoregional recurrence rates, and possible advantageous effects on overall cancer-specific survival.

Long-Term Follow-Up

Life-long follow-up is required after the definitive treatment of rectal cancer to detect and treat local failure and distant metastasis. Local failure is a major component of treatment failure and can occur after definitive combined modality therapy with most recurrences occurring within the first 3 years. The follow-up regimen includes office visits with physical examinations every 3–6 months for 2 years, then every 6 months, for a total of 5 years, and annually thereafter (Robbie et al. 2001; National Comprehensive Cancer Network 2008; Pfister et al. 2004). Postoperative serum CEA testing should be done every 3–6 months for 2 years after diagnosis, then every 6 months for a total of 5 years, for patients with T2 or greater lesions, if the patient is a candidate for additional surgery or systemic therapy. CT scan of the chest, abdomen, and pelvis should be done annually for 3 years for patients who are at high risk for recurrence and who would be candidates for curative-intent surgery. Colonoscopy is done in 1 year, except in the case of an incomplete colonoscopy owing to obstructing lesion; subsequently, colonoscopy is carried out in 3–6 months postoperatively. If any abnormality is detected, then colonoscopy is carried out in 1 year; however, if no advanced adenoma is observed, then colonoscopy can be repeated in 3 years, and then every 5 years. A proctoscopy is recommended every 6 months for 5 years in patients treated with anterior resection, to evaluate for anastomotic recurrence. PET scan is not routinely recommended.

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6

Quality of Life Issues and Rectal Cancer

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Abbrevations *APR* abdominoperineal resection; *AR* anterior resection; *EORTC QLQ-C30/CR38* The European Organization for the Research and Treatment of Cancer's Quality of Life Questionnaires for general and colorectal quality of life; *FACT-G/C* The Functional Assessment of Cancer Therapy (general and colorectal); *HRQOL* health-related quality of life; *RT* radiation therapy; *SF-36* Short Form 36-item Health Survey; *TME* total mesorectal excision.

Introduction

Rectal cancer is diagnosed in approximately 40,000 people each year in the USA, causing approximately 8,500 deaths per year (Bergner et al. 1981; Bleday et al 2007) http://www.cancer.gov/cancertopics/types/colon-and-rectal/). Since Miles' original description of the radical resection for rectal cancer in 1908 (Miles et al. 1908), there have been many oncologic advances in the treatment of this disorder. These advances have evolved from the use of a multidisciplinary approach to treating rectal cancer selectively, utilizing preoperative imaging, neoadjuvant/adjuvant chemoradiation, and total mesorectal excision (TME) along with a range of strategies to enhance sphincter preservation, decreased locoregional recurrence rates, and improve cancer-specific survival (Dahlberg et al. 1999 Bleday et al 2007; Sauer et al. 2001). Despite these advances, there are a multitude of side effects resulting from TME, abdominoperineal resection (APR), and radiation therapy. These treatments for rectal cancer can lead to alteration in continence, changes in body image (with the presence of a stoma), and sexual dysfunction, having a direct effect on quality of life.

Currently, a different perspective, the qualitative effects of the treatment, is emerging in the form of HRQOL. The measurement of quality of life has been applied to various disease processes and its study is presently in evolution. Many different instruments exist to measure the quality of life and no single instrument functions as the gold standard. In this chapter, we have reviewed various instruments used to measure the quality of life and have discussed the impact that rectal cancer treatment has on these measurable parameters.

Effect of Surgery and Radiation on Function

A basic understanding of the anatomy and physiology of the pelvis, rectum, and pelvic neural structures is essential when discussing the various treatment modalities of rectal

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cancer and the subsequent outcomes that impact the quality of life. The rectum is approximately 12–15 cm in length and the upper one-third is covered by peritoneum anteriorly and laterally; the middle third is covered only anteriorly by peritoneum; and the lower third is completely extra peritoneal. The rectum functions as a reservoir, distending when the fecal bolus enters. This compliance of the rectum to accommodate its contents is one of the critical components of continence and is lost after a partial or complete proctectomy. Symptoms of incontinence, increased frequency, and urgency commonly result after low anterior resection with low anastomosis or creation of a colonic reservoir (Karanija et al. 1992; Lewis et al. 1995; Miller et al. 1995) contributing to the development of "low anterior resection syndrome." Bowel dysfunction following low anterior resection has been well reported, typically consisting of a mixture of increased stool frequency, bowel fragmentation, urgency, and fecal incontinence as represented by a definitive "low anterior resection syndrome" (Lewis et al. 1995). This constellation of symptoms has been shown to seriously impact on the quality of life specifically in functional terms (Fischer and Daniels 2006), where it equates with both manometric disappearance of the rectoanal inhibitory reflex (RAIR) as a measure of internal anal sphincter (IAS) function and anorectal sampling, amounting to early poor discrimination between liquid or gaseous rectal content (Miller et al. 1988; O'Riordain et al. 1992) The manometric recovery of the RAIR within the first 2 years after rectal resection roughly correlates with the clinical functional improvement, although the persistence in disturbed rectoanal inhibition and maximal tolerated volumes with rectal balloon distension has shown little correlation with stool frequency (Karanija et al. 1992), reported episodes of incontinence (Williamson et al. 1995), or a low anastomotic level (Jehle et al. 1995).

The development of incontinence following low coloanal anastomosis is a complex issue. There is evidence to suggest some degree of sensory adaptation in neorectal reservoirs where increasing pouch pressures over time may occur with smaller pouch distension volumes, and this phenomenon may predate reported episodes of leakage. This would represent a sensory alteration within the pouch where incontinence episodes appear more to be associated with physical sphincter disruption and where high-pressure waves generated within the pouch itself are only of clinical relevance if they meet a weakened sphincter apparatus (Barrier et al. 1999; Heriot et al. 2006; Machado et al. 2005). This effect, however, is likely to be multifactorial and may also involve the effects of attendant neuropathy where both short- and longer-term overall worse functional outcome is dependent on lower anastomotic level (Koh et al. 2007; Molloy et al. 1992; Otto et al. 1996), male gender, and the presence of significant early pelvic sepsis secondary to partial anastomotic dehiscence compromising the compliance of any neorectal reservoir (Hallböök and Sjödahl 1996; Ho et al. 1993; Nesbakken et al. 2001). Other possible etiologies contributing to post treatment rectal dysfunction occur from damage to the sphincter muscle and pelvic nerves with resulting sphincter weakness and loss of anorectal sensation (Stewart and Dietz 2007).

Radiotherapy (RT) used in the treatment of rectal cancer has also been associated with incontinence, urgency, and bowel dysfunction (Dahlberg et al. 1998; Dehni et al. 2002; Kollmorgen et al. 1994; Paty et al. 1994). There is considerable evidence to show that postoperative RT for rectal cancer has significant effects on anorectal function, where most régimes are delivered as long-course external megavoltage therapy (MVT) over a 4–6 week period in the prone position, with small bowel contrast evaluation and the use of anatomical blocks to diminish extraneous radiation (Nathanson et al. 2003). There has been an increase in reported defecation frequency and bowel clustering following RT as well as a generally detrimental effect on reported continence (Birnbaum et al. 1994; Gervaz et al. 2001) along with a deleterious effect on rectal reservoir compliance, capacity, and evacuation pattern (Van Duijvendijk et al. 2002). In one study by Gervaz et al. (Gervaz et al. 2001) comparing preoperative and postoperative RT, there was a differential effect on mean resting anal pressure (MRAP) and RAIR; both essentially the internal anal sphincter

functions, but no effect was observed on maximal squeeze pressure (MSP), an external anal (voluntary) sphincter activity. The effects of RT are dose-dependent with a principal effect on rectal musculature, innervations (Frykholm et al. 1996; Lim et al. 2005), and direct effects on sphincter morphology (DaSilva et al. 2001). The correlation of functional changes after preoperative RT and chemoradiation may also occur in the absence of recognizable alterations in manometry, suggesting in some cases, a radiotherapeutic small bowel toxicity as well as a distinct pelvic radioneuropathy or lumbosacral plexopathy. The functional changes induced by RT may progress with time (Pietsch et al. 2007) and will probably become more prevalent with an increasing use of RT in this setting (65), sometimes resulting in a generally stiffer, smaller rectum after RT, even in situations where the anastomosis is relatively high and where there is both a normal demonstrated gastrointestinal transit and where the anorectal sphincter is outside the conventional radiation field. This implies that complex changes in the compliance, emptying, and viscoelastic properties of the neorectum may clinically affect post-treatment function independently of the level of the anastomosis and of the inherent sphincter damage. Overall, the severity of post-RT changes has diminished over the past few years because of better definition of the clinical radiation target with improved dose delivery, representing a change from earlier trials where the sphincters were routinely incorporated in the irradiation field (Habr-Gama et al. 2004; Ooi et al. 1999).

The combined effects of surgery and RT, not only adversely affect bowel function but also can cause sexual and bladder dysfunction (Bonnel et al. 2002; Heriot et al. 2005). There is also a close anatomic relationship between the autonomic nerves that innervate the bladder, prostate, and control sexual function and the surgical plane of dissection. These nerves lie in the plane between the mesorectum and endopelvic fascia. Below the sacral promontory, the paired hypogastric nerves carry sympathetic innervation to the pelvis. The periprostatic plexus is closely associated with Denonvilliers' fascia and innervates the seminal vesicles and prostate. There are several specific sites in which the autonomic nerves can be injured. One is during a high ligation of the inferior mesenteric artery where sympathetic nerves can be injured. Another occurs during dissection at the sacral promontory and in the presacral plane. During the anterior dissection of the rectum, the periprostatic plexus can be injured. Both APR and anterior resection (AR) are associated with varying degrees of bladder and sexual dysfunction. After APR, up to 45% of patients can experience impotence, up to 59% can experience bladder paresis, and up to 42% can experience ejaculatory dysfunction (Jorge et al. 2007). Following TME, up to 18% can experience some form of sexual dysfunction (Masui et al. 1996).

Health-Related Quality of Life (HRQOL)

Success of therapy for rectal cancer has been measured by overall survival, disease-free survival, and local and distant recurrence rates. However, as advances in rectal cancer treatment decrease recurrence rates and improve survival, there is increased interest in measuring the treatment outcomes in the patient's HRQOL. The World Health Organization defines HRQOL as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (WHO 1998). Drossman has simplified the definition to a global measure of the patient's perceptions, illness experience, and functional status that incorporates social, cultural, psychological, and disease-related factors (Drossman 1993). The major components of a patient's HRQOL are physical function, emotional/social function, ability to work productively, and the absence of specific disease-related symptoms (Cohen 2002). These four major components are more specifically evaluated in terms of social activity, ability to work or attend school, sports and recreation, body image, and sexual activity (Maunder et al. 1995). A global assessment of HRQOL can also be used to evaluate one's health as a whole (Lagenhoff et al. 2001).

Table 6.1. Requirements for an adequate and useful HRQOL instrument

Reliability – consistency of the results
Reproducibility – the results will be similar if others use the same instrument
Validity – the instrument is truly measuring what it is intended to measure
Responsiveness – allows the detection of small changes relating to a disease

Table 6.2. General health-related quality of life questionnaires used for rectal cancer

Sickness Impact Profile (SIP)
Nottingham Health Profile
Short Form 36-item Health Survey
The European Organization for the Research and Treatment of Cancer's Quality of Life Questionnaire C30
Functional Assessment of Cancer Therapy G

Table 6.3. Disease-specific health-related quality of life questionnaires used for rectal cancer

Functional Assessment of Cancer Therapy C
The European Organization for the Research and Treatment of Cancer's Quality of Life Questionnaire CR 38

In order for a HRQOL questionnaire to be accepted as an adequate and useful measurement tool, it must have reliability, reproducibility, validity, and responsiveness (Table 6.1). Reliability and reproducibility assure that the results will be consistent and similar if the instrument is used in the same population despite the person who administers the questionnaire. Validity is the ability of an instrument to truly measure what it is designed to measure, and is thought to be the most crucial factor. The three types of validity are content, criterion, and construct. Content validity refers to how well the instrument measures what is intended. Criterion validity refers to how well the instrument correlates with a gold standard. Construct validity refers to how well the instrument incorporates or measures the hypothesized concepts of the disease. Responsiveness is the ability of an instrument to detect small but true differences in a disease state (Cohen 2002; Langenhoff et al. 2001; Maunder et al. 1995).

HRQOL instruments are categorized into two broad types, either general/generic or disease-specific. General instruments can be used to evaluate and compare quality of life across many different diseases and can also be used to compare the quality of life with healthy controls. General instruments, however, lack sensitivity and lack the ability to detect disease-specific changes. Disease-specific instruments are very sensitive at evaluating and identifying changes within the specific disease for which they were developed. Disease-specific instruments can neither be used to compare one disease with another, nor can they be applied to other diseases for which they were not developed (Cohen 2002; Langenhoff et al. 2001; Maunder et al. 1995). The various general instruments formulated to evaluate colorectal cancer include the Sickness Impact Profile, the Nottingham Health Profile, and the Short Form 36-item Health Survey (Tables 6.2 and 6.3). The European Organization for the Research and Treatment of Cancer's Quality of Life Questionnaire has both a generalized (EORTC QLQ-C30) and disease-specific instrument for colorectal cancer (EORTC QLQ-CR38) (Langenhoff et al. 2001). The Functional Assessment of Cancer Therapy instrument is another instrument which has both generalized (FACT-G) and disease-specific instrument for colorectal cancer (FACT-C) (Langenhoff et al. 2001; Yoo et al. 2005).

The Nottingham Health Profile consists of 38 items evaluating the following six items: pain, energy, sleep, physical mobility, emotional reactions, and social isolation. The Short Form 36-item Health Survey (SF-36) consists of 36 items evaluating the following eight items: mental health, bodily pain, general health perceptions, vitality, reported health transition, physical functioning, emotional functioning, and social functioning (Essink-Bot et al. 1997). The Sickness Impact Profile consists of 136 items covering physical, psychosocial, and social categories (Bergner et al.1981). The EORTC QLQ-C30 consists of 30 items covering five functional scales, three symptom scales, a global HRQOL scale, and several individual symptoms (Langenhoff et al. 2001). The EORTC QLQ-CR38 consists of 38 items covering several functional and symptom items like sexual functioning,

body image, gastrointestinal symptoms, stoma-related issues, chemotherapy effects, weight loss, and micturition problems (Langenhoff et al. 2001; Urdaniz et al. 2006). The FACT-G consists of 29 items covering physical, emotional, social aspects, as well as many different symptoms (Langenhoff et al. 2001). The FACT-C is composed of the FACT-G plus nine colorectal-specific items covering physical well-being, social/family well-being, emotional well-being and functional well-being (Yoo et al. 2005). All of these instruments have been found to be valid, reliable, and reproducible.

Care must be taken when applying and interpreting quality of life questionnaires with regard to rectal cancer. Two studies have suggested that the SF-36 is not disease-specific enough and not sensitive enough to detect differences in rectal cancer populations (Fazio et al. 2007; Pachler and Wille-Jorgensen 2004). Another study, using the Nottingham Health Profile, was unable to find a difference in HRQOL between two groups in which one of the groups had statistically significant differences in bowel function (Hallböök et al. 1997). Another important factor when using questionnaires is their completion rates. The data reported in studies with low completion rates must not only be looked at critically, but also may be a marker for severe disease. One study found that those who either did not participate in or had poor compliance with the study, were more likely to be older, have more severe disease, and more often underwent palliative therapy only (Kopp et al. 2003).

Quality of Life and Surgery

There have been many advances in the surgical treatment of rectal cancer since Miles' original description. These advances attempt to preserve the anal sphincter and thus decrease the need for a permanent stoma, as well as preserve the autonomic nerves to maintain bladder and sexual function without compromising oncologic outcomes. A review by the Cochrane Collaboration in 2004 compared the quality of life in rectal cancer patients with and without permanent colostomy. The review identified 46 studies, but only 20 studies, including 2,682 patients, met their inclusion criteria of controlled, clinical trials, and observational studies measuring HRQOL after APR or AR using validated instruments. Of the 20 studies, nine demonstrated no difference in HRQOL between those undergoing APR vs. AR. Eleven studies found statistically significant differences in HRQOL in the presence of a stoma. Four studies found statistically significant differences in favor of AR in several domains of HRQOL. Two studies found statistically significant differences in favor of both APR and AR depending on the domain in which HRQOL was being measured. The authors concluded that their review did not demonstrate conclusive evidence that HRQOL is superior in AR than after APR and that larger, prospective trials need to be undertaken (Pachler and Wille-Jorgensen 2004). The heterogeneity between the studies in the Cochrane Review, however, prevented a formal meta-analysis to be done. Cornish et al., in 2007, performed a meta-analysis of quality of life after APR vs. that following AR (Cornish et al. 2007). Eleven of the 24 studies identified, including 1,443 patients, were evaluated, among whom 486 underwent an APR and 957 underwent low AR. All of the studies used either the SF-36 or the EORTC QLQ C30/QLQ CR38 as the validated instrument to measure HRQOL for a period of up to 2 years after surgery. As the Cochrane Review demonstrated, this meta-analysis found no significant difference in global health scores between APR and AR. Differences in favor of AR were found in the domains of vitality, sexual function, and physical function. Patients undergoing APR had higher cognitive and emotional function scores. The authors concluded that a patient cannot be offered a sphincter preserving procedure based on the concept of providing a superior HRQOL (Cornish et al. 2007). In a study of 62 patients not evaluated in the abovementioned two studies, in which 30 had a permanent abdominal stoma, the EORTC QLQ 30/QLQ CR 38 questionnaire was administered at their 5-year follow-up if they were found to be cancer-free. Patients without a stoma had statistically better scores in the domains of physical and role functioning, body image, sexual function, and global health status. They also had improved symptom scales with regard to fatigue, dyspnea, and appetite loss (Fucini et al. 2008).

The standard of care for sphincter preservation is low AR with TME. There are various

types of anastomoses that can be created, either hand sewn or stapled-straight coloanal, colonic J-pouch, coloplasty, or end to side. A systematic review of evidence from randomized trials looked at the effect of anastomotic technique on anorectal function. This review included 18 studies and 904 patients, of which 4 of the studies measured HRQOL. The types of anastomoses included in the studies evaluated were colonic J pouch, straight, coloplasty, and end to side. Of the four studies measuring quality of life, only two comparing colonic J pouch with straight anastomosis found an improvement in HRQOL. The review suggests that the type of anastomosis has no impact on HRQOL and that colonic J pouch has improved postoperative functional results, but the data is lacking to make a definite conclusion (Murphy et al. 2007). In a randomized, multicenter trial, no difference was found in the quality of life of 297 patients who underwent colonic J pouch, coloplasty, or straight coloanal anastomosis. In this study, the SF-36 instrument was used and HRQOL was measured at baseline and up to 2 years postoperatively (Fazio et al. 2007). Another study in which long-term quality of life outcomes were measured in 121 patients with a median follow-up of 65 months, assessed patients who underwent either a stapled or hand sewn colonic J pouch or straight coloanal anastomosis, depending upon surgeon preference (Hassan et al. 2006). The EORTC QLQ C30/QLQ CR38 instrument was used in this approach. Patients without a stoma had better HRQOL with regard to physical and social functioning, and body image with improved symptom scores for fatigue, nausea, pain, dyspnea, urinary problems, and chemotherapy-related side effects. The patients in this study who received a permanent stoma demonstrated such effects secondary to postoperative complications from attempted sphincter preservation. Significant postoperative complications leading to a stoma may have been the primary reason for the decrease in quality of life, although the presence of a stoma itself could have directly impacted upon the decrease in HRQOL (Hassan et al. 2006).

The increased use of a protective, defunctioning loop ileostomy has been associated with the recent increases in sphincter preservation. This has been shown to reduce the sequelae of anastomotic leakage (Tsunoda et al. 2008). Twenty-two patients undergoing AR and loop ileostomy were studied in a prospective, longitudinal manner and compared with 25 patients undergoing AR without loop ileostomy. The patients were evaluated with the EORTC QLQ C30/QLQ CR38 instruments and HRQOL was measured up to 8 months postoperatively. The physical and role functioning scores were lower in the presence of a loop ileostomy when compared with baseline values. These scores as well as the global HRQOL score increased above baseline after loop ileostomy was reversed. Body image score did not increase following ileostomy closure. Those who underwent AR alone had higher scores postoperatively across most categories (Tsunoda et al. 2008). Camilleri-Brennan found similar results with respect to an improvement in quality of life after reversal of loop ileostomy (Camilleri-Brennan and Steele 2002). In this study, 20 patients were prospectively evaluated with EORTC QLQ C30/QLQ CR38 and the SF-36 instruments prior to and 3 and 6 months after reversal. Following stoma reversal, there was an increase in global quality of life and the physical, social, role-physical, and energy-vitality scores. Again, body image did not improve after reversal (Camilleri-Brennan and Steele 2002).

Transanal excision or transanal endoscopic microsurgery (TEMS) are other techniques selectively used to treat rectal cancers. These techniques are offered to carefully selected patients with early rectal cancers, who have been well informed on the risks and benefits of a local procedure vs. a major abdominal operation. If the oncologic outcome for early rectal cancers is the same for local excision vs. TME, then the quality of life after the procedure may play a role in which the procedure is performed. Thirty-one patients undergoing TEMS were compared with 31 undergoing TME and 31 healthy controls. The general HRQOL between the groups did not differ. The TME group had more problems with defecation, and there was a slight trend towards better sexual function in the TEMS group; however, this did not reach statistical significance. Despite the small number of patients, the authors concluded that there is no difference in HRQOL and the increased problems with defecation associated with TME may alter the choice of surgery if the oncologic outcome will not be compromised by the operative procedure decision (Doornebosch et al. 2007).

As laparoscopy became more popular for benign abdominal pathology, it was questioned as to whether laparoscopy can be applied to colorectal cancer without compromising oncologic outcomes. In 2006, a Cochrane Review of 48 studies including 4,224 patients demonstrated that there was no significant difference between laparoscopic and open TME for rectal cancer with regard to disease-free survival rate, local recurrence rate, mortality, morbidity, anastomotic leakage, resection margins, or the number of recovered lymph nodes (Breukink et al. 2006). Others have also demonstrated equivalent survival and recurrence rates with laparoscopic TME (Tsang et al. 2006). Yang et al. prospectively evaluated 125 patients undergoing laparoscopic TME and 103 undergoing open TME for HRQOL using the EORTC QLQ C30/QLQ CR38 instruments for up to 5 years after surgery. They found that physical function, micturition problems, sexual function, sexual enjoyment, and male sexual problems were significantly better in the laparoscopic group for up to 18 months after surgery. Thereafter, the benefits of laparoscopic surgery on HRQOL fade and become equivalent to open surgery, except for sexual enjoyment. The conclusion was that laparoscopy can provide short-term improvements (up to 18 months) in many areas of HRQOL and long-term advantage (> 2 years) in sexual enjoyment (Yang et al. 2007). Another study of 168 patients comparing laparoscopic TME with open surgery demonstrated similar results to those of Yang with respect to improved HRQOL for the laparoscopic arm in the short term. Using the SF-36, the authors found significantly improved general health, physical functioning, and social functioning for up to 1 year postoperatively, but these faded to equivalent scores when compared with open surgery at 2 years of follow-up (Braga et al. 2007).

In a study by Hendren et al. on sexual dysfunction after rectal surgery (Hendren et al. 2005), 81 women and 99 men answered the EORTC QLQ-C30/CR-38 questionnaires in addition to questionnaires on gender-specific sexuality. There was significant sexual dysfunction in both the genders (males more than females), associated with a negative body image in both the genders, but there was no negative impact on the global quality of life. APR was also found to be associated with a greater impairment in sexuality. Another important point raised in the article was that a majority of patients did not have a discussion preoperatively on sexual dysfunction, and it was rarely treated postoperatively. A 10-year historic cohort examining APR vs. AR similarly found that both the genders have sexual impairment with men incurring more of an impact than women. APR again was found to be associated with a greater impairment in sexuality (Schmidt et al. 2005). In a study by Breukink and colleagues, laparoscopic TME did not appear to result in improvements in sexual dysfunction, where up to 1 year after laparoscopic TME, either AR or APR, sexual function was impaired more following laparoscopic APR. Despite this impairment, global quality of life was improved in this group (Breukink et al. 2006).

Quality of Life and Radiotherapy

It has been shown that radiotherapy can improve survival and lower recurrence rates when used selectively to treat rectal cancer (Dahlberg et al. 1999; Sauer et al. 2001). Despite these benefits, evidence exists that RT adversely affects bowel, bladder, and sexual function (Dahlberg et al. 1998; Dehni et al. 2002; Kollmorgen et al. 1994; Paty et al. 1994). Many have studied these adverse events and how they affect HRQOL. Surprisingly, RT does not have a significant impact on global HRQOL and one study found an improved global HRQOL (Allal et al. 2005; Murata et al. 2008; Pollack et al. 2006a, b; Rothenberger et al. 2004; Urso et al. 2006). Using the American Society of Colon and Rectal Surgeons quality of life questionnaire, Pollack found that those patients with incontinence had a lower quality of life despite the lack of difference in HRQOL if they had received radiation or not (Rothenberger et al. 2004). In a study on 990 patients who underwent TME, among whom 497 received preoperative short-course RT (5 × 5–25 Gy), RT was found to have a statistically significant negative effect on sexual functioning in males and females, on male ejaculatory disorders, and on erectile function over time. Despite this negative impact, there was no effect on HRQOL (Marijnen et al. 2005). Another study, in which the patients received 50 Gy over 40 fractions followed by TME, a statistically significant impairment in

sexual function, but an increase in global HRQOL 1 year after surgery Was observed (Allal et al. 2005).

Quality of Life and Long-Term Follow-Up and Recurrence of Rectal Cancer

Despite improvements in the multimodality treatment of rectal cancer, recurrence is a major problem with rates ranging from 2.0 to 32%, and the majority occurring within 2 years of the initial surgery (Camilleri-Brennan and Steele 2002). Treatment for locally recurrent rectal cancer is associated with 5-year survival rates between 21 and 58%, but with associated morbidity and mortality (Esnaola et al. 2002). Recurrence can be detected with close post-operative follow-up and can have a significant impact on HRQOL. A study comparing HRQOL in 25 patients with recurrent rectal cancer with 50 patients without recurrence demonstrated significantly lower HRQOL in almost every category measured. The questionnaires used to measure HRQOL were the EORTC QLQ-C30, CR38, and the SF 36 II. This study underscores the need to address not only the physical components associated with recurrence (such as pain), but also the social and psychological components (Camilleri-Brennan and Steele 2002). Another study investigated on how pain impacted HRQOL in those treated for locally recurrent rectal cancer. Of the 45 patients enrolled in the study, 15 patients were treated non-surgically and 30 surgically. Their HRQOL was measured with the FACT-C questionnaire. Treatment of locally recurrent rectal cancer, whether it treated surgically or not, is associated with significant pain. Those with higher post treatment pain had worse HRQOL. The surgically treated group was found to have minimal pain and an improvement in HRQOL if they survived beyond 3 years (Esnaola et al. 2002).

As stated earlier, after a curative surgical resection, patients undergo close post-operative follow-up in an attempt to detect recurrence. Two studies have been done to determine if frequent follow-up improves HRQOL after curative resection for rectal cancer. One study (Kjeldsen et al. 1999) had one group followed up every 6 months for 3 years, and then at 4, 5, 7.5, 10, 12.5, and 15 years after surgery whereas the other group had a follow-up every 5 years. In a further study (Stiggelbout et al. 1997), 54% of the patients were seen every 6 months, 32% every 3 months, and 15% annually. Both the studies found that the frequency of follow-up does not have a significant impact on HRQOL to justify the increased use of resources. The studies did, however, find an improvement in the doctor–patient relationship and patients were reassured that they were being provided with better care.

Conclusion

As the treatment of rectal cancer continues to improve the survival rates and decrease recurrence rates, HRQOL should become a more integral part of the preoperative assessment of the patients. Patients should be informed about how a particular treatment, either operative or non operative, may impact their chance of local recurrence or survival. They should also be informed as to how that treatment will impact their quality of life. When using HRQOL questionnaires to study those with rectal cancer, care must be taken to use an appropriate questionnaire to detect differences in the patient populations. In addition, study results must be critically evaluated, with respect to the completion rates and reasons as to why completion rates may be low. A preoperative discussion on all the risks and benefits, including survival, recurrence, bowel, sexual dysfunction, and HRQOL should be undertaken. Patient selection for sphincter preservation should continue to be individualized based on tumor and patient's characteristics. With no significant difference in HRQOL found between patients with or without a permanent stoma and between various types of anastomoses, decisions on surgical technique should not be based on HRQOL if sphincter preservation will compromise oncologic outcome. Recurrent rectal cancer continues to present multiple dilemmas for both physicians and patients. Those with recurrent rectal cancer have poor HRQOL but more than just pain needs to be addressed to improve HRQOL. Patients and their families need to be involved with support groups and family counseling in an attempt to improve coping and HRQOL. Research involving large, prospective trials in the area of HRQOL

should continue for both doctors and patients to become better informed on how to best treat rectal cancer, particularly in the ways HRQOL will be impacted upon by adjuvant treatment, locoregional and distant recurrence detection and management, and by the methodology and intensity of follow-up.

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7

Managing Presacral Tumors

Richard M. Devine

Presacral Tumors: General Considerations

Presacral or retrorectal tumors are uncommon. At the Mayo Clinic, a large tertiary care center, only 120 patients with retrorectal tumors were seen over a 20-year period (Jao et al. 1985). Uhlig reviewed the medical records of Portland Oregon's major hospitals over a 30-year period prior to 1975 and identified 63 cases, approximately 2 per year in major metropolitan area (Uhlig and Johnson 1975). In a more recent report from Washington University in St. Louis, only 32 patients with retrorectal tumors were seen over a 22-year period ending in 2003 (Glasgow et al. 2005).

The retrorectal space has been defined as the potential space bordered posteriorly by the presacral fascia (Waldeyer's fascia) (Crapp and Cuthbertson 1964), anteriorly by the fascia propria of the rectum, laterally by the ureters and lateral stalks of the rectum, inferiorly by the pelvic floor, and superiorly by the peritoneal reflection of the rectum (Hobson et al. 2005). The presacral space contains the same area but extends superiorly to the sacral promontory.

The retrorectal space is an area where the three embryologic germ cell layers meet (ectoderm, mesoderm, and endoderm), and therefore congenital tumors of all the three cell types can be found in this area. Uhlig proposed the earliest classification of presacral tumors and separated them into five categories: congenital, inflammatory, neurogenic, osseous, and miscellaneous (Uhlig and Johnson 1975). More recent authors have recommended a classification of congenital vs. acquired, and benign vs. malignant (Glasgow et al. 2005; Lev-Chelouche et al. 2003; Wolpert et al. 2002).

Glasgow and associates combined the data from five large series of retrorectal tumors and divided the tumors into benign and malignant (Glasgow et al. 2005). There were 154 benign tumors and 144 malignant tumors in the combined series. The most common benign tumors, comprising 82% of the total, were dermoid and epidermoid cysts, tailgut cysts, benign teratomas, schwannomas, and leiomyomas. The most common malignant tumors, comprising 85% of the total, were chordomas, neurogenic tumors, sarcomas, teratocarcinomas, and metastatic carcinoma.

A patient's presenting complaint depends largely on whether or not the tumor is benign or malignant. In the review by Glasgow, 43% of patients with benign tumors were asymptomatic, whereas only 7% of the patients with malignant tumors were without symptoms (Glasgow et al. 2005). Pain, change in bowel habits, and lower extremity symptoms were the most common symptoms in both groups. Urinary and fecal incontinence, sexual dysfunction, and lower extremity weakness are the signs of advanced tumors with sacral or sciatic nerve involvement. Most retrorectal and presacral tumors can be palpated on digital rectal exam; in the series of 120 cases from the Mayo Clinic,

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97% of the tumors could be felt on digital exam (Jao et al. 1985).

Evaluation of suspected presacral tumors should start with a careful digital exam. This exam can reveal the size, shape, consistency, location, and give a sense whether or not the tumor is fixed to the surrounding structures. Endoscopy should be done to evaluate the possibility of rectal involvement. If a presacral mass is palpated, then a coronally reconstructed CT scan or magnetic resonance image (MRI) of the pelvis should be obtained to determine the nature of the mass, to make sure the mass is not an anterior meningocele and to define sacral infiltration or destruction in mid-sagittal plane (Lee et al. 1988; Wetzel and Levine 1990; Moulopoulos et al. 1999).

Although plain pelvic radiographs may show sacral bone destruction, they add no additional information to that obtained by computerized imaging. Some surgeons recommend the use of transrectal ultrasound that may be useful in determining the extent of rectal wall involvement. If malignancy is suspected, appropriate studies should be done to rule out metastases.

The role of preoperative biopsy in the evaluation is controversial. Some surgeons feel that preoperative biopsy should rarely be part of the preoperative evaluation because of the risk of tumor seeding, the risk of possible infection, and the conviction that "the best biopsy is complete removal of the tumor" (Jao et al. 1985; Bohm et al. 1993). Other surgeons recommend the selected use of preoperative fine-needle aspirate of suspected malignant tumors (Cody et al. 1981; Fourney Gokaslan 2003). Jao et al. found that the recurrence rate of chordomas was higher in patients who had preoperative biopsy when compared with those who did not have preoperative biopsy, but the numbers were small and the two groups may not have been similar. There may have been other factors causing the higher recurrence rate in the group that had preoperative biopsy (Jao et al. 1985). In a review of literature the author could find no well-documented cases where recurrent tumor was attributed to preoperative biopsy. There was, however, a death from sepsis after a transrectal core needle biopsy (Verazin et al. 1986), and Jao reported two perirectal abscesses and a fecal fistula in the nine patients who had preoperative biopsy (Jao et al. 1985).

The author disagrees with those individuals who state retrorectal lesions should never be biopsied. If knowing the preoperative pathology, has the potential for changing the treatment approach , by using preoperative chemotherapy or radiation for example, or changes the surgical approach, then a preoperative biopsy is indicated. A CT-guided fine-needle aspirate through a posterior or transperineal approach is safe and carries little risk of tumor seeding or infectious complications. A core biopsy should be considered if an experienced cytopathologist cannot determine the diagnosis on a fine-needle aspirate. Preoperative biopsy should be judiciously used; transrectal and transvaginal core biopsies should be avoided. If a transrectal or vaginal route is used, pretreatment of the patient with antibiotics is recommended (Verazin et al. 1986).

The surgical approach to presacral tumors depends on tumor size, location, and whether or not malignancy is suspected. Low-lying tumors, both presacral cysts and sacral tumors at or distal to S3 generally can be removed via a posterior (Kraske style) approach (Gellhoed and Kotz 1983; Kraske 1985; Buchs et al. 2007). Tumors that extend higher into the pelvis are best removed through an abdominal incision or a combined abdomino-trans-sacral (Localio-style) approach (Localio et al. 1980; Guillem et al. 2001). Large sacral tumors proximal to S3 will require a combined approach with both abdominal and posterior incisions.

The surgical team is also determined by the size and location of the tumor. Tailgut cysts or pelvic dermoid cysts can usually be well managed by a colon and rectal surgeon or experienced pelvic surgeon without assistance. Conversely, large bulky sacral chordomas will require the coordination of specialists in plastic, spine, pelvic, and possibly urologic surgery.

Specific Presacral Tumors

Sacral Chordomas

Chordomas are slow-growing malignant bone tumors arising from embryonic remnants of the notochord. They are relatively rare tumors; the Mayo Clinic, a major tertiary care center, reported 52 sacral chordomas over a 21-year period, only two cases per year on average

(Fuchs et al. 2005). They have a predilection for both ends of the spine; approximately 50% occur in the sacrum, 35% in the skull base, and the remainder in the cervical, thoracic, or lumbar spine. They are the most common malignancies of the sacrum (Zileli et al. 2003; Ozdemir et al. 1999). Although chordomas arise in the sacrum, they displace the rectum anteriorly or present as retrorectal masses and are often included in the discussion of presacral tumors (Lev-Chelouche et al. 2003; Wang et al. 1995; Stewart et al. 1986).

The peak incidence occurs in the 6th or 7th decade but they have been reported in patients as young as 13 years (Fuchs et al. 2005). There is a slight male predominance; in a combined series of 176 patients the male to female ratio was close to 3:2 (Fuchs et al. 2005; Yonemoto et al. 1999; Park et al. 2006; Cheng et al. 1999; Bergh et al. 2000; Hulen et al. 2006; Baratti et al. 2003).

Most patients present with slowly progressive pain in the sacral region. In a series of 52 patients investigated by Fuchs et al., patients had symptoms for an average of 27 months prior to diagnosis (Fuchs et al. 2005). In a series of 39 patients from Göteborg Sweden, 87% presented with pain, 13% with a painless mass. Twelve of 39 patients had neurologic symptoms with radiculopathy or bladder or bowel dysfunction (Bergh et al. 2000).

The most common sites of metastatic disease are lung and bone, and therefore preoperative evaluation should include CT scan of the lungs and a bone survey. The primary tumor should be imaged with magnetic resonance imaging. Sung et al. described the MRI findings in 30 patients with sacrococcygeal chordomas (Sung et al. 2005). They describe the characteristic findings as a sacral mass with heterogeneous intensity, crisscrossing septa, lobulated appearances, and frequent gluteal invasion (see Fig. 7.1). Twenty-two of 30 patients had the involvement of the first or second sacral vertebra, 16 patients had gluteal muscle involvement, and 7 patients had sacroiliac joint involvement.

There is little information on the use of positron emission tomography (PET scan) in evaluating chordomas. Zhang et al. evaluated 15 patients with chordomas using carbon-11-methionine PET scan (Zhang et al. 2004). Twelve of the 15 chordomas in this study were clearly visible on the baseline scan; none of the patients had known metastatic disease.

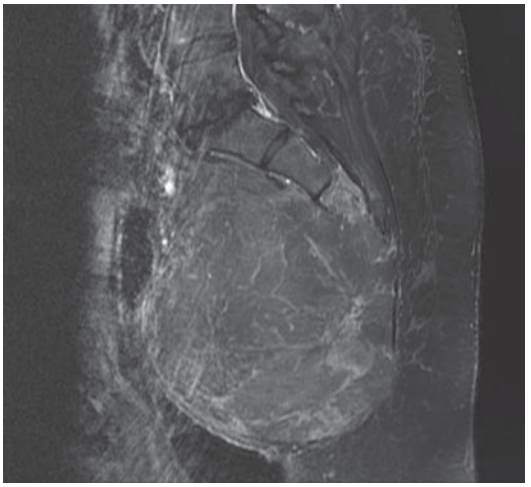

Figure 7.1. MRI of sacral chordoma with crisscrossing septa in tumor and destruction of S3 vertebra.

Because the differential diagnosis of a sacral tumor includes tumors that may benefit from preoperative treatment, if a sacral chordoma is suspected on the MRI scan, then a biopsy should be considered to establish the diagnosis. The cytologic appearance of fine-needle aspirates of chordomas has been described (Nijhawan et al. 1989; Walaas and Kindblom 1991). Bergh et al. used fine-needle cytology to establish the preoperative diagnosis in 16 of 29 patients initially treated at their tumor center (Bergh et al. 2000). The tract of the biopsy needle should be placed such that it can be excised at the time of surgery. Transrectal or transvaginal biopsies should not be done because of the potential for seeding these structures with tumor cells.

The only known cure for sacral chordomas is complete surgical excision and therefore wide en-bloc resection should be the goal of the surgery. Fuchs et al. found surgical margin to be the single most important predictor of survival (Fuchs et al. 2005). Because over 50% of patients with sacral chordomas have tumors involving the S_2 sacral vertebra or above, complete resection is often a formidable undertaking that requires a team of surgeons including orthopedic, neurosurgical, spine, plastic, urology, vascular, and colorectal surgeons. Tumors that are at or distal to S_3 or lower can be removed via a posterior approach, whereas those lesions involving S_2 or more cephalad should have a combined anterior–posterior approach. In a report from

the Mayo Clinic spanning 21 years, there was a trend of using the combined approach more often in an attempt to obtain an adequate surgical margin (Fuchs et al. 2005).

In the combined anterior–posterior approach, the abdomen is opened through a midline incision and if the rectum is not involved by tumor, it is mobilized away from the tumor. If both S_3 sacral nerves are sacrificed, it is appropriate to remove the rectum and create a colostomy since the patient will become incontinent. If a rectus abdominis myocutaneous flap is planned, it is mobilized and placed into the pelvis. Omental flaps with mesh have also been described (Hulen et al. 2006). Laparotomy pads or plastic sheeting are placed in front of the sacral tumor to prevent injury to the rectum or mobilized rectus flap during the posterior portion of the surgery. The abdomen is closed, the patient repositioned in the prone position, and an incision is made from the spinous process of L_5 to the coccyx. The nerve roots cephalad to the tumor are identified and preserved if they are uninvolved. The sacrum is divided 2 cm cephalad to highest extent of the tumor. Sacrectomy above the S_1 vertebra is destabilizing and requires mechanical fixation (Zileli et al. 2003). Once the tumor is removed, the wound is closed using rectus abdominis or gluteal flaps.

In Fuchs series, the most common complication was local wound breakdown (Fuchs et al. 2005). This occurred early in the series, prior to the use of rectus abdominis myocutaneous flaps. Other complications included persistent spinal fluid leak, stress fractures of the alae of the pelvis, and persistent stool incontinence.

Postoperative bowel or bladder dysfunction is dependent on which sacral nerve roots are sacrificed. If both S_3 nerve roots are preserved, patients should not experience any bowel or bladder dysfunction (Cheng et al. 1999). If one S_3 nerve root is preserved, patients could potentially retain bladder and bowel control (Hulen et al. 2006). If both S_3 nerves are sacrificed but the S_2 nerves are preserved, the patient may still retain control of bowel and bladder function (Cheng et al. 1999; Hulen et al. 2006; Baratti et al. 2003) but the sacrifice of the S_2 nerves will invariably result in bowel and bladder dysfunction (Fourney and Gokaslan 2003). Transection of S_1 nerve roots will result in motor deficits in the legs.

Local recurrence is frequent; in the Mayo Clinic series, the cumulative probability of local recurrence at 5 and 10 years was 46% and 54%, respectively. The 10-year risk of metastatic disease was approximately 50% and was usually associated with local recurrence. The overall survival rates in 52 patients in the Mayo Clinic series was 74%, 52%, and 47% at 5, 10, and 15 years, respectively (Fuchs et al. 2005).

No firm recommendations can be made concerning the value of radiation therapy as an adjuvant to surgery. There is some evidence, however, that it may be helpful. In a report from Milan Italy, 16 patients had an inadequate resection of the primary tumor, 10 of whom were treated with radiation therapy. All six who did not receive radiotherapy had a local recurrence whereas only five of the ten patients who did receive radiation had local recurrence (Baratti et al. 2003). Park et al. described the use of radiation therapy in addition to surgery in 14 patients with primary sacral chordomas. Eleven of the 14 had positive tumor margins and only one of the 11 developed a local recurrence with a mean follow-up of 8.8 years (Park et al. 2006). The mean dose delivered to the patients with positive margins was 73 Gy.

Tailgut Cysts

Tailgut cysts, also referred to as retrorectal cystic hamartomas, are rare cystic lesions thought to arise from the remnants of embryonic tail gut (Vega Menéndez et al. 2008). At approximately 35 days of gestation, the human embryo has a true tail, which regresses over the next 20 days. The primitive gut extends into this tail, hence the name tail gut. This tail gut regresses along with the true tail and it is hypothesized that remnants of this primitive gut give rise to tailgut cysts. The embryonic neuroenteric canal is also a possible source of congenital cysts in the retrorectal space (Hjermstad and Helwig 1988).

Because these lesions are so rare, the reports in the literature are either single case reports or small series. The largest series was 53 cases from the Armed Services Institute of Pathology in 1988 (Hjermstad and Helwig 1988). Killingsworth and Gadacz published an extensive review of the literature in 2005 (Killingsworth and Gadacz 2005).

In the Armed Forces series, approximately half of the cysts appeared grossly multilocular, whereas the other half appeared to be a single cyst. Microscopically, however, 81% of the lesions

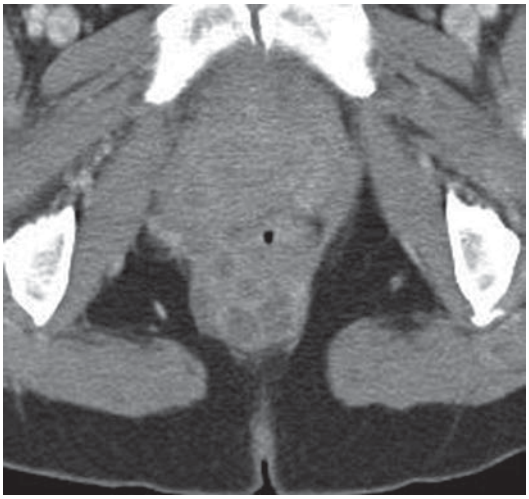

Figure 7.2. CT scan of tailgut cyst showing multicystic mass just posterior to rectum.

were multicystic. The CT scan in Fig. 7.2 demonstrates the multilocular nature of these cysts.

Tailgut cysts are usually confined to the retrorectal space and there is no communication to the rectal lumen. The lining of the cysts varies but all cysts had some columnar epithelium without villi or crypts seen in normal bowel mucosa. Seventy-five percent of the cysts in the series by Hjermstad and Helwig contained squamous epithelium. Smooth muscle fibers are usually seen in association with the cyst but there is an absence of any well-defined muscle wall and the myenteric plexus is absent.

In the review by Killingsworth and Gadacz of 43 cases, the male to female ratio was approximately 1:3 and the mean age at presentation was in the 5th decade. Half of the patients presented with symptoms owing to an enlarging mass; pain, decreased stool caliber, and a feeling of fullness, whereas only four (10%) of the patients were asymptomatic. In 17 cases, a malignancy was associated with the tailgut cyst; 11 adenocarcinomas, five carcinoids, and one neuroendrocrine tumor. Because of this risk of malignant degeneration, all tailgut cysts should be removed, even if they are asymptomatic (Tampi et al. 2007; Prasad et al. 2000; Song et al. 2004; Jacob et al. 2004; Mourra et al. 2003; Schwarz et al. 2000; Krivokapic et al. 2005).

Preoperative evaluation should include CT scan or MRI. If there is any question that the lesion may be an anterior sacral meningocele, an MRI should be performed to make sure that there is no connection to the thecal sac. Yang et al. described the MRI findings in five cases, all of which were multilocular but in two there was one large cyst with a smaller peripheral cyst. The size ranged from 4.5 to 12 cm and on T1-weighted images the cysts are hypointense, whereas on T2-weighted images the masses are hyperintense (Yang et al. 2005). If preoperative evaluation is consistent with a tailgut cyst, biopsy is not recommended.

The surgical approach depends on the size and location of the cyst. Smaller cysts in the coccygeal area can be removed through a posterior approach, whereas larger cysts extending cephalad into the pelvis may require an abdominal approach. In the review by Killingsworth and Gadacz, 46% of the cysts were removed via a posterior approach.

The author and the editors have removed these cysts via a paracoccygeal incision. The patient is placed in the prone position with the hips flexed and an incision is made extending from just lateral to the coccyx to within 2 cm of the anal verge (Fig. 7.3). The side of the coccyx on which the incision is made depends on the preoperative imaging. The incision is carried down through the perirectal fat to the levator muscle. The lower portion of the gluteus muscle can be divided to improve exposure of the cyst,

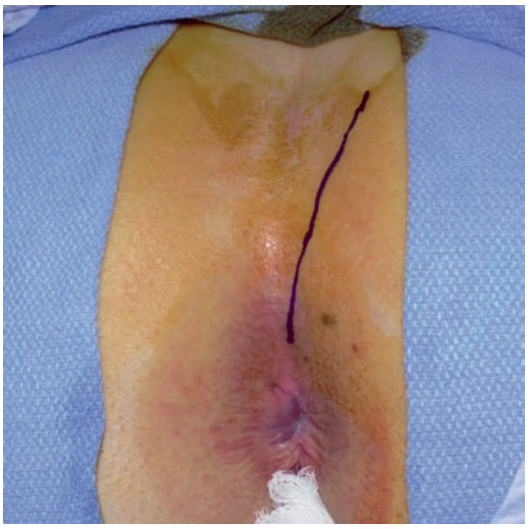

Figure 7.3. Parasacrococcygeal incision for the removal of tailgut cyst.

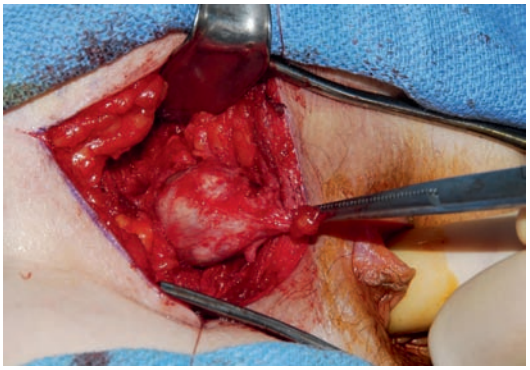

Figure 7.4. Removal of tailgut cyst through parasacrococcygeal incision with finger in distal rectum to assist in dissection of the cyst off the rectum.

which will lie just deep in this muscle. Removal of a portion of the coccyx may facilitate the exposure if necessary. A finger in the rectum helps to lift the cyst up into the wound and also allows identification of the rectal wall, so injury to rectum can be avoided (Fig. 7.4). Diligence should be taken to remove all of the cysts completely to avoid recurrence. The surgeon should try to avoid rupturing the cysts but it is difficult to avoid rupture because of the cysts' thin wall and surrounding fibrosis.

Because of the paucity of reports in the literature, the rate of recurrence is unknown. In the review by Killingsworth and Gadacz, 23 patients had excision of a benign tailgut cyst, there were two reported recurrences; one occurred 2 years after laparotomy and one occurred 1 year after transanal excision.

Dermoid and Epidermoid Cysts

In the review of retrorectal tumors by Glasgow, 14% of benign retrorectal tumors were dermoid or epidermoid cysts (Glasgow et al. 2005). Epidermoid and dermoid cysts are both lined by keratinizing stratified squamous epithelium, but dermoid cysts also have dermal appendages present in the lining of the cyst such as sweat glands, hair follicles, or sebaceous cysts. Like other patients with presacral cysts, the symptoms depend on the size and location of the cyst and whether or not it is infected. Presacral cysts may be asymptomatic or may present with perianal sepsis. These cysts have been misdiagnosed as fistula-in-ano, pilonidal cysts, or perianal abscess (Singer et al. 2003). An MRI should be done to assess the size and location of the cyst and to exclude an anterior sacral meningocele. Nishie et al. described the use of chemical shift and diffusion-weighted MR imaging to demonstrate the presence of keratinous substance within a dermoid cyst, which helps one to distinguish a dermoid cyst from other developmental cysts such as tailgut cysts or rectal duplication cysts (Nishie et al. 2003). Preoperative biopsy is not recommended.

Cases of squamous-cell cancer arising in dermoid cysts have been reported (Tangitgamol et al. 2003) and like other developmental cysts they should all be excised even if they are asymptomatic. Areas of solid components with contrast enhancement in what appears to be a dermoid cyst is suspicious for malignancy.

Epidermoid and dermoid cysts can be removed via either an abdominal or posterior approach depending on the size and location of the cyst. In a review of 15 cases in the Japanese literature, six cysts were removed via an abdominal approach and nine were removed via a posterior approach (Ueda et al. 1998).

Rectal Duplication Cysts

Intestinal duplications can occur anywhere in the gastrointestinal tract. They are uncommon and only 3–8% of these rare anomalies occur in the rectum (MacLeod and Purves 1970). Three criteria were proposed by Ladd and Gross in 1940 to establish the diagnosis of a duplication cyst: (1) contiguity or strong adherence to some part of the alimentary tract, (2) a smooth muscle coat, and (3) a mucosal lining consistent with one or more types of cells normally seen in the gastrointestinal tract (Ladd and Gross 1940). Tailgut cysts are differentiated from duplication cysts by their lack of a smooth muscle coat and the absence of any connection to the rectum.

The majority of recent reports are in children (Knudtson et al. 2003; La Quaglia et al. 1990). La Quaglia published a series of 11 children with a mean age of 17 months (range 1 month to 18 years). All of the cysts were palpable and ranged in size from 1.0 to 8.0 cm. All the lesions were located in the retrorectal space with one lesion extending through the levators into the ischiorectal fossa. Intermittent prolapse was the presenting symptom in three children caused by a mass bulging into the distal posterior rectum.

Five of the 11 had an associated fistula. Two fistulas extended from the duplication cyst to the posterior perianal area and three other fistulas entered the anal canal just inside the anorectal ring. Eight of the 11 were removed through a transanal approach, three were removed via a postanal or posterior approach (La Quaglia et al. 1990).

In adults, duplication cysts can present as chronic perianal sepsis (Flint et al. 2004; Atlinli et al. 2004). MRI can help establish the diagnosis by demonstrating the presacral cyst and possibly a fistula tract from the cyst to the rectum, anal canal, or perineum.

Like tailgut cysts, adenocarcinomas have been reported to arise from duplication cysts and therefore all of these cysts should be removed regardless of the symptoms (Michael et al. 1999; Shivnani et al. 2004). The surgical approach is determined by the size and position of the cyst. Cysts low in the pelvis can be removed through a perineal or posterior approach, although a Kraske or even a posterior proctotomy approach may be useful to circumferentially extirpate larger duplication cysts. Laparoscopic removal of a rectal duplication cyst has also been described (Salameh et al. 2002).

Anterior Sacral Meningocele

Anterior sacral meningocele is a rare congenital malformation, in which the thecal sac herniates anteriorly through a defect in the sacrum. Because the sac is connected to the dural pouch, it is filled with spinal fluid. Unlike posterior meningoceles, neurologic deficits are rare but anterior meningoceles can cause bowel and bladder dysfunction, meningitis, and interfere with labor and delivery. Anterior meningoceles may also be incidentally discovered on pelvic or rectal exam. Eighty-five percent of adult patients with anterior sacral meningoceles are female (Krivokapic et al. 2004). MRI scanning will establish the diagnosis by demonstrating the sacral defect and the connection between the meningocele and the thecal sac.

Currarino syndrome, described in 1981, is characterized by the triad of a sacral bone defect, congenital anorectal anomalies, and a presacral tumor (Currarino et al. 1981). In a report of 29 cases of Currarino syndrome by Cretolle et al. 8 of the cases were noted to have an anterior sacral meningocele. The most common associated anorectal anomaly was imperforate anus (13 cases). Eight patients also had chronic intestinal pseudo-obstruction (Cretolle et al. 2006). There is a case report of an adult with Currarino syndrome presenting with meningitis due to a fistula between the rectum and a meningocele arising from a stercoral perforation of the rectum as well as reports of the triad being associated with colonic malrotation (Daoud et al. 2007).

Adults with asymptomatic, nonexpanding anterior meningoceles may be followed without surgery (Massimi et al. 2003; Tuzun et al. 2005). Most cases, however, will require surgery owing to symptoms or the expansion of the cyst (Massimi et al. 2003). The goal of surgery is to interrupt the connection between the cyst and the thecal sac and this can be done via either a posterior or anterior approach. Some authors recommend removing the sac (Massimi et al. 2003; Tuzun et al. 2005), whereas others indicate that the sac will spontaneously resolve with disconnection alone (Schijman et al. 2005).

Schwannomas

Schwannomas, also called neurilemomas, are the most common benign tumors of the peripheral nervous system and also the most common type of neurogenic tumor found in the presacral area. In Glasgow's review of five large series of retrorectal tumors, 14% of benign retrorectal tumors were schwannomas or neurofibromas (Glasgow et al. 2005). They are slow growing, usually solitary tumors, and malignant transformation is rare (Hughes et al. 2005).

Hughes and associates described the imaging characteristics of 13 patients with pelvic and retroperitoneal schwannomas (Hughes et al. 2005). Nine of these tumors were located in the presacral space. Twelve of the 13 schwannomas had a well-defined smooth margin (Fig. 7.5). The indistinct border on one tumor was the result of the tumor eroding the sacrum. Five of the tumors were homogeneous and eight were heterogeneous, indicating cystic degeneration of the tumor. In the five patients who had magnetic resonance imaging, the solid portion of the tumor on T1-weighted images was isointense to skeletal muscle and on T2-weighted images they were hyperintense to skeletal muscle. Three of the tumors extended through the sacral intervertebral foramina. In all cases, the diagnosis

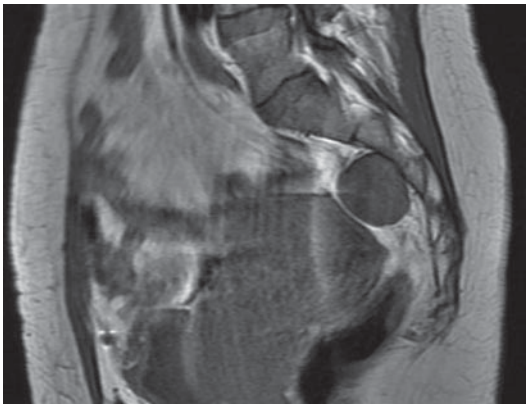

Figure 7.5. MRI of presacral schwannoma showing well-circumscribed homogeneous mass.

was established preoperatively by core-needle biopsy. Five of the nine pelvic tumors were biopsied through either the vagina or rectum with preprocedure antibiotic coverage.

The goal of surgery is to remove the tumor while preserving the nerve if possible. There have been cases where the pelvic schwannoma arose from the sciatic nerve and extended through the sciatic notch (Consales et al. 2006). The nerve can be preserved by incising the epineurium over the mass and bluntly dissecting the tumor away from its capsule. In some cases, adequate exposure of the nerve can only be obtained by piecemeal resection of the tumor. Retrograde ejaculation and erectile dysfunction have been described as sequela of removing presacral schwannomas in men (Popuri and Davies 2002).

Teratomas

Teratomas arise from embryonic rests of totipotential cells and contain cells from more than one germ cell layer. Mature or benign teratomas contain epithelial lined structures and mature elements of striated or smooth muscle. Immature teratomas have areas of primitive mesoderm, ectoderm, and endoderm. Malignant teratomas can have malignant tissue of germ cell origin, such as a seminoma, or have malignant tissue that is a result of degeneration of more mature elements (Ng et al. 1999).

The vast majority of teratomas are found in infants or children and represents one of the commonest forms of infantile malignancy (Altman et al. 1974). Reports of sacrococcygeal teratomas presenting in adults are rare (Head et al. 1975; Bull et al. 1999). Ahmed and Pollock reviewed 29 cases reported in the medical literature through 1982 and Ng added another 28 patients reported between 1961 and 1999 (Ng et al. 1999; Ahmed and Pollock 1885). In the series of 28 cases reviewed by Ng and associates, the average age was 43 with a range between 17 and 76. There was a female predominance with a male to female ratio approximately 1:2. Eleven of the 28 patients had malignant teratomas and all those with malignancy who were followed died of their disease.

Because of the potential for malignant degeneration, all sacrococcygeal teratomas should be removed. The majority can be removed through a posterior approach (Miles and Stewart 1974). Coccyx removal is recommended to lower the risk of recurrence (Ng et al. 1999; Miles and Stewart 1974; Mahour1988). Partial removal of the sacrum may be required in some cases.

Miscellaneous Tumors

The presacral lesions already discussed account for approximately 60% of presacral tumors: chordomas, developmental cysts, schwannomas, and anterior sacral meningoceles (Glasgow et al. 2005). A wide variety of benign and malignant lesions make up the remaining 40%. Table 7.1 lists the majority, but not all, of the types of tumors that have been reported to occur in the presacral space. Although imaging studies and physical exam can often give a good clue to the correct diagnosis, the differential diagnosis of a presacral mass is quite broad.

Conclusion

Presacral (retrorectal) tumors represent a rare but eclectic mix of benign and malignant masses presenting to the coloproctologist. Classification is confusing because of the wide variety and rarity of these tumors. Preoperative coronal (or coronally reconstructed) imaging is advisable with selective biopsy of noncystic lesions particularly where there is an evidence of sacral infiltration and where preoperative therapy may be of value. The operative approach is dependent on the principal tumor level and the likely diagnosis with the posterior (Kraske-style) procedure being most commonly performed for

Table 7.1. Presacral tumors

Congenital – benign	Congenital – malignant
Dermoid cyst	Malignant teratoma
Epidermoid cyst	Chordoma
Benign teratomas	
Tailgut cyst	
Rectal duplication cyst	
Anterior sacral meningocele	
Acquired – benign	**Acquired – malignant**
Schwannoma	Osteogenic sarcoma
Ependymoma	Ewing's sarcoma
Giant cell tumor	Chondrosarcoma
Osteochondroma	Neuroblastoma
Aneurysmal bone cyst	Plasmacytoma
Leiomyoma	Liposarcoma
Lipoma	Leiomyosarcoma
Hemangioma	Lymphoma
Hematoma	Desmoid tumor
	Carcinoid
	Hemangiopericytoma
	Metastatic cancer

low-lying tumors below the third sacral piece and an abdominal or abdomino-trans-sacral (Localio-style) approach adopted for higher and more infiltrative cases. Trans-sphincteric, transanal, transvaginal, paracoccygeal, and paravaginal (Schuchardt-Schaute) approaches have been selectively reported (Kanemitsu et al. 1993; Meissner et al. 1996; Pidala et al. 1999; Schauta 1902; Madanes et al. 1981). Recently, both laparoscopic and TEMS-related approaches have been described for selective excision of these tumors (Zoller et al. 2007; Chen et al. 2008). Chordomas, malignant teratomas, anterior sacral meningoceles, and cases of the Currarino triad require a multidisciplinary approach shared by coloproctologists, neurosurgeons, orthopedists, pediatric specialists, and plastic reconstructive surgeons.

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8

Revisional Pouch Surgery

R. John Nicholls and Paris P. Tekkis

Introduction

Restorative proctocolectomy is the elective surgical procedure of choice for most patients with ulcerative colitis or familial adenomatous polyposis. It results in good functional outcomes and quality of life in most patients but fails in between 3.5 and 17%, necessitating excision of the pouch or indefinite fecal diversion. The failure rate increases with the duration of follow-up (Meagher et al. 1998) and may occur early, within the first postoperative year, or at any time thereafter. The overall cumulative failure taking all patients irrespective of diagnosis is approximately 5% at 5 years, 10% at 10 years, and 15% at 15 years (Tulchinsky et al. 2003). Age does not appear to be an absolute contraindication to pouch surgery and is not associated with an increased incidence of failure (Delaney et al. 2002). The diagnosis of Crohn's disease or indeterminate colitis, prior anal pathology (fistula-in-ano or abscess), and weak anal sphincter are the known preoperative factors that can adversely affect long-term pouch survival. The development of pouch-perineal or pouch-vaginal fistula, pelvic sepsis, anastomotic stricture, and leakage were the most important factors associated with ileal pouch failure in a multivariate analysis (Fazio et al. 2003)

For patients in whom failure is threatened, revisional or redo surgery may be indicated. There are four causes of ileal pouch failure as shown in Table 8.1:

- Acute and chronic sepsis
- Poor function for mechanical or functional reasons
- Mucosal inflammation (pouchitis)
- Neoplastic transformation

Of these, sepsis is the most common being responsible for over 50% of all failures. Poor function accounts for about one-third of failures and pouchitis for 10% (Tulchinsky et al. 2003). Neoplastic transformation is uncommon (Borjesson et al. 2004; Das et al. 2007) and in these patients excision of the pouch is indicated thereby excluding them from salvage surgery and thus from this chapter.

For the larger group of patients without neoplastic transformation in whom failure is threatened, various factors need to be considered when advising revisional pouch surgery. These include the feasibility of success, the magnitude of the proposed operation, the overall duration of treatment, and the patient's wishes. The potential morbidity of excision of the reservoir resulting in a permanent ileostomy should also be discussed, including the possibility of a high-output ileostomy, pelvic nerve damage, and an unhealed perineal wound. These complications occur in 50% or more of patients undergoing excision of the pouch (Karoui et al. 2004).

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Table 8.1. Causes of failure (excision of pouch or indefinite defunctioning)

- Sepsis
  - Acute
  - Chronic
    - Pelvic sepsis
    - Fistulation
- Poor function
  - Mechanical outlet obstruction
    - Ileoanal anastomotic stenosis
    - Long efferent limb
    - Retained rectum
  - Small-volume reservoir
  - Sphincter dysfunction
- Mucosal inflammation
  - Pouchitis
    - Crohn's ileitis
- Neoplastic transformation

Sepsis

Pelvic sepsis after restorative proctocolectomy occurs between 3 and 25% of cases and its incidence appears to decrease as surgical experience increases (Meagher et al. 1998; Everett 1989; Keighley et al. 1993; Scott et al. 1988). Pelvic sepsis may present in the early postoperative period or it may be delayed, manifesting as abscess formation (usually presacral) or fistulation, often with a history of an anastomotic complication.

Early Sepsis

Patients who develop sepsis in the early postoperative period have a cumulative incidence of subsequent failure five times that of the whole population of patients undergoing restorative proctocolectomy. In a series of 706 patients that included 494 with colitis, 131 developed sepsis. There was a cumulative failure rate of 19.6% at 3 years rising to 39.2% at 10 years. The failure rate was significantly greater when the site of sepsis involved the anal sphincter than when it was located more proximally (5-year failure rate 50.1 and 29.2%, respectively) (Heuschen et al. 2002). Symptoms of early pelvic sepsis include fever, anal pain, tenesmus, and discharge of pus or secondary hemorrhage through the anus. The diagnosis is established by digital examination (under anesthesia if necessary), combined with imaging, including contrast pouchography, computed tomography (CT), and magnetic resonance imaging (MRI).

Management

In a proportion of patients, the condition resolves spontaneously. Others need operative endoanal, or imaging-guided percutaneous, drainage. If drainage of the cavity is unsatisfactory, an attempt can be made to de-roof the abscess and curette the cavity through the anus, creating a large communication between the abscess and the reservoir. Sometimes, several local procedures are needed to eradicate sepsis. Rarely, an abdominal approach is indicated. When sepsis is severe enough to warrant a laparotomy, the functional outcome is poor, often followed by failure (Scott et al. 1988).

When anastomotic disruption is the cause of pelvic sepsis, after drainage and curettage a transanal repair of the anastomosis or advancement of the ileum and resuturing of the ileoanal anastomosis has been advocated. In a report of 15 patients who were found to have partial anastomotic disruption between 7 and 90 days after surgery, seven were treated by resuturing of the anastomotic defect and counter drainage, with success in three. Seven others underwent a pouch advancement procedure, with success in five. Thus, over a follow-up of 1–22 months, successful salvage was achieved in eight of the 15 patients (Fleshman et al. 1988b).

Severe acute pelvic sepsis with extensive anastomotic breakdown occurs in 5–15% of patients and results in early failure in around 30% of patients, despite adequate drainage. Attempts at salvage by direct suture may work for some patients. The occurrence of early sepsis renders the patient at increased risk of subsequent failure when compared with the total population. In a report by Heuschen et al. (2002), only 16.8% of the 131 patients with sepsis could be managed conservatively, the rest requiring some form of surgical procedure. However, patients with early postoperative sepsis were not distinguished from those in whom sepsis developed during subsequent follow-up, although there was no significant difference in the failure rate when salvage surgery was

undertaken within or beyond 6 months of restorative proctocolectomy. As might be expected, failure was related to the magnitude of the procedure, 6.1% after minor intervention (33 patients) when compared with 47.3% after major surgery (74 patients).

Delayed Sepsis

Delayed abdominal or pelvic sepsis presents as chronic abscess formation with or without fistulation. MRI using short-tau inversion recovery (STIR) settings may make the diagnosis in some patients in whom clinical examination, contrast radiography, or CT has not been successful. When sepsis is limited, there is a good chance of healing provided that drainage is adequate. If resolution does not occur, there are two surgical options including excision of the pouch or an attempt at salvage, usually via an abdominal approach.

Management

There is a considerable variation in the reported success of abdominal salvage surgery (Table 8.2). Satisfactory success rates were reported in a series of 35 patients with chronic sepsis, either abscess or fistulation (Fazio et al. 1998), including 22 with ulcerative colitis, ten with Crohn's disease, one with indeterminate colitis, and two with FAP; 29 had leakage from the ileoanal anastomosis and four from the upper pouch. Overall, a pelvic abscess was present in 25 patients, and ten had a vaginal and 12 a perineal fistula. All underwent abdominal revision with detachment of the ileoanal anastomosis, curettage of any chronic abscess cavity with drainage or repair of fistula, and reanastomosis. The median interval between the first operation and revision was 24 months. At a median follow-up of 18 (range 6–105) months, 30 had preserved anal function. Twenty-one of the 22 patients with ulcerative colitis retained anal function but the functional outcome was not satisfactory in all cases. The median frequency of defecation per 24 h was 9.6, but the range was considerable, from 4 to 35. Urgency was common, and was constantly present in four patients and intermittent in 14. The quality of life was reported as good or excellent by 17 patients and fair or poor by 13. Despite disappointing function in some patients, it is clear that major surgical revision can result in worthwhile salvage in many.

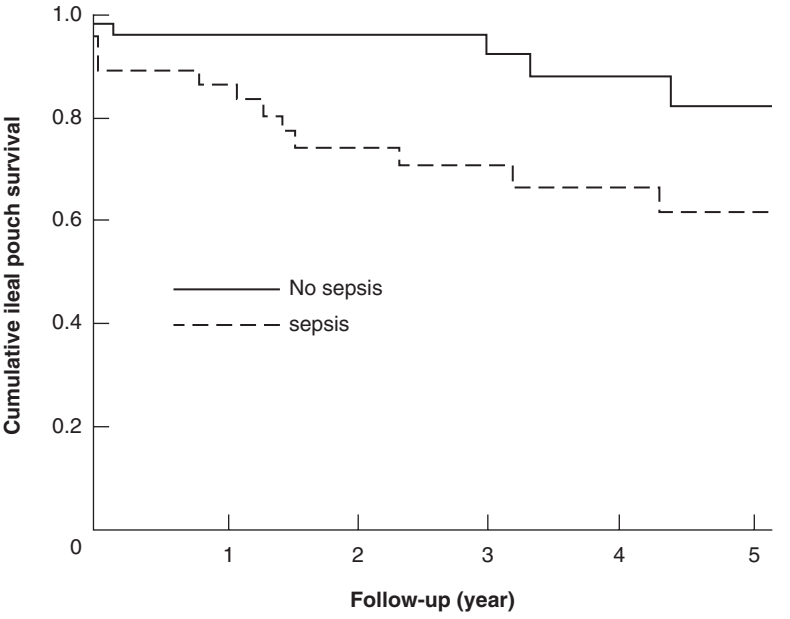
Table 8.2. Abdominal revision for sepsis

References	Number of patients	Follow-up (months)	Failure (%)
Galandiuk et al. (1990)	29	1–98 (47)	17
Poggioli et al. (1993)	8	>24	5
Cohen et al. (1998)	24	7–97 (35)	4
Ogunbiyi et al. (1997)	8	6–84 (34)	3
Heuschen et al. (2002)	74	31–96 (51)	35
Baixauli et al. (2004)	85	(32)	15
Dehni et al. (2005)	45	(30)	3
Tekkis et al. (2006)	112	1–147 (46)	24

Values in parentheses are means. *UC* ulcerative colitis; *CD* Crohn's disease.

Similarly, in a report of 24 patients who underwent salvage abdominal surgery after multiple local procedures had failed, salvage was achieved in 20 (Cohen et al. 1998). The mean time from ileostomy closure to revision was 35 (range 7–97) months and success was defined as an intact pouch after ileostomy closure provided that there had been no further complications for at least 6 months. In 18 such patients, the median frequency of defecation was 5.2 (range 3–8) bowel movements per day and 1.5 (range 0–3) at night. Continence was normal in 13 of these 18 patients during the day and in nine at night.

Others, however, have reported poorer results. In a series of 114 patients who underwent abdominal reoperation for various reasons after pouch surgery, 29 had procedures for intra-abdominal sepsis (Galandiuk et al. 1990). These included drainage of abscess (three patients), diverting ileostomy (18), and revision of the pouch (six), and primary closure of fistula (four). Of the 29 patients, 17 still had an ileostomy at the time of assessment and in ten the pouch had been removed. Only ten had satisfactory anal function. The authors showed, importantly, that failure continues with the passage of time; at 2 years 34 procedures had failed and at 5 years the probability of remaining free of pouch excision was 75%.



No. at risk						
No sepsis	57	37	29	23	18	14
sepsis	45	32	23	17	15	8

Figure 8.1. Cumulative pouch survival after abdominal salvage for patients with and without sepsis. Log rank statistic = 5.78, 1 d.f., p = 0.016 (log rank test) (Tekkis et al. 2006).

A similar experience was reported in 131 patients who developed early sepsis out of a total of 706 who had restorative proctocolectomy for ulcerative colitis (494) and polyposis (212) (Heuschen et al. 2002). The occurrence of early sepsis conferred a higher chance of cumulative failure when compared with that in patients who did not develop early sepsis. Furthermore, failure after attempted salvage rose from 20% at 3 years to 40% at 10 years. Of the 131 patients followed for 51 (interquartile range 31–96) months, sepsis was due to fistulation in 76%, anastomotic separation in 15%, and abscess formation alongside the pouch in 10%. The authors classified the site of fistulation into three levels: level I (upper pouch) in 19%, level II (lower pouch, rectal cuff) in 31%, and level III (ileoanal anastomosis) in 50%. Sepsis was treated conservatively in 24 (18%), by minor surgery in 33 (25%), and by major surgery in 74 (56%). As might be expected, the failure rate was higher after major (47%) than after minor (6%) surgery. Overall, failure was related to sepsis at level III, the presence of a pouch-vaginal fistula (43%), an original diagnosis of ulcerative colitis, and the number of salvage procedures. It was also cumulative with time, even after salvage intervention.

The largest series of abdominal salvage surgery published to date included 112 patients, with the following original pathology: ulcerative colitis ($n = 86$), indeterminate colitis ($n = 11$), familial adenomatous polyposis ($n = 10$), and other conditions ($n = 5$). At a median follow-up of 46 (range 1–147) months, 24 (21%) patients experienced pouch failure, the incidence of which increased with time. The pouch failed in all patients with Crohn's disease. Successful salvage at 5 years was significantly associated with a nonseptic (85%) rather than a septic (61%) indication ($p = 0.016$) as shown in Fig. 8.1. Frequency of nighttime defecation and fecal urgency improved after salvage surgery (Tekkis et al. 2006).

Summary

- The effectiveness of salvage surgery when chronic sepsis is treated by abdominal operation is unclear.
- Success following abdominal pouch revisional surgery is less likely if the sepsis is near the sphincter.
- Pouch failure after abdominal salvage continues steadily over time.

- Functional outcomes following abdominal revisional surgery can improve significantly.
- The success of abdominal salvage surgery for sepsis is less than that for a nonseptic indication.

Fistulation into the Vagina

The reported incidence of pouch-vaginal fistula ranges from 2.6 to 16%, and depends on the accuracy and duration of follow-up (Fleshman et al. 1988a, b; Breen et al. 1998; Fazio et al. 1995; Groom et al. 1993; Keighley and Grobler 1993; O'Kelly et al. 1994; Ozuner et al. 1997; Paye et al. 1996; Wexner et al. 1989). Since first reported in 1985 (Wong et al. 1985), its incidence may have increased (Groom et al. 1993; Keighley and Grobler 1993). It has been suggested that the complication is more likely in patients with anal pathology (fistula-in-ano or perianal abscess) preceding restorative proctocolectomy (Tekkis et al. 2005). It is certainly related to the occurrence of pelvic sepsis during the early postoperative period (Groom et al. 1993). Patients with Crohn's disease are known to have a 3.2-fold increased risk of developing a pouch-vaginal fistula in comparison with patients with ulcerative colitis. In a study of 68 patients with pouch vaginal fistula, the 5-year fistula-free survival of patients with ulcerative colitis was 56.1% following attempted repair. Repair in those patients with Crohn's disease (n = 8) uniformly failed within 5 years from primary fistula repair (Heriot et al. 2005).

The patient usually complains of a vaginal discharge and clinical examination often demonstrates the fistula. Occasionally, it is only detected by radiological contrast enema (pouchogram). It is important to exclude pouch-vaginal fistula by careful examination under anesthetic of the vagina as well as the anal canal, before closing the defunctioning ileostomy. The fistula may present early before ileostomy closure, or afterwards even several years later (Carraro et al. 1992).

In a series of 22 patients, pouch vaginal fistula developed in five before closure and in 17 at a median interval of 7 (range 1–144) months after perhaps owing to subclinical pelvic sepsis (Groom et al. 1993). Patients in the former group may have a better prognosis, with spontaneous healing in some of them (Groom et al. 1993; Wexner et al. 1989). The internal opening is usually located at the ileoanal anastomosis, but less often it may arise at the dentate line, perhaps as a form of cryptoglandular sepsis. In a series of 17 patients, the internal opening was found at the anastomosis in 15 and at the dentate line in two (Groom et al. 1993). In a larger series of 59 patients, the internal opening was at the anastomosis in 37 and at the dentate line in 14 (Ozuner et al. 1997). Causative factors may include injury to the vagina or rectovaginal septum during the rectal dissection (Keighley and Grobler 1993; O'Kelly et al. 1994; Ozuner et al. 1997) or anastomotic dehiscence with pelvic sepsis (Fleshman et al. 1988b; Groom et al. 1993; Keighley and Grobler 1993; Parker and Nicholls 1992). The latter is probably the major predisposing factor as pelvic sepsis rates are significantly higher in patients with pouch-vaginal fistula than in those without (Groom et al. 1993; Lee et al. 1997; Marcello et al. 1993). Crohn's disease has been reported to be more common in patients with fistula (Lee et al. 1997; Grobler et al. 1993; Hyman et al. 1991), but in a series of 22 patients with this complication only one had proven Crohn's disease after review of all histopathological material (Groom et al. 1993).

A survey of colorectal surgeons from 11 hospitals in the USA and Canada reported 21 pouch-vaginal fistulas (6.9%) in 304 patients who underwent restorative proctocolectomy (Wexner et al. 1989). Five further patients were referred from elsewhere. Of these 26 patients, the original diagnosis was ulcerative colitis in 23, indeterminate colitis in two, and FAP in one. There were 27 fistulas among the 26 patients. The fistula appeared before closure of the ileostomy at a mean of 11 weeks in eight patients and at an interval after closure of 35 weeks in the remaining 19. Twenty-five were recognized clinically and two that were asymptomatic were discovered on routine pouchography.

Management

Management depends on the severity of symptoms. When these are minimal and acceptable to the patient, either no action or the placement of a seton may be all that is necessary. There are no published data on the long-term effectiveness of seton drainage, although Table 8.3 shows success in all four patients in one study treated by this technique (Keighley and Grobler 1993). In

Table 8.3. Successful closure of pouch-vaginal fistula

References	Endoanal advancement or flap	Trans-vaginal	Trans-abdominal	Seton	Fistulectomy	Fibrin glue
Keighley et al. (1993)		1 of 1	1 of 1	4 of 4	1 of 1	
O'Kelly et al. (1994)		5 of 7				
Paye et al. (1996)			4 of 5			
Shah et al. (2003)	21 of 52	0 of 2	10 of 16	0 of 5		
Heriot et al. (2005)	1 of 2	22 of 54	9 of 11	1 of 6		
Johnson et al. (2005)	2 of 14	0 of 1	9 of 17			0 of 2
Tsujinaka et al. (2006)	3 of 5	0 of 1	3 of 5	1 of 7		1 of 2
Total	27 of 73	28 of 66	36 of 55	6 of 22	1 of 1	1 of 4

Values are number of successful procedures as a proportion of total number of procedures.

those with a clinically significant degree of incontinence, a diverting ileostomy should be established if not already present. At the same time any sepsis is drained with or without placement of a seton suture. The seton technique is the preferred option when the origin of the fistula is cryptoglandular, but there is no information on the longer-term outcome of this approach. Once the acute sepsis has settled, repair is indicated.

Simple defunctioning does not appear to be sufficient in itself. In a series of 21 patients, no instance of closure of the fistula occurred in the six patients who had an ileostomy only (Paye et al. 1996). Surgical repair is therefore the treatment of choice. The options are divided into abdominal and local procedures. The former includes abdominoanal revision with advancement of the ileoanal anastomosis and the latter fistulectomy with or without sphincter repair, endoanal advancement flap repair, and transvaginal repair. The height of the ileoanal anastomosis from the anorectal junction is the essential feature that influences the choice.

For a stapled anastomosis at or above the anorectal junction, an abdominoanal advancement procedure should be advised as there is sufficient distance to advance the anastomosis distally below the fistula. The reservoir is dissected from the surrounding pelvic structures down to the anastomosis. The bowel is divided at this level, the track excised, and the defect in the vagina repaired. Any retained rectum is removed and, after a mucosectomy, a manual endoanal anastomosis is performed thereby advancing the pouch distally. Table 8.3 shows success in 36 (65%) of 55 patients treated by this technique (Cohen et al. 1998; Keighley and Grobler 1993; Paye et al. 1996; Wexner et al. 1989; Lee et al. 1997; Grobler et al. 1993).

For a fistula arising from an ileoanal anastomosis lying within the anal canal or just above the sphincter, abdominal advancement of the anastomosis is impractical as there is not sufficient distal anal canal length to be clear of the fistula. A local procedure is necessary in such circumstances and various approaches have been tried. Fistulectomy with direct perineal repair appears to give poor results (Table 8.3). The use of muscle flap procedures has been reported, but the long-term results are unknown. Two patients who had a gracilis muscle repair had no recurrence 3 months after ileostomy closure (Gorenstein et al. 1988), and four treated by transposition of the rectus abdominis muscle were without recurrence between 6 and 30 months (Tran et al. 1999).

Most surgeons would use either of the following options:

- An endoanal ileal advancement of the pouch or local flap
- A transvaginal closure technique

The former has a success rate of 31.5%, with closure reported in 23 of 73 cases (Groom et al. 1993; Ozuner et al. 1997; Wexner et al. 1989; Lee

et al. 1997) (Table 8.3). Transvaginal repair may have advantages over the endoanal technique as it allows a direct approach to the fistula, avoiding possible sphincter damage. In one study, the use of an endovaginal advancement flap was successful in five of seven patients at a mean follow-up of 26 (range 14–72) months (Galandiuk et al. 1990). Function was satisfactory and no fistula had recurred. In another study, a direct approach through the posterior vaginal wall, with repair of the internal opening in the bowel followed by closure of the vaginal wound, was successful in 11 of 14 patients at a median follow-up of 18 (range 6–60) months, with repeated procedures being required in 5 of the 11 patients (Burke et al. 2001). The frequency of defecation ranged from 2 to 10 bowel actions per 24 h with no incidence of fecal incontinence. Combining the results of several studies of transvaginal repair suggests that successful closure was achieved in 28 (42%) of 66 patients (Galandiuk et al. 1990; Groom et al. 1993; Keighley and Grobler 1993; Wexner et al. 1989; Lee et al. 1997; Burke et al. 2001).

Pouch-vaginal fistula from an "ileo-anal" anastomosis at or above the anorectal junction should be approached abdominally. In one series of 24 patients with a pouch-vaginal fistula, 9 out of 17 had a successful abdominal revision. Local perineal repair was successful in 2 of 14 cases (Johnson et al. 2005). In another series of 68 women with pouch-vaginal fistula, surgery was undertaken in 59 (87%) patients with 14 (20.6%) undergoing pouch excision/diversion or seton drainage. Forty-five (66%) patients underwent primary repair. First recurrence of pouch-vaginal fistula occurred in 27 of 45 (60%) patients with a median pouch-vaginal fistula-free interval of 1.6 years. Fourteen (51.9%) patients with recurrent pouch-vaginal fistula experienced healing following one or more repeat procedures. There was a trend toward improved primary healing with abdominal repair when compared with local repair, although this did not reach statistical significance (Fig. 8.2). The diagnosis of Crohn's disease was made in eight (12%) patients, with pouch-vaginal fistulas persisting or recurring in all patients with Crohn's disease within 5 years of the primary treatment (Fig. 8.3). Median pouch vaginal fistula-free survival was 1.4 years for patients with Crohn's disease and 8.1 years for patients with ulcerative colitis

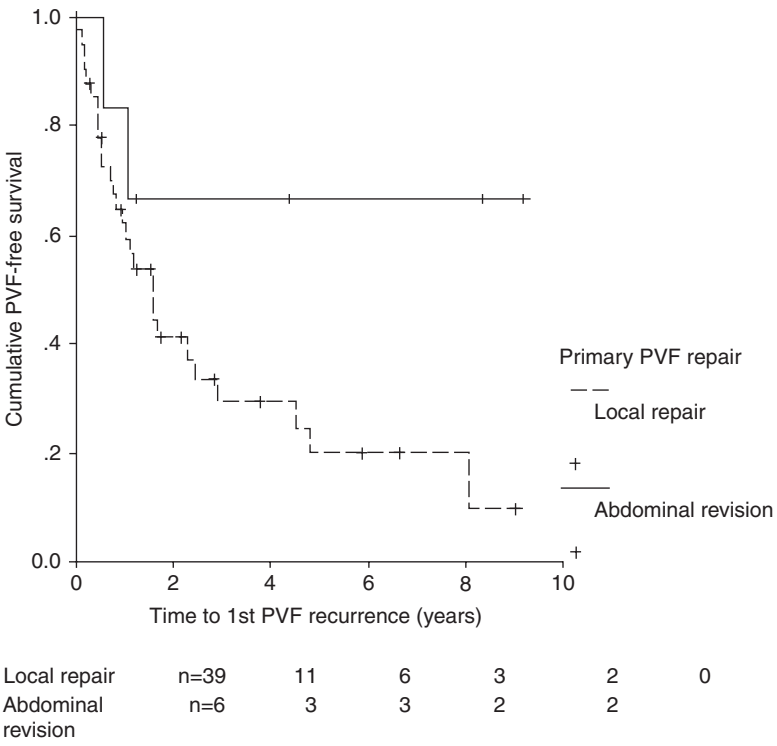


Figure 8.2. Kaplan-Meier survival curves displaying cumulative pouch-vaginal fistula (PVF)-free survival by type of primary repair (local vs. abdominal). Log-rank test = 2.8, 1df, p = 0.0941 (Heriot et al. 2005).

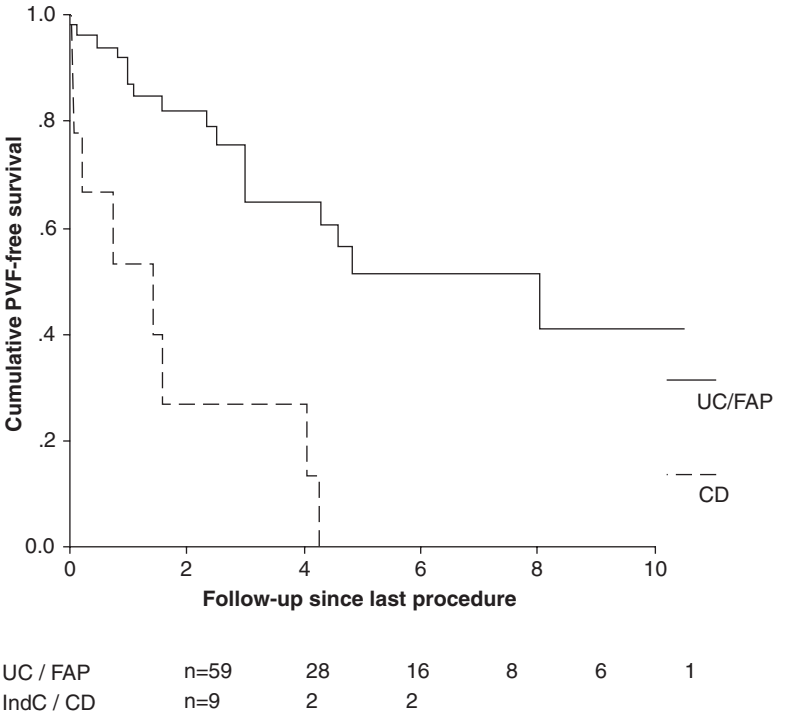


Figure 8.3. Kaplan-Meier survival curves displaying cumulative pouch-vaginal fistula (PVF)-free survival by histopathologic diagnosis for all patients presenting with a pouch vaginal fistula (n = 65). Log-rank test = 17.56, 1 df, p < 0.001. CD Crohn's disease; FAP familial adenomatous polyposis; UC ulcerative colitis (Heriot et al. 2005).

or familial adenomatous polyposis. The pouch-vaginal fistula-free survival improved with repeated local or abdominal repairs for patients with ulcerative colitis (Heriot et al. 2005).

Summary

- Patients with pouch vaginal fistula should be defunctioned unless the symptoms are minor and tolerable.
- Fistula arising from an internal opening (whether anastomotic or cryptoglandular) within the anal canal should be treated by either endoanal or transvaginal repair.
- Fistula at the anorectal junction or more proximally (usually stapled) should be treated by abdomino-anal pouch advancement.
- Abdominal pouch advancement achieves better long-term results than perineal repair.

Poor Function

Function varies from day to day and the patient's own perception is probably the most important factor in the identification of poor function. Most patients with poor function have a stool frequency of ten evacuations per 24 h or more, usually associated with the passage of small-volume stool. There may also be urgency, incontinence, and difficulty in evacuation. An assessment of the extent to which these impair the quality of life should be made. Pouch function tends to improve with time, and a reasonable period should be allowed to pass before considering any form of salvage surgery. In a prospective study of patients over 12 years, however, there was no change in bowel frequency, although there was an increase in major day continence in 18% of patients and improvement in only 1% of patients. Most patients had stable function over the 12 years (Bullard et al. 2002) (Fig. 8.4)

Differential Diagnosis

Poor function accounts for 20–40% of failures (Galandiuk et al. 1990; Tulchinsky et al. 2003; Foley et al. 1995; MacRae et al. 1997). The causes are given in Table 8.1. The diagnosis is made on clinical examination combined with investigations, including pouchoscopy with mucosal biopsy, contrast pouchography, physiological

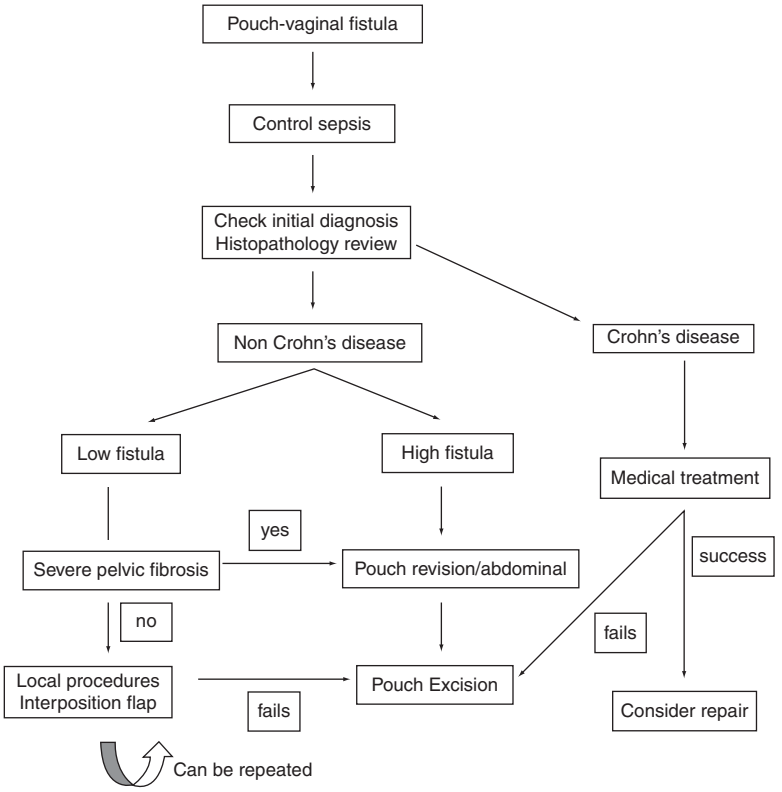


Figure 8.4. Algorithm for management of pouch-vaginal fistula. Diversion should be considered if an abscess or sepsis is associated with the fistula or an initial attempt at repair has failed.

tests of sphincter function, and estimation of reservoir capacity. Pouchitis is often invoked as the cause of poor function, but a degree of acute inflammation in a mucosal biopsy is often seen and this may not necessarily be the reason. Frequently more than one lesion coexists. For example, stenosis of the ileoanal anastomosis, chronic abscess, and retained rectum may all occur in the same patient.

Mechanical Outlet Obstruction

The causes of mechanical outlet obstruction include:

- Stricture of the ileoanal anastomosis
- Retained rectum after ileorectal anastomosis
- Long efferent limb of an S-reservoir (no longer relevant at present)

Examination and contrast radiology may show evidence of narrowing or obstruction either at the level of the ileoanal anastomosis or in the distal part of the reservoir. In some patients, outlet obstruction may not be associated with the evidence of mechanical narrowing; it is then presumed to be due to a functional disorder of unknown etiology. Surgery is not indicated in these patients. The symptoms of outflow obstruction are typical and almost diagnostic. The patient experiences difficulty in evacuation with the characteristic frequent passage of small volumes of stool. Frequency may be as high as 20–30 defecations per 24 h with the expulsion of no more than a few milliliters of stool on each occasion. Such symptoms are an indication for further investigation (see above).

Long Efferent Limb

The original ileal reservoir (Parks and Nicholls 1978) and the isoperistaltic reconstruction (Fonkalsrud and Bustorff-Silva 1999) both involved the creation of an efferent limb of terminal ileum that formed the proximal side of the ileoanal anastomosis. Neither reconstruction is carried out today. With a limb of up to 8 cm in length in the early years of the reservoir,

Table 8.4. Abdominal revision for mechanical outlet obstruction

Reference	*n*	Follow-up (months)	Failure	Good function	Poor function
Efferent limb					
Liljeqvist and Lindquist (1985)	7	–	2	5	2
Sagar et al. (1996)	9	12–120 (60)	2	7	–
Herbst et al. (1996)	8	>6	1	4	3
Ogunbiyi et al. (1997)	2	>6	0	2	–
Tekkis et al. (2006)	9	1–147 (46)	1	–	–
Stricture					
Sagar et al. (1996)	3	>12	0	3	0
Herbst et al. (1996)	5	>6	0	4	1
Ogunbiyi et al. (1997)	4	>6	1	3	–
Tekkis et al. (2006)	13	1–147 (46)	1	–	–
Retained rectum					
Sagar et al. (1996)	1	>12	0	1	0
Herbst et al. (1996)	2	>6	0	2	0
Tulchinsky et al. (2001)	22	4–14 (22)	5	15	2

Values in parentheses are means.

over 50% of patients were unable to evacuate spontaneously and needed to catheterize the pouch through the anus to do so. Contrast radiological studies showed outflow obstruction that was roughly proportional to the length of the limb (Pescatori et al. 1983). Accordingly, this was shortened to 2 cm, resulting in spontaneous evacuation in around 90% of patients (Dozois et al. 1986; Vasilevsky et al. 1987).

The need for catheterization was usually accepted by patients as a reasonable price to pay for avoiding an ileostomy, but some were unable to tolerate the situation. Further surgery has some prospect of improving matters for such patients, with restoration of spontaneous evacuation. It may be possible to remove the problematic segment endoanally, but this is technically possible in less than 30% of patients (Fonkalsrud and Bustorff-Silva 1999; Nicholls and Gilbert 1990). In most, an abdominoanal salvage procedure is required. The technique is similar to that described for stricture. The pouch is mobilized and the ileoanal anastomosis detached. The efferent limb is excised and a new anastomosis is constructed manually between the pouch and anal canal. The results are summarized in Table 8.4. Of a total of 35 patients, failure occurred in six and improved function, including conversion from catheterization to spontaneous evacuation occurring in 18 of 26 patients where a functional assessment was made (Nicholls and Gilbert 1990; Fonkalsrud and Phillips 1990; Herbst et al. 1996; Liljeqvist and Lindquist 1985).

Stricture of the Ileoanal Anastomosis

Narrowing of the ileoanal anastomosis requiring at least one dilatation under anesthesia has been reported in 4–40% of patients (Galanduik et al. 1990; Breen et al. 1998; Fleshman et al. 1988a; Marcello et al. 1993; Beart 1986; Senapati et al. 1996). Factors leading to fibrosis include pelvic sepsis and anastomotic tension causing separation (Breen et al. 1998; Herbst et al. 1996; Sagar et al. 1996; Lewis et al. 1994), although no statistical difference has been shown in the incidence of stenosis in patients who develop septic complications when compared with those who do not (Senapati et al. 1996). Stenosis may be more common in patients with ulcerative colitis than in those with FAP (Galanduik et al. 1990;

Lewis et al. 1994; Schoetz et al. 1988), and also after a stapled anastomosis, particularly when an instrument with a small head has been used (Lewis et al. 1994). In a series of 266 patients, stenosis occurred in 14.2 and 39.6%, respectively, after manual and stapled anastomosis (Senapati et al. 1996).

The severity of the stricture is assessed by digital examination to determine the diameter, longitudinal length, and the extent of surrounding induration. Contrast radiology is used to assess the length and the degree of dilatation of the proximal bowel. An apparent stricture may be noted when digital examination is carried out for the first time after operation. This is often due to lateral adhesions across the anastomosis creating a web effect, which is easily divided by gentle passage of the finger. Usually this resolves the problem.

In one study, 35 of 50 patients with stenosis were treated by dilatation, including 26 with and nine without general anesthesia (Senapati et al. 1996). Repeated dilatations were necessary in the former group. The stenosis persisted in 37 of the 50 patients and in only 13 did it resolve. In another study, 42 patients who developed a stricture of 982 undergoing restorative proctocolectomy were followed up for 31 (range 1–98) months (Galanduik et al. 1990). All underwent dilatation under anesthetic, with recurrence in 25 and failure in seven. In 23 patients who required repeated dilatation, function was satisfactory and in 11 it was poor. Thus, reasonable function was achieved by dilatation in about half the patients. The incidence of stenosis in another series was 39 of 102 patients, of whom 16 were considered to have severe stenosis that required a median of eight dilatations during a 12-month period (Lewis et al. 1994). Dilatation failed in only one of these patients; in the remaining 15, function was no different from that in patients without stricture.

If symptoms of outflow obstruction persist despite dilatation, surgery may be indicated depending on their severity. In some patients with a tight but short stricture, a posterior stricturotomy may be successful, although there are no published data on the results. This operation runs the risk of sepsis and hemorrhage, and should be carried out under direct vision by means of electrocoagulation. A transanal approach involving excision of the stricture and advancement of the pouch distally has been described in three patients with stricture, two of whom had a simultaneous vaginal fistula. At follow-up of 3–11 months, all had satisfactory function (Fazio and Tjandra 1992).

The endoanal approach is difficult for patients who are unsuitable for this or who do not respond to dilatation. The available options include removal of the reservoir with the establishment of a permanent ileostomy or a major salvage procedure. Removal has been reported to be necessary in 2.5–15% of patients with stricture (Galanduik et al. 1990; Breen et al. 1998; Lewis et al. 1994; Schoetz et al. 1988; Senapati et al. 1996). Abdominal salvage involves mobilization of the reservoir from the pelvis, followed by excision of the stenosis and reanastomosis of the apex of the reservoir to the distal anal canal. It is usually necessary to perform a mucosectomy to achieve this (Fazio et al. 1998; Herbst et al. 1996). Technical details of importance include the need to dissect close to the reservoir to avoid damage to pelvic structures, including the autonomic nerves, and removal of as much of the fibrosis in the area of structuring as possible. Any associated chronic abscess cavity should be curetted and the operation covered by a defunctioning ileostomy.

There is little information in the literature on the outcome of major abdominal surgery for stricture (Table 8.4). In one study, out of 23 patients who underwent abdominal salvage for various reasons, only three showed an indication of anastomotic complication, all of whom had a successful result (Sagar et al. 1996). In another study, five patients treated for stricture were followed for a minimum of 6 months (Herbst et al. 1996). The median frequency of defecation fell from 17 (10–26) to 6 (4–24) after operation with a successful outcome in four.

Retained Rectum After Ileorectal Anastomosis

The aim of restorative proctocolectomy is to remove all disease-prone mucosa. The original technique therefore included a mucosectomy of the upper anal canal with an anastomosis just above the dentate line. With the introduction of stapling techniques (Heald and Allen 1986), the anastomosis usually came to lie more proximal at, or above, the level of the anorectal junction. Some degree of inflammation in biopsies taken

from the anal columnar epithelium is common. This may be severe enough to cause symptoms in 2–15% of patients (Curran and Hill 1992; Lavery et al. 1995; Schmitt et al. 1992; Thompson-Fawcett and Mortensen 1999). In a series of 217 patients who had a stapled anastomosis, 48 (22.1%) had evidence of persisting inflamed mucosa distal to the anastomosis (Laveryet al. 1995). Of these, 32 were symptomatic and 28 needed treatment.

The symptoms of retained inflamed mucosa are those of proctitis, including bleeding, burning, and urgency (Oresland et al. 1990; TULCHINSKY et al. 2001). Disordered evacuation with the frequent passage of small amounts of stool may also occur, and patients are at continuing risk of neoplastic transformation (Sequens 1997). The diagnosis of retained rectum may be made on digital palpation, which will demonstrate the anastomosis to be above the level of the anorectal junction. This will be confirmed by contrast radiology and endoscopy by taking biopsies from above and below the anastomosis.

Treatment with local steroids may relieve the symptoms in some patients, but in others it may not result in a satisfactory long-term solution. Thus, in patients with unacceptable function despite medical treatment, surgery is indicated (Sagar et al. 1996; Curran and Hill 1992; Tuchinsky et al. 2001; Fazio and Tjandra 1994). If there is a short longitudinal length of persisting inflamed mucosa, it may be possible to remove it via an endoanal approach (Fazio and Tjandra 1994). In most patients, however, a combined abdominoanal approach is necessary, with removal of the retained rectal stump followed by mucosectomy of the anal stump and a manual ileoanal anastomosis.

Initial reports of one (Sagar et al. 1996) and two (Herbst et al. 1996) patients with a satisfactory outcome were promising. In a larger series of 22 patients followed for a median of 22.5 (range 4–114) months, failure with excision of the reservoir occurred in five. Seventeen patients had anal function and in these the median 24-h frequency before and after surgery was 12 (range 4–20) and 6 (range 3–12), respectively (Tuchinsky et al. 2001). Median night-time frequency fell from 4 (range 0–8) to 0.5 (range 0–4). Fifteen of the 17 patients reported subjective improvement in the quality of life, giving an overall success rate of 15 of 22.

Summary

Retained rectum is a specific cause of dysfunction and is remediable in most circumstances. It should, however, be avoidable at the time of restorative proctocolectomy by ensuring that the anastomosis is at or below the anorectal junction. This may sometimes be difficult using stapling techniques, but in cases in which there is difficulty, the surgeon should be able to perform a manual anastomosis in this eventuality. The failure rate of over 30% after attempted salvage surgery for this complication is greater than that reported in general series of restorative proctocolectomy.

Small-Volume Reservoir

A compliant pouch of good volume appears to be a factor determining function. There is an inverse relationship between the maximum tolerated volume of the reservoir and frequency of defecation (Oresland et al. 1990; Heppell et al. 1982; Klas et al. 1998; Lazorthes et al. 1986; Nicholls et al. 1985). Patients with a small-capacity reservoir have high stool frequency, sometimes with urge incontinence. The original straight ileoanal anastomosis reconstruction (Ravitch 1947) is an extreme example of this. The diagnosis is made by contrast radiology to give a direct image of the size of the reservoir, and by balloon volumetry, which gives a functional measure of urge and maximum tolerated volume.

If medical treatment fails to reduce unacceptable stool frequency, a reservoir augmentation procedure should be considered using an abdominal approach. It may be possible to add a loop of immediately proximal ileum to the upper part of the reservoir. When this is not technically possible, it is necessary to mobilize the reservoir entirely, including detachment of the ileoanal anastomosis, to allow a complete remodeling. In a report of five patients with functional failure due to low pouch capacity whose reservoir was converted to a pouch, mean for 24 h and nocturnal stool frequency fell from 13.8 and 3.0 to 5.8 and 0.3, respectively, after augmentation (Klas et al. 1998).

Sphincter Dysfunction

Some degree of anal discharge occurs in up to 30% of patients but fecal incontinence due to poor sphincter function is less common, with a

reported frequency of less than 5% (Fazio et al. 1995; Ogunbiyi et al. 1997; Setti-Carraro et al. 1994a). Preoperative assessment of the sphincter may avoid some failures by appropriate patient selection (Pemberton et al. 1982). Previous anal surgery is not, however, necessarily a contraindication to the operation (Fazio et al. 2003; Parker and Nicholls 1992; Richard et al. 1997). In patients with postoperative incontinence, the nature of the sphincter lesion should be determined by clinical examination, anorectal physiological testing, and anal ultrasonography (Korsgen et al. 1996; Thompson and Quigley 1995; Thompson-Fawcett et al. 1997).

There is little information in the literature on the results of salvage surgery for an incompetent sphincter. One study reported two patients who underwent sphincter repair, both with a satisfactory outcome (Thompson and Quigley 1995). Unsatisfactory results were obtained in a series of 11 patients who underwent sphincter reconstruction. Only four retained the reservoir and seven required a permanent ileostomy (unpublished data). The prospect of salvage surgery for sphincter dysfunction appears to be poor.

Pouchitis

The creation of an ileoanal reservoir leads to mucosal changes whether the operation is done for ulcerative colitis or FAP. These include villous atrophy and the infiltration of chronic inflammatory cells to a varying degree. Acute inflammation leading to symptoms is mostly confined to patients with ulcerative colitis (Dozois et al. 1989; Heuschen et al. 2001; Moskowitz et al. 1986). The reported incidence of pouchitis ranges from 9% to more than 50% (Fazio et al. 1995; Fleshman et al. 1988a; Heuschen et al. 2001; Moskowitz et al. 1986; Keranen et al. 1997; Luukkonen et al. 1994; Setti Carraro et al. 1994b; Stein and Lichtenstein 2000; Veress et al. 1995) and increases with the duration of follow-up (Pemberton 1993). However, it is recorded as the main cause of failure in only 7–15% of patients (Tulchinsky et al. 2003; Fazio et al. 1995; Marcello et al. 1993; Setti-Carraro et al. 1994a).

The clinical features of pouchitis are similar to those of colitis and the treatment is medical. The recently reported use of probiotics as maintenance treatment offers some hope for those with chronic unremitting pouchitis (Gionchetti et al. 2000), but surgery appears to have no useful role. Defunctioning does not influence the degree of inflammation in the reservoir mucosa, as demonstrated by poor results in three of a group of 28 patients with pouchitis who were treated by a loop ileostomy. In one, the ileostomy was subsequently closed and further attacks of pouchitis occurred (Shepherd et al. 1989). Surgical revision with construction of a new reservoir also results in recurrent pouchitis and up to 5% of patients with chronic unremitting pouchitis have undergone excision of the reservoir (Hurst et al. 1996; Tygat and van Deventer 1988).

Conclusion

Abdominal salvage surgery for pelvic sepsis is successful in the intermediate term in around 60% of patients. This is less than the 80% or more success rate for patients in whom the indication is nonseptic, including those with mechanical outlet obstruction, retained rectal stump, and small volume reservoir. Pouch vaginal fistula in patients in whom the internal opening lies above the anorectal junction after a stapled anastomosis is cured in 65% by abdomino-anal pouch advancement. In patients with a fistula opening into the anal canal, local repair is successful in about 40%. There is no place for redo surgery for pouchitis. Crohn's disease is a significant risk factor for failure and revisional pouch surgery is not indicated when this is diagnosed.

Abdominal salvage surgery is a major undertaking for the patient. Complications may occur and the duration of treatment, including stay in hospital, may have a serious impact on a patient who has already suffered disappointment and ill health owing to the threatened failure after primary restorative proctocolectomy. The chance of success is an essential part of the consultation process and must be discussed fully.

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9

Surgery for Fecal Incontinence

Klaus E. Matzel

Introduction

Fecal incontinence is the inability to prevent involuntary loss of bowel content. Its psychological and social consequences are devastating. Even though fecal incontinence is a widespread problem, its true prevalence is unknown. Approximately 2% of the general population suffers from the inability to control bowel emptying (Nelson et al. 1995), but this rate rises with age, with up to 11% in men and 26% in women reporting this problem over the age of 50 years (Roberts et al. 1999), reaching up to 40% in nursing-home patients most of the time in combination with urinary incontinence (Chiang et al. 2000).

With better diagnostic methods, the understanding of the physiology and pathophysiology of the various components of the anorectal continence "organ" has improved in recent years. Fecal continence is maintained by coordinated, synergistic, organic functions of the reservoir system of the rectum, the outlet resistance of the sphincteric complex, and the sensory lining of the anal canal. Their functional interaction is attained by a convergence of somatomotor, somatosensory, and autonomic innervation.

Causes of lesions are frequently multiple. Trauma to each of the components can cause functional deficit resulting in fecal incontinence. Rectal reservoir function can therapeutically be addressed with surgical replacement after resection or refixation in cases of rectal prolapse, but most surgical procedures for fecal incontinence aim to improve, augment, or substitute sphincteric function, as trauma to the sphincter complex is the most common cause of uncontrolable loss of bowel content.

Diagnostics and Treatment Considerations

As the causes of fecal incontinence are multifactorial, it is important to identify the morphologic and functional deficits to establish a meaningful therapeutic concept. Endoanal ultrasound and MRI provide imaging to exclude or detect morphologic defects of the rectum and sphincteric complex. Interestingly, comparable morphologic and functional lesions may result in clinical pictures of varying severity. This is a further proof of the complex interaction of various anatomical structures and their ability to compensate one another at least partially. Endoanal ultrasound, in particular, is relatively easy to perform and can be considered as an essential part of the diagnostic workup.

Anorectal manometry can test and quantify the muscular function of the smooth-muscle internal anal sphincter and the striated-muscle external anal sphincter, the perception of rectal filling and distension, the compliance of the rectal reservoir, and the reflexive interaction of the rectum and anal sphincter. Electromyographic recording of the striated muscles of the external anal sphincter and the pelvic floor permits

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differentiation of the muscular from neurogenic defects and estimates the extent of reinnervation. Measuring the conductance of peripheral nerves (pudendal nerve terminal motor latency [PNTML]) helps to identify neural lesions.

The diagnosis of fecal incontinence is based on a standard anorectal examination (to exclude pathologic conditions that may result in secondary incontinence) and a focused history including stool frequency, urge symptoms, incontinence for gas, liquid or solid stool, difficulties in passing stool, necessity of digital help when emptying, and day-time-dependence of symptoms.

As decision-making is based not only on the extent of symptoms, but also on its impact on the quality of life, standardized questionnaires and general and disease-specific quality of life scores (Rockwoor et al. 2000; Brazier et al. 1992) are being widely used in recent years to objectively quantify the extent and severity of fecal incontinence and its the impact on the quality of life and to monitor the therapeutic effect.

Deficits of single functional components of the continence organ can be compensated partly and for a certain period of time until the compensating structures fail, i.e., due to changes in the tissue strength after menopause. Most cases of incontinence can be sufficiently treated with relatively simple pragmatic measures, and a commonly accepted principle is to proceed first with the simplest, least invasive treatment modalities: If sphincteric lesions amenable to direct repair are excluded, conservative treatment such as diet, medication, and retrograde irrigation can – without further diagnostic steps – be initiated to improve stool consistency, delayed colonic transit, and establish a normal periodicity to bowel emptying. If these fail or do not produce adequate results, further diagnostic procedures are indicated to differentiate muscular from neurogenic and combined lesions. Based on the diagnostic findings, two concepts of treatment can be discussed: functional rehabilitation in patients with no morphologic defects and morphologic reconstruction in patients with morphologic defects of functional relevance aiming to reestablish morphologic integrity and thus function.

Functional Rehabilitation

Biofeedback

Biofeedback, as a conservative modality, can be considered as the first choice for functional rehabilitation. Based on the principle of operant conditioning, visual or acoustic signals are used to create awareness in the patient regarding the use of specific physiologic functions and thus to recruit residual function. There is no standardized protocol for biofeedback and various techniques such as electromyography, manometry, and intrarectal balloon distension are applied to modify voluntary sphincter function, anorectal sensation, or coordination. Reported success ranges widely (Table 9.1), Baseline test have limited predictive value regarding the outcome of biofeedback (Terra et al. 2008; Byrne et al. 2007). Outcome has been found to be poorer for male

Table 9.1. Biofeedback, published results of outcome since 1999, including series with ten or more patients, general measures of continence (Adapted from Norton and Kamm 2001)

References	Number of patients	Mean or median follow-up (months)	Method of biofeedback	Percentage (%) improved	Percentage (%) of patients without fecal incontinence
Feyes et al. (1999)	40	ns	Manometry	79	56
Leroi et al. (1999)	27	ns	Balloon	30	19
Norton et al. (1999)	100	ns	Manometry	67	43
Ryn et al. (2000)	37	44	EMG	41	40
Wiesel et al. (2000)	13	na	Manometry	78	78
Musial et al. (2000)	41	9	EMG	ns	58
Chiarloni et al. (2002)	24	12	Balloon	71	54

ns not stated.

gender, passive fecal incontinence, previous third degree tear, and more severe symptoms. How severity of fecal incontinence related to outcome of biofeedback remains controversial (Terra et al. 2008; Byrne et al. 2007). A recent Cochrane review concluded that there is no evidence that one specific method of biofeedback is superior to others, or that biofeedback is better than other conservative treatment modilities (Norton et al. 2006).

Another conservative measure, retrograde irrigation, is intended to improve rectal reservoir function (by distension and improved perception through a defined stimulus) and to establish a rhythm for sufficient bowel emptying (to ensure time intervals free of fecal loss). Only if these conservative therapies fail to improve symptoms should surgical intervention be considered.

Sacral Nerve Stimulation

Sacral nerve stimulation (SNS) is based on the concept of recruiting residual function of the continence organ by stimulation of its peripheral nerve supply (Matzel et al. 1990a). Various physiologic functions contributing to continence are activated by low-frequency electrostimulation of one or more sacral spinal nerves by a fully implantable neurostimulation device (Matzel et al. 1995, 2004a). Patients for permanent implantation of a neurostimulation device are selected by a therapeutic trial and a timely limited phase of percutaneous test stimulation. The results of the test stimulation have a highly predictive value for success. Implantation of the final permanent neurostimulation device is commonly advised if the frequency of episodes of fecal incontinence documented by a bowel-habit diary is alleviated by at least 50% during the screening with test stimulation and if the improvement is reversible after stimulation discontinuation.

The technique of SNS has become a minimally invasive technique with low morbidity. The surgical technique can be divided into two stages: This first stage, termed as percutaneous nerve evaluation (PNE), is used to confirm a satisfactory nerve response and then evaluate the clinical effect of stimulation prior to the implantation of a permanent device. Two technical options are used for subchronic PNE: a temporary, percutaneously placed, test stimulation lead (or multiple leads) that will be removed at the end of this phase (Matzel et al. 1990b); or operative placement of a quadripolar lead, the so-called "foramen electrode" close to a target nerve. This electrode can stay in place and be used for permanent stimulation, if the test stimulation is effective. Today, this foramen electrode is most commonly placed by a minimally invasive technique with the help of fluoroscopy that uses a foramen electrode with an anchoring device, the so-called "tined lead" placed through a trochar (Spinelli et al. 2002). For screening, both the types of leads are connected to an external pulse, the latter with a percutaneous extension cable.

The second stage is implantation of a permanent electrode and neurostimulator if screening is successful. Those with a temporary lead require simultaneous implantation of the pulse generator and the quadripolar lead, most commonly as a tined lead procedure. Those with a foramen electrode already in place for screening will undergo removal of the percutaneous extension before placement of the pulse generator (so-called "two-stage implant") (Janknegt et al. 1997). Bilateral placement of foramen electrodes remains as an exception, based either on improved outcome of bilateral stimulation during the screening phase (Matzel et al. 2002) or on conceptual considerations (Ratto et al. 2005). The pulse generator is placed subcutaneously in the abdominal wall or gluteal area. The pulse generator is activated and stimulation parameters are set early after surgery by telemetry. The pulse generator can be deactivated by the patient with a small, hand-held device commonly referred to as a "patient programmer."

With the help of test stimulation, the spectrum of indications for SNS has been continuously expanded to patients suffering from fecal incontinence owing to a wide variety of causes resulting in the lack of function: weakness of the external anal sphincter (Matzel et al. 2003), with concomitant urinary incontinence (Leroi et al. 2001) or a defect and/or deficit of the smooth-muscle internal anal sphincter (Malouf et al. 2000a); status postrectal resection (Matzel et al. 2002); limited structural defects of the external anal sphincter combined with limited defects of the internal anal sphincter (Malouf et al. 2000a); and neurogenic incontinence (Rosen et al. 2001).

The therapeutic effects of SNS have been demonstrated in multiple trials (Table 9.2). With chronic SNS, the frequency of involuntary loss of bowel content is reduced, the ability to postpone defecation and quality of life is improved (Matzel et al. 2004b), and a substantial

Table 9.2. Sacral nerve stimulation, published results of outcome since 1999, including series with ten or more patients (Adapted from Madoff et al. (2009))

References	Number of patients	Follow-up (months)	Incontinent episodes per week		Incontinence-score (CCIS)	
			Before SNS (baseline)	After SNS (last FU)	Before SNS (baseline)	After SNS (last FU)
Rosen et al. (2001)	16	15[a]	6	2	ns	ns
Ganio et al. (2001a)	16	15.5	5.8	0	ns	ns
Matzel et al. (2003)	16	32.5	ns	ns	16	2
Altomare et al. (2004a)	14	14[a]	7	0.5	15	2
Matzel et al. (2004a)	34	24[a]	16.4	2.0	ns	ns
Jarrett el al. (2004)	46	12[a]	7	1	14	6
Rasmussen et al. (2004)	34	6	ns	ns	18	7
Leroi et al. (2005)	34	7[a]	3.5[a]	0.5[a]	16[a]	10[a]
Kenefick et al. (2006)	19	24[a]	12	0	ns	ns
Holzer et al. (2007)	29	35[a]	2.3	0.67	ns	ns
Hetzer et al. (2007)	37	13	ns	ns	14	5
Tan et al. (2007)	53	12	9.5	3.1	16	1.2
Melenhorst et al. (2007)	100	25.5	10.4	1.5	ns	ns

CCIS Cleveland Clinic Fecal Incontinence Score: 0 = fully continent, 20 = worst incontinence.
[a]Median, otherwise all data presented as mean.

percentage of patients gain full continence (Matzel et al. 2004a). Morbidity of the procedure is low and complications are rare. In less than 5% of patients, device removal becomes a necessity (Matzel et al. 2004a; Tjandra et al. 2004a), mostly because of pain or infection. After removal of the device because of infection, reimplantation can be performed successfully at a later date (Matzel et al. 2004a).

The physiologic mode of action of SNS is not yet clearly understood. Clinical outcome of SNS has been correlated with the results of anorectal physiology studies, but the effect of chronic stimulation varies greatly among the published reports (Matzel et al. 2004a; Tjandra et al. 2004a). Data are partly contradictory and inconclusive, and sometimes not reproducible. Some studies have demonstrated increased resting anal pressure (Matzel et al. 1990b; Spinelli et al. 2002; Ganio et al. 2001b; Kenefick et al. 2002), but others have not (Matzel et al. 2001a). Several studies have documented an increase in anal squeeze pressure (Matzel et al. 2001a, 2004a, b; Spinelli et al. 2002; Ganio et al. 2001b; Tjandra et al. 2004a). SNS appears to increase rectal sensitivity; and improvement in anal sensory function and sensibility of the perianal and perineal skin during SNS has been reported (Rosen et al. 2001). Rectal manometry (24-h) has indicated qualitative changes in anal and rectal motility: Reduction in spontaneous rectal motility complexes and spontaneous anal sphincter relaxation has been observed (Vaizey et al. 1999). A consistent decrease in corticoanal representation and overall excitability immediately after the onset of temporary SNS was reversible and ceased after discontinuation of the stimulation. This finding indicates a dynamic central effect of peripheral stimulation (Sheldon et al. 2005). The effect of SNS on continence is complex and multifactorial, involving somatomotor, somatosensory, and autonomic functions of the anorectal continence organ and modulation of the peripheral and central functions.

Reconstructive Techniques

Bioinjectables

The concept of injection of bulking agents into the anal sphincter complex has been adapted from its use in increasing urethral resistance at the leval of the bladder neck. However, the exact

mechanism of action of biojectables is not fully understood, and it is still unclear whether continence is augmented by increasing the hemorrhoidal cushion or the filling of small sphincteric gaps or by other mechanisms. Internal sphincter defects or degeneration are the most common indication for bioinjectables. A variety of substances has been applied in the past, only few have gained broader acceptance with injectables made out of silicone biomaterials (PTP, PTQ) being the most widely used. Intersphincteric application at four sites appears to be the most efficient; endoanal ultrasound guided application was found to be better than digital-guided application of the substance: Cleveland Clinic Continence scores in the ultrasound-guided group decreased from 14.5 to 3 and that of the nonguided group decreased from 14.5 to 11 at 12 months (Tjandra et al. 2004b). The risk profile is low. Long-term data are pending for various substances.

The outcome of other techniques, aiming to augment anal sphincter function, such as radiofrequency energy delivery, has been mixed, and only reported in small cohort studies (Takahashi-Monroy et al. 2008).

Sphincter Repair

Morphologic reconstruction is indicated if a defined, functionally relevant, sphincteric defect is diagnosed. Sphincter repair aims to reestablish function by reconstructing the morphologic defect: a muscular gap is closed by coaptation of the dehiscent muscle. The term sphincter repair is used to describe primary repair of the anal sphincter mechanism immediately following direct trauma. The most common indication is following childbirth and repair in this situation is usually performed by the obstetrician. In colorectal surgery, the common cause of primary repair is an injury that is the result of blunt or penetrating trauma. A secondary or delayed reconstruction of the anal sphincter musculature in conditions where the injury is either not recognized at the time of injury or the outcome of primary repair has been unsatisfactory is termed as anal sphincteroplasty. Anterior sphincteroplasty is the most common type of reconstruction performed because of the association with obstetric injury.

The results of anal sphincteroplasty have not been reported uniformly, and thus, it is difficult to evaluate the series and to compare the outcome of this technique with that of other procedures. Moreover, prospective outcome recording is rare; most reported results are based on patients' recall and are limited to functional issues without addressing the quality of life. Approximately half of the patients report a significant improvement in continence (Table 9.3). However, the long-term therapeutic effect of sphincter repair has recently been questioned, as several studies have reported a deterioration in function over time (Malouf et al. 2000b; Karoui et al. 2000; Zorcolo et al. 2005).

Table 9.3. Anal sphincteroplasty, published results of outcome since 1999, including series with 50 or more patients (Adapted from Madoff et al. (2009))

References	Number of patients	Follow-up (months)	Continent (%) (excellent/good)
Malouf et al. (2000a)	55	77	49
Karoui et al. (2000)	74	40	47
Osterberg et al. (2000)	51	12	58
Morren et al. (2001)	55	40	56
Tan et al. (2001)	50	28	50
Halverson et al. (2002)	71	69	25
Bravo Gutierrez et al. (2004)	130[a]	120	6
Norderval et al. (2005)	71	27	41
Zorcolo et al. (2005)	93	70[b]	55
Trowbridge et al. (2006)	86	67	11
Barisic et al. (2006)	65	80[b]	48

[a]130/190 available for 10-year follow-up.
[b]Median follow-up.

If sphincter repair – despite reestablishment of morphologic integrity – fails to achieve success, or if function deteriorates over time, patients can be considered for functional rehabilitation, such as biofeedback, irrigation, and sacral nerve stimulation as well as repeat sphincter repair (Pinedo et al. 1999). Recently, the body of evidence has indicated that SNS may also be a treatment option for patients with sphincter defects, not only after attempted anatomic reconstruction, but also in those primarily unrepaired (Conaghan and Farouk 2005; Chan et Tjandra 2008; Melenhorst et al. 2008).

Sphincter Replacement

Sphincter replacement procedures are indicated if conservative treatment fails, if functional rehabilitation is not successful, if incontinence is the result of a substantial muscular defect that is not suitable for sphincter repair, or if a neurologic defect is present. Two techniques have gained broad acceptance: dynamic graciloplasty (DGP) (Baeten et al. 2000) and the artificial bowel sphincter (ABS) (Lehur et al. 2000). The indications for both the procedures are similar: end-stage incontinence in patients with a substantial muscular and/or neural defect of the anal sphincter complex. Both the procedures represent an alternative to the creation of a stoma.

Dynamic Graciloplasty

Dynamic Graciloplasty is a modification of the transposition of the gracilis muscle around the anus to function as a neosphincter, which was described in the early 1950s (Pickrell et al. 1952). The aim of this transposition is to encircle the anal canal completely with muscle tissue. Thus, the configuration of the muscle sling – alpha, gamma, episilon configuration – is determined by the length of the muscle and its tendon. This passive muscle wrap is rendered dynamic by the implantation of a neurostimulation device consisting of two electrodes and an impulse generator that is placed subcutaneously. To function, the innervation of the gracilis muscle must be intact. To adapt the muscle to prolonged contraction, the periods of stimulation are increased in a stepwise fashion, resulting in a transformation of the muscle fiber type to ensure fatigue resistance. The gracilis muscle is predominately composed of type II, fast-twitch fatigable muscle fibers. Application of graded electrical stimulation by the implanted device has been shown to convert the muscle phenotype of the transposed gracilis muscle to predominantly type I fibers, which are fatigue-resistant and slow-twitching (Konsten et al. 1993; Salmons and Vrbova 1969; Rongen et al. 2003). Once continuous low frequency stimulation is established, the stimulator is deactivated by an external magnet for muscle relaxation and anal opening. Thus, bowel emptying becomes a voluntary act (Table 9.4).

Artificial Bowel Sphincter

The ABS (Acticon neosphincter, American Medical Systems) consists of three components: An inflatable silastic cuff placed around the anus via perianal tunnels; a liquid-filled, pressure-regulating balloon positioned in the preperitoneal fat; and a manual pump connecting these components, which is placed in either the labia majora or the scrotum (Lehur et al. 2000). The anal canal is closed as the cuff is filled with the

Table 9.4. Dynamic graciloplasty, published results of outcome since 1999, including series with 40 or more patients (Adapted from Madoff et al. (2009))

References	Number of patients	Follow-up (months)	Percentage continent[a]
Madoff et al. (1999)	131	24 (median)	66
Mander et al. (1999)	64	16 (median)	69
Baeten et al. (2000)	123	23 (mean)	74
Wexner et al. (2002)	83	24	53
Rongen et al. (2003)	200	16.3 (median)	72
Pennickx et al. (2004)	60	48 (median)	55
Tillin et al. (2006)	49	43 (median)	70

[a]Variable definitions; is not necessarily equivalent to perfect continence.

liquid. At the time for defecation, the device is deactivated via the manual pump; the cuff empties and the anus opens to pass the stool. The cuff is refilled and the anus is closed after a few minutes (Lehur et al. 1998).

As with dynamic graciloplasty, opening of the ABS becomes a voluntary act and closure of the anal canal is maintained without conscious effort – mimicking the initiation of defecation in the healthy individual. However, when compared with DGP, there is a higher risk of infection with this implanted artificial material. The risk is higher especially if the silastic cuff of ABS can not sufficeniently be covered by soft tissue owing to trophic alterations after trauma, or following irradiation.

Short- and long-term effects on function have been published in several studies (Table 9.5). DGP patients with incontinence secondary to trauma had the best results with up to 82% success rate, whereas outcome with a 52% success rate was less favorable in patients with incontinence owing to congenital neorectal malformations (Rongen et al. 2003). Longitudinal observations report stable success for DGP in a multicenter study with 63% at 1 year, 55% at 18 months, and 56% at 24 months follow-up (Wexner et al. 2002). In a 5-year outcome evaluation, 33/38 patients revealed that the DGP was still in use and it was found to be clinically efficient in 22/33 patients; however, 50% of the patients reported obstructed defecation (Wexner et al. 2002). Improvement in function was associated with improvement in the quality of life. Owing to the heterogenicity of the reported outcome measurements, data must be interpreted with caution.

In virtually all the reports, both the sphincter replacement procedures are associated with substantial morbidity (Chapmann et al. 2002; Mundy et al. 2004), and in few studies comparing ABS vs. DGP, the outcome and complication rates were similar for both the techniques (Ortiz et al. 2003; Da Silva et al. 2004). In a large multicenter study with 123 patients treated with DGP at 20 centers, 18 major and 31 minor complications were recorded in 89 patients: therapy-related pain occurred in 42 instances and lead dislodgements in 11. No lead breakage or IPG malfunction was experienced. 87% of the patients recovered fully or partially from these complications. The need for operative revision reached 42% for the DGP in this trial (Matzel et al. 2001b) when compared with 46% for the ABS (Wong et al. 2002), with treatment having to be discontinued in 8 and 37%, respectively.

In the largest multicenter trial for ABS, 75/115 patients (65%) retained a functioning device after a median follow-up of 12 months with an overall complication rate of 87%. In a 5-year follow-up in longitudinal cohort study, only 24% patients retained a functioning device and a

Table 9.5. Artificial bowel sphincter, published results of outcome since 1999, including series with ten or more patients, general measures of continence (Adapted from Madoff et al. (2009))

References	Number of patients	Mean or median follow-up (months)	Number (%) of functioning devices	"Success" in patients with a functioning device (%)	"Success" in intention to treat
Lehur et al. (2000)	24	20	20 (83%)	90	75
O'Brien et al. (2000)	13	ns	10 (77%)	90	69
Malouf et al. (2000c)	18	26	7 (39%)	ns	39
Altomare et al. (2001)	28	19	21 (75%)	67	50
Devesa et al. (2002)	53	26.5	26 (49%)	65	53
Wong et al. (2002)	115	12	75 (65%)	85	54
Ortiz et al. (2002)	22	28	15 (68%)	60	41
Lehur et al. (2002)	16	25	12 (75%)	92	69
Parker et al. (2003)	37	39	17 (46%)	49	47
Michot et al. (2003)	25	34.1	20 (80%)	79	60
Casal et al. (2004)	10	29	9 (90%)	44	40
Altomare et al. (2004b)	25	ns: long-term	6 (24%)	50	12

ns not stated.

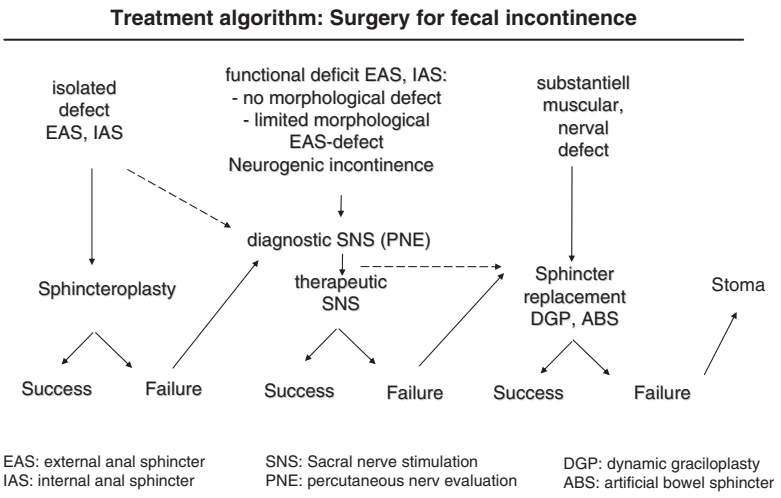

Figure 9.1. Treatment algorithm: surgery for fecal incontinence.

good clinical effect was maintained in half of them (Malouf et al. 2000c).

For both the techniques, the most severe complications were infections (Mundy et al. 2004; Ortiz et al. 2003). Their occurrence is not surprising if one bears in mind that the operation is performed in a naturally contaminated area (Matzel et al. 2001b; Christiansen 2000). In most cases of infections, device removal is unavoidable. The functional complication most relevant clinically is outlet obstruction (Penninckx 2004; Mundy et al. 2004; Matzel et al. 2001b). This may be caused by a preexisting obstruction not identifiable because of incontinence or by "hypercontinence" subsequent to neosphincter creation. Frequently, this functional problem can be successfully treated with the application of regular enemas (Rongen et al. 2003; Mundy et al. 2004).

Antegrade Continence Enema (ACE)

The idea of ACE is to ensure regular emptying of the colon and rectum and thus, preventing involuntary loss of bowel content. Anterograde bowel lavage is performed through an artificial opening involving operative construction of an appendicostomy, cecostomy, or sigmoidostomy (Krogh and Laurberg 1998; Kielyet al. 1994; Marsh and Kiff 1996; Gerharz et al. 1997). Reported improvement ranges from 65 to 78% in heterogenous patient populations, some which include patients with defecation disorders (Hirst et al. 2005; Poirier et al. 2007); wound complication at the stoma site is the most common complication occurring in up to 45% of the patients, but less frequent in stoma out of ileum and designed as a neo-appendicostomy.

Stoma Creation

The creation of a diverting stoma should be considered as an alternative to surgery for end-stage incontinence, even though it does not address incontinence per se, if comorbidity or intellectual or physical inability precludes the above-described sphincter replacements. Stoma creation carries its own risks, however, and patient counseling and performance of the procedure and postoperative management should be done with great care.

Summary

The surgical options for fecal incontinence have advanced during the recent years. Depending on the underlying condition, various surgical treatment modalities can be offered and a new treatment alogrithm has evolved (Fig. 9.1). Surgical options should be considered if conservative treatment has failed or is suboptimal. Symptoms and quality of life can be improved if patient selection is appropriate. Although these procedures carry some morbidity, they may act as an alternative to the creation of a diverting stoma.

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10

Recurrent Rectal Cancer

Sowsan Rasheid, Dana R. Sands, and Laurence R. Sands

Introduction

Recurrent rectal cancer poses a significant morbidity and mortality. Survival is ultimately shortened while patients concurrently suffer far greater disability with the recurrence. Recurrent pelvic disease often results in a diminished quality of life and is often associated with increased pain, incontinence, sexual and urinary dysfunction, and possibly colonic obstruction. The primary goal of therapy for rectal cancer is preventing recurrence by properly managing the disease on initial presentation. The secondary goal is to develop proper follow-up for patients with recurrent rectal cancer in order to detect recurrence early enough so that potentially curative surgery may be undertaken. Determining whether the patient may be cured needs a careful history, physical examination, and selected utilization of radiographic imaging modalities. Surgical intervention is often multidisciplinary combining the resources of colorectal, orthopedic, urologic, gynecologic, and plastic surgeons.

Incidence

The overall incidence of rectal cancer recurrence ranges from 5 to 50% (Spiliotis and Datsis 2004; Salo et al. 1999) and the 5-year survival rate for these patients is 5% (Boyle et al. 2005). In a review of 113 patients who underwent abdominoperineal resection (APR), there was a 31.8% incidence of recurrence with approximately 70% of these recurrences occurring within 2 years after surgical resection (Adloff et al. 1985). The median time to local recurrence in another study was noted to be 14 months with a range of 3–60 months. The presence of pelvic recurrence was diagnosed at a median of 15 months while the median time for anastomotic recurrence was 12 months (De Chaisermartin and Penna 2009).

Factors most likely predisposing to local recurrence are lymph node involvement, the grade of malignancy, the lower level of tumor in the rectum, and local spread into perirectal fat or serosa (Adloff et al. 1985). Other studies affirm the direct relationship between the pathologic stage of the primary tumor and the incidence of local failure. Rich and his colleagues demonstrated an 8% recurrence rate for Dukes' A stage, 31% for B stage, and 50% for C stage. The presence of primary tumor that is locally invasive to adjacent structures without lymph node involvement also increased the likelihood of subsequent recurrence to 54% when compared with 17% with only microscopic extension through the wall and no lymph node involvement. Other factors found to be strongly predictive of local recurrence were tumor location, T-stage, number of lymph nodes involved, and blood vessel invasion (Rich et al. 1983; Yun et al. 2008).

Probably, the most important factor for predicting local recurrence is circumferential margin involvement by the cancer. The first study to

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report the association between circumferential margin and risk for local cancer recurrence was carried out by Quirke and his colleagues in 1986. Quirke prospectively evaluated the entire surgical specimens of 52 patients with rectal carcinoma using whole-mount and serial transverse sectioning techniques to examine the lateral margins of the specimens. He discovered that 14 out of these 52 patients had positive radial margins. Twelve of these 14 patients subsequently developed pelvic recurrence making the positive predictive value for this finding 85%. His findings implicated a positive circumferential resection margin as a predisposing factor for pelvic recurrence (Quirke et al. 1986). These observations were further corroborated by a prospective study by Adam and his colleagues who evaluated 190 patients and demonstrated that 90% of patients with negative circumferential margins were free of recurrence in 5 years. Alternatively, patients who had positive margins had a much higher incidence of pelvic recurrence. Only 23% of patients who had margin involvement by cancer remained free of cancer recurrence at 5 years.

The significant increase in the risk of rectal cancer recurrence in the presence of positive margins reinforces the importance of the role of prevention and maintaining clear margins when operating on patients with rectal cancer. The importance of this concept is underscored by the development of total mesorectal excision as the standard surgical technique for accomplishment of complete resection of rectal cancer. As an example of this, Heald was able to demonstrate a local recurrence rate of 4% at 10 years following curative resection of rectal cancer with total mesorectal excision and no adjuvant radiation in all patients he treated. Patients treated with this complete mesorectal excision method by Heald who had Astler-Collar B2 and C stages were noted to have a 5-year recurrence rate of 5%. Patients in the control group of this study who underwent conventional surgical excision were found to have a local recurrence rate of 25%. However, when adjuvant radiation was employed postoperatively, the local failure rate was reduced to 13.5%. While adjuvant chemotherapy and radiation were found to improve outcomes following conventional surgical excision, it is not a substitute for negative margins, which are best obtained by using the approach of a total mesorectal excision (Temple and Saettler 2000).

Surveillance Following Primary Therapy

There remains intense debate as to the benefits of close follow-up for patients with colorectal cancer. There is even greater debate for those who believe in intense follow-up as to what that follow-up should actually be. A meta-analysis of six randomized trials addressing the intensive follow-up of patients with colorectal cancer proved that there was an overall reduction in mortality of 10% in those undergoing intensive follow-up (Renehan et al. 2005). As such, there have been many different regimens proposed as to the most effective follow-up for postoperative rectal cancer patients. All protocols combine obtaining a detailed history asking questions specific to symptoms of recurrence (including rectal bleeding, weight loss, changes in bowel habits, pelvic pain, genitourinary dysfunction) along with a physical examination and a careful digital rectal examination.

The digital rectal exam is perhaps one of the most important ways to detect recurrent rectal cancer. Those patients who underwent a low anterior resection with a total mesorectal excision will often have an anastomosis low enough so that it is readily palpable on digital rectal exam. An experienced clinician may be able to instantly detect recurrence on this exam alone. While there have been many methods and protocols that have been proposed to monitor patients after primary resection, the authors have adopted the protocol outlined in Table 10.1. While there may be little utility in monitoring CEA levels in those patients who have never had an elevated CEA level, the authors still use this as part of the protocol.

Whichever follow-up protocol is adopted, it is important to continuously monitor patients who have undergone surgery for rectal cancer. Early detection of recurrent disease remains the best means of achieving a surgical cure for these patients as well as relieving their symptoms and preventing the morbidity of recurrent disease.

Diagnosis of Recurrence

Patients with rectal cancer recurrence may or may not be symptomatic. Those individuals who present with anastomotic recurrence are usually initially discovered on careful follow-up physical examination. A palpable irregularity or

Table 10.1. Follow-up protocol for postoperative colorectal cancer patients

First follow-up	Routine Hx[a] and PE[b] Medical Oncology referral for all patients with advanced cancer (T3 or greater and/or nodal disease)
1 Month	Hx, PE, DRE[c], CEA[d]
3 Months	Hx, PE, DRE, CEA Schedule colonoscopy within first six months if not performed preoperatively due to obstruction (If positive, repeat annually. If negative, repeat at 3 years)
6 Months	Hx, PE, DRE, CEA
9 Months	Hx, PE, DRE, CEA
12 Months	Hx, PE, DRE, CEA, CBC, LFTs Colonoscopy CXR and CT scan of the abdomen and pelvis
15 Months	Hx, PE, DRE, CEA
18 Months	Hx, PE, DRE, CEA
21 Months	Hx, PE, DRE, CEA
24 Months	Hx, PE, DRE, CEA, CBC, LFTs Colonoscopy if the first annual scope was positive CXR
2 Years, 6 months	Hx, PE, DRE, CEA
3 Years	Hx, PE, DRE, CEA, CBC, LFTs Colonoscopy for all patients CXR
3 Years, 6 months	Hx, PE, DRE, CEA
4 Years	Hx, PE, DRE, CEA, CBC, LFTs, Colonoscopy if any previous postoperative scope was positive CXR
5 Years	Hx, PE, DRE, CEA CBC, LFT Colonoscopy every 3–5 years CXR

[a]Postoperative history.
[b]Physical examination.
[c]Digital rectal exam.
[d]Carcinoembryonic antigen.

stricture may be found on digital examination of the anastomosis. Sometimes, patients may complain of rectal bleeding or change in bowel function. Those patients with large anastomotic recurrence will usually complain of decreased stool caliber, bleeding, or rectal pain.

Anastomotic abnormalities can also be seen during endoscopic examination where a biopsy should be obtained to confirm the diagnosis. Tissue confirmation is essential to confirming recurrence and must be done prior to initializing any further therapy. If the tissue necessary for histologic confirmation of recurrence is not obtainable through endoscopic means, then an exam under anesthesia with deeper biopsies may be performed for intraluminal disease or extraluminal and palpable disease.

Patients presenting with rectal cancer recurrence following an APR may be noted to have ulcerating masses or nodules in the perineum, which may be biopsied. These patients may require CT-guided biopsies if the recurrence is inaccessible due to its location.

In the presence of pelvic recurrence, symptoms may include pain resulting from invasion of bony and neural structures. Urinary retention and bowel obstruction are other presentations of pelvic recurrence (De Chaisermartin and Penna 2009).

Radiographic Studies

Radiographic evaluation is necessary in both the surveillance of patients after primary therapy and the characterization of recurrences after they are diagnosed. There is, however, no standardized protocol for routine radiographic surveillance after primary therapy. Table 10.1 outlines one potential protocol for clinical and radiologic surveillance. Once recurrence has been confirmed, radiologic imaging is imperative to detail the extent of the lesion and the feasibility of resection. CT scans are often the initial study done to look for distant metastases as well as determine the extent of the pelvic recurrence, particularly searching for extramural disease. Figure 10.1 demonstrates sacral involvement by

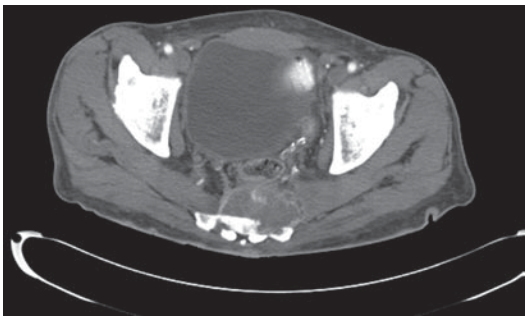

Figure 10.1. CT scan of the pelvis demonstrating posterior rectal cancer recurrence involving the sacrum.

recurrent rectal cancer. CT scans are also helpful in determining the involvement of other adjacent pelvic organs as well as assessing whether or not there is evidence of distal ureteral encasement.

Recent literature suggests that PET scans may provide additional information and may complement the use of CT scans. A recent study from the Netherlands evaluating 32 patients with recurrent rectal cancer with a total of 37 recurrences revealed overall concordance of results between PET scans and other imaging methods. PET scans differed from both MRI and CT findings in 13 cases, detecting disease in seven patients on PET imaging where the MRI and CT scans did not. PET scans, however, failed to reveal disease that was seen on CT scans and MRI in the remaining six patients. In summary, the PET scan altered surgical therapy in a total of five patients, three of whom were able to undergo less extensive surgery because PET imaging did not reveal as extensive disease. One patient in this study avoided surgery because of a positive inguinal lymph node seen on PET imaging and one additional patient was able to undergo more extensive surgery rather than simple palliation (Fanyete et al. 2008).

A comparison study evaluating multidetector CT and PET/CT scans in the diagnosis of recurrent rectal cancer showed a near equal sensitivity and specificity for the detection of local recurrence with both methods approaching 100%. Both techniques were also equivalent in evaluating for liver metastases (Bellomi et al. 2007).

PET scans have been shown to be useful in distinguishing patients with isolated local recurrence from those who have metastatic disease. This fusion would most likely exclude patients with diffuse recurrent disease from undergoing extensive resection. This concept is reinforced by findings from Meta and his colleagues who reported in their study that PET scans changed the management of 41% of patients with colorectal cancer (Meta et al. 2001).

The fusion of PET and CT scans has also been shown to improve the sensitivity and specificity of this fusion when compared with either study imaging modality alone. In a multicenter, prospective trial by Scott et al. from Australia, 119 patients were assessed for changes of management resulting from the use of combined PET/CT scan. The patients were divided into two groups: the first group included those patients who had suspicious areas of local recurrence while the second group included patients who had potentially resectable hepatic or pulmonary metastases. In the first group, 48% of the patients were found to have other sites of disease, which had not been detected on initial studies prior to PET/CT scans. Forty-four percent of the patients in the second group had additional areas of disease. These findings resulted in significant changes in management for 66 and 49% of patients in the first and second groups, respectively (Scott et al. 2008).

The endorectal ultrasound has a rather limited role in looking at recurrent disease, particularly after total mesorectal excision has been performed. However, this modality can be useful in the surveillance of the retained mesorectum after transanal excision of rectal cancer.

The use of endorectal ultrasound as a means for obtaining tissue biopsy for confirmation of suspected recurrent rectal cancer has been well described. The ability to visualize extraluminal structures such as peri-rectal soft tissues and lymph nodes is advantageous for direct guidance of biopsy needles to obtain tissue for pathologic evaluation. Specialized biopsy probes have been developed for this purpose. The actual biopsy procedure is well tolerated by patients and many studies report no associated morbidities. Studies utilizing endorectal ultrasound-guided techniques demonstrate sensitivities ranging from 83 to 91% and specificities in the range of 93–100% in detecting recurrence of rectal cancer (Hunerbein et al. 2001; Morken et al. 2006).

Pelvic MRI has also been used as a means of detecting and staging patients with recurrent rectal cancer. In some centers, it remains the diagnostic test of choice and the most accurate modality in staging patients (Hosein and Rocha-Lima 2008). MRI findings suggestive of recurrence include perivascular encasement and the presence of perirectal spiculate nodules (Oh et al. 2005). More problematic areas of differentiation on MRI imaging include pelvic sidewall disease, particularly in the face of previous radiotherapy and previous surgical therapy (Messiou et al. 2008).

A new and innovative modality to help in the detection of rectal cancer recurrence is radioimmunoscintigraphy. This approach combines the methods of nuclear medicine with the advances of molecular biology. The basic design involves

growing anti-CEA monoclonal immunglobulins in mice. These antibodies are grown specifically to bind the CEA molecules with high affinity and are shown not to react with other types of cells in the body. They are then labeled with a radioactive isotope such as ^{99m}Technicium (^{99m}TC). A patient is injected with this preparation and then subjected to single photon emission computed tomography (SPECT) at serial intervals following the injection according to various protocols. The first imaging is done in 4–6 h followed by a second imaging in 22 h. A positive study is identified by increased activity of the isotope in a certain region of the body over time (Lunnis et al. 1999; Yao et al. 2007).

One study utilizing this method in the management of recurrent rectal cancer assessed 40 patients who underwent 47 such scans using ^{99m}Tc-radiolabeled PR1A3 monoclonal antibody. In this group of patients, sensitivity was demonstrated to be 96%, specificity was noted to be 50%, with a positive predictive value of 73% and a negative predictive value of 89%. The authors observed that the PR1A3 scan as an addition to other follow-up modalities improved the management in 5 of the 40 examined patients. However, the authors concluded that because of the small population size and the short follow-up periods, a definitive recommendation regarding the clinical use of this modality could not be made. There may, however, be patients who may benefit from the addition of this modality to the follow-up protocol (Lunniss et al. 1999).

Another more recent study utilized another monoclonal antibody known as CL-58. Thirty-six patients suspected of having recurrent rectal cancer underwent ^{99m}Tc-labeled CL58 SPECT scans in addition to CT scans, PET scans, and colonoscopy. Thirty-one of these patients were found to be positive on ^{99m}Tc-CL58 in different areas such as the pelvis, presacral region, liver, and retroperitoneal lymph nodes. The tumor was confirmed pathologically in 30 of these patients. The specificity was 83% and the sensitivity was 100%. The authors concluded that radioimmunoscintigraphy is useful and could eventually be incorporated into a follow-up regimen for rectal cancer (Yao et al. 2007). However, it is still not clear what the practical applicability of this modality will be in daily clinical practice and the characteristics of the patients who would benefit from such a study.

Patterns of Recurrence

There are essentially four patterns of recurrence that are noted for rectal cancer. Recurrences may occur following transanal local excision, at the level of the anastomosis, in the perineum after APR, or within the pelvis as extramural disease. If the recurrence occurs after local resection or within the anastomosis, radical surgery is repeated in an attempt to clear the remaining disease. If the patient has not as yet received neoadjuvant therapy, one should strongly consider instituting this modality prior to surgical intervention.

If the recurrence is following APR or as extraluminal disease, once again, neoadjuvant therapy should be utilized if not previously given and radical surgery offered when possible. This type of exenterative surgery may require a team of surgeons including a spine or an orthopedic surgeon, plastic surgeon, colorectal surgeon, urologist, and possibly a gynecologist.

Multiple classification systems have been proposed to describe the patterns of recurrent disease. The goal of each proposed nomenclature is to define the extent of the recurrence and delineate the degree of invasion of related pelvic structures. In a review of 412 patients with rectal cancer treated by anterior or APRs, Pilipshen and his colleagues attempted to characterize patterns of recurrence. Sites of recurrence were classified as pelvic, liver, distant viscera, and intraabdominal/retroperitoneal sites. Forty-four percent of the patients studied developed recurrence of their rectal cancer following a curative resection. Of the patients who did recur, 57.6% had a pelvic recurrence, which was the most common site of recurrence either alone or in conjunction with other extrapelvic sites (Pilipshen et al. 1984).

A different classification system suggested by Wanebo et al. is based on modification of the TNM staging system for primary rectal tumors. The depth of penetration of the recurrent tumor into the bowel wall is taken into account in a manner corresponding to the T-stage of the primary tumor. Still another classification system proposed by the Memorial Sloan Kettering group takes into account the anatomical region of the pelvis in which recurrence takes place. In this system, the pelvis is divided into axial, anterior, posterior, and lateral regions. Axial recurrence refers to involvement of structures such as the anastomosis or perirectal soft tissue. The

perineum is also included in the axial division when recurrence develops following an APR. Anterior recurrence indicates involvement of the genitourinary tract by tumor while posterior recurrence involves the sacrum and presacral fascia. Finally, the lateral location signifies tumor recurrence in the soft tissues of the pelvic sidewall and lateral bony pelvis.

In a study by Heriot, which also categorized recurrence by the region within the pelvis, central recurrence, which corresponds to the axial location, was found in 44% of the 160 patients undergoing radical resection. Anterior recurrence occurred in 16% of patients, posterior in 12%, anteroposterior in 6%, lateral in 13%, anterolateral in 4.5%, and posterolateral in 4.5% (Heriot et al. 2008).

Surgical Management

Determination of Resectability

Surgical management for recurrent rectal cancer is often radical and extensive. The main goal for surgical resection of recurrent disease is to achieve a curative R-0 resection, which has been shown to improve overall survival. Rates of resectability vary from 8 to 46% when considering patients undergoing R-0 resections with or without metastatic disease (Bedrosian et al. 2006; Bergamaschi et al. 2001).

In considering a patient for re-operative surgery, he or she must be physically fit to undergo such a radical procedure and must have an overall good performance level. Contraindications to surgery include unresectable distant metastases, unresectable lateral pelvic sidewall involvement, compression or infiltration of the iliac vessels, lower extremity edema, sciatic nerve involvement, sacral nerve involvement above S2, peritoneal carcinomatosis, or prohibitive comorbidities.

The presence of distant metastases is generally accepted as a contraindication to resection of recurrent rectal cancer. However, multiple studies suggest that in a highly select group of patients having recurrent rectal carcinoma and concomitant distant disease, it is reasonable to perform a resection of the recurrent disease followed by resection of the metastasis. A report by Maetani et al. examined 59 patients with locally recurrent rectal carcinoma who underwent repeat resection. A total of 12 patients in the group had developed distant metastases. Seven of these patients underwent resection of their metastatic disease prior to undergoing surgery for resection of recurrent disease while four others had both metastatic and recurrent disease resected simultaneously. Eleven of the 12 patients with metastatic disease died within 36 months. The 5-year survival for these patients with metastases was 0% in contrast to the 32% 5-year survival observed in patients without distant disease (Maetani et al. 1998). Another study evaluated 42 patients for resection of recurrent colorectal cancer with concurrent distant metastases. Twenty-two of these patients were able to undergo potentially curative surgery. Thirteen of these 22 patients underwent simultaneous resection of the recurrence and the metastases, while the remaining nine patients had this done as a staged procedure. An additional eight patients were considered for staged resection as well following the resection of primary disease; however, owing to progression of metastatic disease, a lengthy recovery from postoperative complications, or the development of another pelvic recurrence, these patients never underwent additional surgery. The remaining patients in this study group (12) underwent resection of their recurrent disease but were not considered candidates for resection of the metastases owing to the presence of peritoneal seeding or distant nodal disease that was uncontrollable at the time of resection of the recurrence. The median survival for all 42 patients was 14.5 months. The 22 patients who were able to undergo both a complete resection of the recurrence and the metastases had a better outcome with a median survival of 23 months. This median survival compares favorably with the much lower median survival of 7 months observed in patients who had remaining residual disease. The authors concluded that the ability to remove all gross recurrent and metastatic disease was found to be the most significant factor in improving median survival on both univariate and multivariate analysis. However, the long-term survival for all patients in this study was 2.3% with only 1 of the 42 patients surviving at 5 years. As such, the authors also concluded that the natural history and the long-term survival of the disease are not really altered by aggressive surgical management; however, there does seem to be a benefit in terms

of median survival. They recommended that patients with metastatic and recurrent disease should still be considered for surgical therapy. However, the selection criteria of the patients who would truly benefit from this approach needs to be better defined (Hartley et al. 2003).

In a study by Moore assessing the resectability of 119 patients with colorectal cancer with pelvic recurrence, the location of the recurrent tumor significantly affected resectability. Patients found to have axial and/or anterior recurrences were significantly more likely to undergo an R-0 resection, while those found to have lateral tumor recurrence had decreased likelihood of such a curative surgery. On evaluation of available preoperative imaging in 70 patients of the study group, involvement of pelvic sidewall by recurrent tumor was found to be significantly associated with less R-0 resections (Moore et al. 2004).

Patients who present with recurrent tumor fixation in increasing sites in the pelvis were found to be significantly more likely to undergo a palliative resection on multivariate analysis. Patients whose initial treatment of the primary cancer required an end-colostomy and those having symptomatic pain due to recurrent disease were more likely to undergo palliative surgery on univariate analysis (Hahnloser et al. 2003).

The presence of hydronephrosis has historically been considered a contraindication to curative resection (Rodriguez-Bigas et al. 1992). A retrospective review of 27 patients with recurrent rectal cancer and unilateral or bilateral hydronephrosis revealed that 55% of these patients had metastatic disease at the time of the presentation. Of the remaining 12 patients, only 6 underwent surgery and all were deemed unresectable with a median survival of 14 months. The authors concluded that the presence of hydronephrosis portends a poor prognosis similar to that of distant metastatic disease and that there is no role for curative surgery in locally recurrent disease in the face of hydronephrosis (Cheng et al. 2001). Larsen and his colleagues demonstrated a median survival of 27 months and a 5-year survival of 11% in patients with local recurrence in the setting of hydronephrosis. They found that even in the setting of hydronephrosis, two-thirds of the patients achieved some benefit from surgery with potentially improved survival and local control (Larsen et al. 2005). Henry et al., more recently, concluded that hydronephrosis should not be an independent contraindication to attempted curative resection. After retrospective review of their recurrent rectal cancer patient population, the authors found no statistical difference in disease-free or overall survival in the 15 patients with hydronephrosis when compared with the 56 patients operated on in the same time interval without hydronephrosis (Henry et al. 2005). The presence of hydronephrosis should certainly raise the suspicion of any surgeon planning to care for a patient with recurrent pelvic disease. Newer data with small groups of patients may suggest that isolated hydronephrosis should not be an absolute contraindication; however, the surgeon should use exhaustive measures to look for other potential causes for unresectability.

Pelvic Exenteration

Total pelvic exenteration may be the only feasible option in patients with recurrent rectal cancer after previous curative intent surgery. Once metastatic disease has been ruled out and resection deemed possible, there are several options facing the surgeon depending on the pattern of recurrence. For disease that is confined to the anastomosis in a previously resected patient, the best surgical option is to offer the patient neoadjuvant therapy if not previously given and then re-resect the patient with another restorative procedure with total mesorectal excision and a proximal diverting stoma with clear margins. If there is no ability to restore bowel continuity, then APR should be performed and a permanent stoma created. If the patient has undergone initial APR and experiences pelvic recurrence, the most logical approach is often total pelvic exenteration with or without sacral resection. Operative morbidity remains high after total pelvic exenteration. Saito et al. reported a 28% local re-recurrence at 2 years after radical resection and an overall 5-year survival of 39% after curative intent surgery alone. The survival rate in the group receiving preoperative radiotherapy followed by surgery was as high as 51%. It should be noted that these patients did not receive neoadjuvant radiotherapy as part of the treatment of the primary cancer, as this was not the usual protocol for treatment in Japan (Saito et al. 2003). Kakuda and his colleagues reported on

22 patients with recurrent rectal cancer. His retrospective review of these patients who underwent total pelvic exenteration revealed that only 17 of these patients were able to undergo potentially curative surgery. There was one operative death while the morbidity exceeded 68%. Ten patients required readmission to the hospital. The mean survival was 20.4 months for curative intent surgery while it was only 8.4 months for palliative surgery. Considering the high operative morbidity and the poor survival, the surgeon must clearly think of alternative means of palliation for recurrent rectal cancer (Kakuda et al. 2003).

Another retrospective review of 12 patients with recurrent rectal cancer undergoing total pelvic exenteration revealed a 3- and 5-year survival of 32 and 16%, respectively. Incomplete resection and preoperative pelvic pain were identified as poor prognostic factors in determining overall survival and local disease control (Vermaas et al. 2007).

While pelvic exenteration may be done for both primary and recurrent rectal cancer, the general consensus reflects that the outcome is worse in those undergoing this radical surgery for recurrent disease. In fact, Gannon and his colleagues reported that the only factor that altered outcomes related to whether or not the procedure was being done for recurrent or primary disease. He showed a disease-free 5-year survival of 13% for recurrent disease when compared with 52% survival for primary disease. In addition, re-recurrence after initial recurrence was significantly higher at 52% than recurrence after initial primary resection, which was seen at 22%. The overall complication was 43% for both primary and recurrent rectal cancer and was not noted to be significantly different for either group of patients (Gannon et al. 2007).

Combined Sacrectomy with Exenteration

Abdominosacral resection for recurrent rectal cancer requires a multidisciplinary surgical approach with cooperation from colorectal, orthopedic, and plastic surgeons experienced in such procedures (Figs. 10.2–10.4).

Combined pelvic resections require tremendous operative and hospital resources for this high-risk procedure.

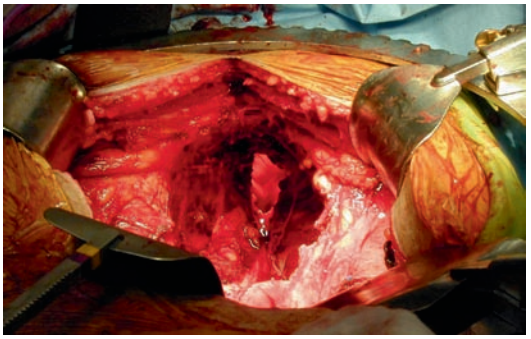

Figure 10.2. Abdominal view of total pelvic exenteration.

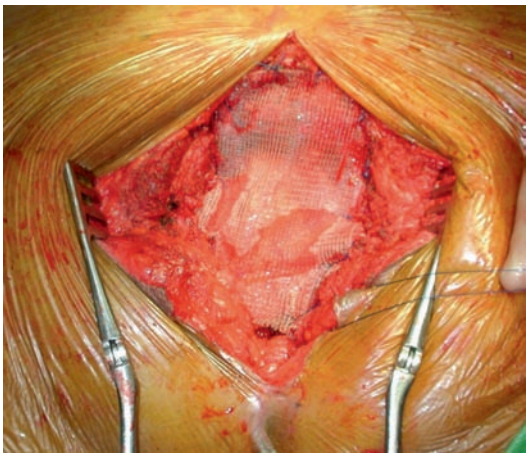

Figure 10.3. Abdominosacral resection. The perineal defect has been closed using mesh following the sacrectomy phase of the procedure.

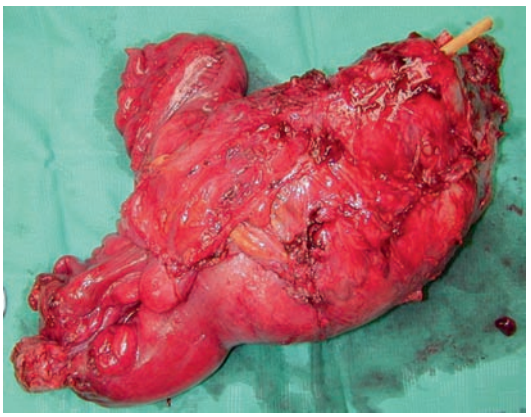

Figure 10.4. En-bloc specimen consisting of rectum, prostate, and urinary bladder after total pelvic exeneteration (note Foley catheter on the *right side* of the photo).

While complication rates may be high, reasonable results may be obtained if patient selection is appropriate. In a series of 57 patients who underwent this type of surgery, 48 patients had clear margins and overall survival at 3 and 5 years was 62 and 42%, respectively (Moriya et al. 2004). Another study of 42 patients with recurrent rectal cancer subjected these patients to a wide variety of procedures including APR with sacral resection, anterior pelvic exenteration, total pelvic exenteration, and total pelvic exenteration with sacral resection. Thirty patients underwent curative resection while 12 patients underwent surgery for palliation. The authors demonstrated an operative morbidity of 60%, a mortality of 2.4%, and a 5-year survival of 22.9%, provided the surgery was done for curative intent. There were no 5-year survivors in those who underwent surgery for palliation (Yamada et al. 2002).

Memorial Sloan Kettering reported on 29 patients retrospectively reviewed who underwent this radical type of surgery for locally recurrent disease. Nearly all the patients underwent preoperative radiotherapy prior to sacral resection, with only ten patients receiving this radiotherapy prior to the initial resection. Intraoperative radiotherapy was used in 12 patients. Most of the patients who had undergone previous APR now underwent total pelvic exenteration with sacrectomy while those who underwent sphincter salvage surgery now underwent APR without exenteration. The complication rate was 59% overall mostly consisting of perineal wound breakdown followed by pelvic abscess. The 2- and 5-year recurrence rates were 47 and 85%, respectively, while the survival rate at 5 years was 20%. Better survival was seen in those with complete resection, fewer blood transfusions, no anterior organ involvement, and no cortical bone involvement (Melton et al. 2006).

One series reported in 2007 of patients who underwent radical surgery for recurrence including total pelvic exenteration and some patients who underwent exenteration with pelvic bone resection; the authors predicted that the disease-free interval was the most important predictor of curability with a disease-free interval of more than 3 years being of greatest benefit. Being female and having no distant metastases were also similar predictors of better outcome. In addition, the extent of re-resection was not found to alter curability. They also found that a rise in CEA level was not associated with curability; however, the rising CEA was predictive of shorter survival in incurable patients (Maetani et al. 2007).

Other authors reported their outcome for patients undergoing surgery for locally recurrent rectal cancer. In their series of 160 patients, all patients who did not receive radiation therapy prior to their initial resection did undergo neoadjuvant therapy prior to their re-resection. In some cases, intraoperative radiotherapy was also used if there was concern for clear margins. While most patients underwent an extended radical resection, this group found that positive margins and the use of intraoperative radiotherapy were associated with poorer survival. The overall cancer-specific survival at 5 years was 41.5%. Twenty seven percent of patients experienced major complications. They concluded that even though complications were greater in the extended radical resection group, survival was best if this extended radical resection resulted in negative surgical margins (Heriot et al. 2008).

A Japanese study looking at total pelvic exenteration identified 45 patients who underwent this type of surgery. They reported an in-hospital death rate of 13.3%, an operative morbidity of 77.8% consisting mainly of pelvic abscess, and a 5-year overall survival of 14.1%. This long-term survival was stratified based on whether it was felt that the exenteration was done with absolute curative intent (31.6% – no residual tumor on histology), relative curative intent (7.8% – no obvious residual tumor), or noncurative intent (0% – residual tumor). They also found that a shorter disease-free interval was associated with better survival unlike other studies possibly due to earlier detection of this recurrence. In addition, this series showed a 64.1% re-recurrence after total pelvic exenteration suggesting that local recurrence was not well controlled after surgery (Ike et al. 2003).

Table 10.2 summarizes the survival results as well as the morbidity and mortality from the latest studies regarding radical resections of recurrent cancer.

In attempting a composite abdominosacral resection for recurrent rectal cancer, great care should be taken in determining the level at which the sacrectomy will be performed so as to limit the associated morbidities. Involvement of

Table 10.2. Survival following surgical resection for recurrent rectal cancer

References	Number of patients with recurrent cancer	Type of resection	Duration of follow-up (median)	Morbidity (%)	Perioperative mortality (%)	Disease specific survival (%)
Yamada et al. (2002)	42: 30 curative intent 12 palliative surgery	APRa, APEb, TPEc ± sacral resection	–	60	2.4	5-year: 22.9 for curative intent 5-year: 0 for palliative surgery
Saito et al. (2002)	43	Pelvic exenteration or APR ± sacral resection	39.7 months	49	9	3-ye ar: 46 5-year: 39
Kakuda et al. (2003)	22	Pelvic exenteration	17 months	68	4	5-year: 12
Bakx et al. (2004)	40	APR, Abdominosacral resection, APE, TPE	100 months	72.5	5	5-year: 28
Moriya et al. (2004)	57	TPE with distal sacrectomy	43 months	58	3	3-year: 54 5-year: 36
Melton et al. (2005)	29	Composite sacrectomy (in combination with exentera-tion, APR or LAR)	23 months	59	3	2-year: 63 5-year: 20
Weiser and Land man (2005)	50	APR, LAR, TPE, transanal excision	33 months	34	0	5-year: 53
Akasu and Yamaguchi (2006)	44	Abdominal sacral resection	4.7 years	61	2	5-year: 34
Vermaas et al. (2007)	12	TPE	28 months	83	0	3-year: 32 5-year: 16
Schurr et al. (2008)	72: 45 underwent surgical resection	Anterior resection, APR, TPE ± sacrectomy	–	24	9	Median overall survival: 54.9 months
Sagar and Gonsaleves (2009)	40 R0: 20 R1: 20	Composite abdominosacral resection	25 months	60	2.5	Median overall survival: R0: 55.6 months R1: 32.2 months

[a]Abdominoperineal resection.
[b]Anterior pelvic exenteration.
[c]Total pelvic exenteration.

the sacrum by the tumor above the S1–S2 junction renders these patients unresectable as transaction of the S1 nerve roots results in weakness of plantar flexion. It is recommended, therefore, that a sacrectomy be limited to the S2–S3 junction as the most cephalad margin for resection so as to allow for perseveration of the S2–S3 nerve roots. In doing this, bladder function may be maintained in those patients for whom a cystectomy is not necessary (Sagar and Gonsaleves 2009).

Laparoscopic Surgery

Employment of laparoscopic surgery for the treatment of recurrent rectal cancer is not well defined. Its role is limited by the nature of the disease, the extensive involvement of pelvic structures by the tumor, and the technical difficulty that may be encountered in working in a re-operative field. Laparoscopic surgery may be helpful as an exploratory tool to be used prior to open surgical resection. It may be useful in excluding those patients who may have carcinomatosis or distant organ metastasis not previously diagnosed on preoperative imaging. In effect, a patient with more extensive disease than previously thought may be spared the morbidity associated with open exploration.

As such, there are only two reports in the literature where laparoscopy has been utilized for resection of recurrent rectal cancer. In the first report from China, the authors employed laparoscopic-assisted surgical resection with or without hand-assistance for a total of seven patients with recurrent rectal cancer of the central type. The types of resections were laparoscopic-assisted anterior resection in three patients, laparoscopic-assisted APR in one patient, laparoscopic-assisted posterior exenteration in one patient, laparoscopic-assisted proctocolectomy with end ileostomy, and a laparoscopic-assisted sigmoid colostomy in one patient who had unresectable disease. The authors were able to perform R-0 resection on the first six patients as evidenced by the final pathologic examination. The use of a hand-assisted device was required in two cases. The mean operation time was reported to be 211 ± 13 min and mean estimated blood loss was 200 ± 90 mL. The authors concluded that the use of laparoscopy is feasible and safe in selected patients who have central rectal cancer recurrence (Lu et al. 2003).

Another more recent case report involves a multimedia article regarding a female patient who presented with an anastomotic recurrence after having undergone a laparoscopic ultralow anterior resection 13 months prior to the cancer recurrence. The patient was able to undergo subsequent laparoscopic APR and posterior vaginectomy for treatment of the recurrent cancer. The patient had no reported morbidity following the surgery. The authors concluded that salvage re-laparoscopy in patients who had previously undergone laparoscopic resections for their primary rectal cancer should be considered and patient anatomy should not discourage surgeons from attempting such procedures (Kim et al. 2008). However, laparoscopy may be limited to a highly select group of patients who may have had previous laparoscopic resections of their primary cancer and/or have a central pattern of disease recurrence.

While these initial reports seem to be encouraging, more information is needed to clearly define the role of laparoscopic surgery for resection of recurrent rectal carcinoma and the characteristics of patients who may benefit from this approach in mainstream clinical practice. The ability to perform a laparoscopic exploration is applicable for ruling out carcinomatosis or distant metastasis or for creation of stomas for diversion of unresectable disease. Implementation of this approach can be useful in reducing morbidity and preventing patients from undergoing unnecessary open exploratory surgery to determine resectability.

Palliative Surgery

While curative surgical resection of recurrent rectal cancer provides some improvement in overall disease-specific survival, patients who undergo palliative resections do not benefit from R-1 or R-2 resections. Mean survival for patients who undergo palliative resections is reported to vary from 8.4 to 19 months (Kakuda et al. 2003; Law and Chu 2000; Garcia-Aguilar et al. 2001; Miner et al. 2003). Five-year survival is also poor for palliative surgery ranging from 0 to 6% (Yamada et al. 2002; Garcia-Aguilar et al. 2001). These figures bring into question the efficacy of performing such extensive surgery with morbidities as high as 83% and mortalities up to 9% (Saito et al. 2003; Vermaas et al. 2007).

In a study by Miner and his colleagues, patients who underwent palliative surgical intervention for symptomatic relief of recurrent cancer had only little improvement in their symptoms and this was short-lived. Palliative procedures were performed on 24 of 105 patients. Nineteen of these patients underwent the surgery to alleviate symptoms of obstruction (42%), bleeding (21%), and pain (20%). In the asymptomatic group, palliative surgery was done for prevention of future complications such as gastorintestinal obstruction. The surgical treatment included colostomy for fecal diversion from internal bypasses, local tumor excision or fulguration, and abdominoperineal resections. Nearly half of these patients noted clinical improvement in their symptoms in the first month after palliative surgery. However, most of these relapsed quickly and developed worsening of their symptoms following surgery. In fact, pain after surgery was actually worse than it was prior to the surgery while bleeding and obstructive symptoms improved. Moreover, even this improvement was not for long. Improvement in pain lasted for 3 months. The authors noted that symptomatic relief was best in those who underwent surgery with a nonpalliative intent. These patients, in fact, had a significantly longer median symptom-free survival period of 23 months as opposed to 4 months for those undergoing palliative surgery. The authors recommended that palliative procedures could be carried out to achieve some relief of symptoms but with the understanding that this relief is not long-lasting (Miner et al. 2003).

Use of Intraoperative Radiation Therapy

The use of multimodality treatment is being offered with the anticipation of improving the overall outcome for patients with recurrent disease. The goals for this type of treatment are rapidly shifting to improving the overall survival and potentially curative resections rather than just palliation alone. Proponents of intraoperative radiotherapy argue that this modality allows for direct delivery of radiation to the affected tissue without significant harm to other normal organs. In addition, biologic tissue levels of radiation given intraoperatively reach two to three times those administered by the same dose of conventional external beam radiation. Some surgeons have advocated radical surgery with sacrectomy and the concomitant use of intraoperative radiotherapy. The Mayo Clinic reported the outcomes of 16 patients who underwent this type of therapy. They described a 50% operative morbidity, no mortalities, and a 68% 1-year and a 48% 2-year survival. Nearly all the survivors reported a decrease in pain and improved quality of life after this combined therapy (Magrini et al. 1996).

In a study from Japan, a total of 51 patients underwent resection for recurrent rectal cancer. Twenty-seven out of these patients were administered IORT in addition to surgery. The study noted significantly improved 3- and 5-year survival in patients who underwent IORT in conjunction with surgical resection. The 3- and 5-year survival rates for patients who had surgery alone were 5 and 0%, respectively. In contrast, patients who underwent multimodality treatment that included surgery and IORT had a 43% 3-year and a 21% 5-year survival. Moreover, the application of IORT seemed to improve control of local disease particularly in patients who had negative margins on resection. Only one of nine patients (11%) receiving IORT following negative margins had recurrence of their cancer, while three out of eight patients (38%) who had negative margins following surgery alone without IORT had local failure (Hashiguchi et al. 1999).

In another study by Hahnloser and his colleagues, the use of IORT as part of multimodality approach to treatment of recurrence was evaluated. Three hundred and four patients underwent aggressive surgical resections for the intent of curing recurrent disease. A variety of different procedures were undertaken including APR, Hartmann's procedure, wide local excision of the pelvic recurrence, and radical surgery such as sacrectomy and pelvic exenteration. One hundred and thirty-eight patients had negative microscopic margins following surgical resection of their recurrent disease. One hundred and sixty-six patients had positive margins and therefore were considered to have undergone palliative resection. IORT was administered to patients with positive margins as long as the entire disease site could be included within the radiation field. More than half of the palliative surgery group underwent IORT while 33% of patients who had curative surgery were also given IORT. The authors found that the 5-year

survival for patients with negative margins following surgical resection was 37%. Five-year survival was significantly decreased to 16% in patients who had positive surgical margins despite the use of IORT. Although not statistically significant, the authors noted that patients who had positive microscopic margins fared better than those who had macroscopic disease. The addition of IORT, those patients who underwent palliative surgery demonstrated an overall 21% 5-year survival for that particular group. In contrast, patients who had curative surgery and IORT had a 27% 5-year survival. The factors that were predisposing patients for local failure and recurrent disease were positive macroscopic margins and the degree of fixation of the recurrent tumor to adjacent pelvic structures. Overall morbidity was noted to be 26%. The authors concluded that therapeutic options may include combined surgical resection and intraoperative radiation therapy (Hahnloser et al. 2003).

In another study from the Mayo Clinic, which reviewed the effects of treating 51 previously irradiated patients with surgical resection and IORT followed by the addition of external beam radiation (EBRT), there appeared to be a benefit with improved local control in patients receiving aggressive multimodality therapy. However, the overall long-term survival remained dismal at 12% (Haddock et al. 2001).

In contrast, a study from Norway by Wiig did not demonstrate a significant difference in overall survival or local failure in patients who received IORT when compared with those who did not receive IORT. In the 44 patients evaluated, prolonged survival was found to be dependent on the ability to obtain an R-0 or R-1 resection. The 5-year survival for R-0 resection was 65%, R-1 resection was 25%, and there were no survivors in the R-2 resection group. The addition of IORT did not appear to add survival benefit (Wiig et al. 2002). This finding was corroborated in other similar studies where factors that may contribute to prolonged survival after surgery with IORT were assessed. The absence of vascular invasion was found to be an independent predictor of improved local control and disease-free survival (Shoup et al. 2002). The ability to affect a radical surgical resection of the recurrent disease with negative microscopic margins conferred a significant survival advantage on these patients as well (Hahnloser et al. 2003; Dresen et al. 2008).

Vermaas and his colleagues noted a high morbidity and only 5 months of a pain-free period in 11 patients who underwent surgery and IORT. These patients had previous neoadjuvant irradiation. Although the study did not question the value of IORT as an important modality in the treatment of recurrent rectal cancer, it did bring into question the use of IORT in treating patients who had previous neoadjuvant irradiation (Vermaas et al. 2008).

Common complications following multimodality treatment for recurrent rectal cancer include bleeding, pelvic abscess, bowel obstruction, fistula formation, and perineal wound complications.

The radical nature of the surgical resection necessary to gain tumor-free margins and the radiation utilized for treatment can lead to severe functional disability resulting from tissue loss and the involvement of adjacent structures by tumor and inflammatory tissue. The functional outcomes for these patients are rarely discussed. However, as more patients undergo such aggressive management of their recurrent disease and survival is improved, the functional outcome is now being assessed. In a study from the Netherlands, significant functional impairment was noted in such patients causing limitation in their daily activities and lifestyles. Many patients reported fatigue, perineal pain, leg pain, and more than one-third of these patients had difficulty in walking and voiding. These many patients also required assistance with daily living and more than half had sexual inactivity. Finally, there were significant social handicaps resulting from multimodality therapy, as 44% of patients were unable to resume their former lifestyles and many had to stop working (Mannaerts et al. 2002).

In conclusion, one must also take into account the resulting morbidity and long-term functional outcomes following such treatment. A multidisciplinary team approach is necessary for selection of patients who would benefit from such procedures and in their subsequent care and follow-up.

Perineal Reconstruction

Radical surgical resection of recurrent rectal cancer results in tissue loss that can pose a challenge for subsequent closure of the resulting defect. Often, the resulting wound is large and

the surrounding tissue is previously irradiated resulting in a greater chance for poor healing. The size of the defect also usually prevents primary closure. In a study evaluating primary closure of APR wounds in patients who have undergone neoadjuvant radiation, wound complications were found to be significantly elevated when compared with those patients who did not receive neoadjuvant radiation. The study assessed a total of 160 patients who underwent primary closure following APR. One hundred seventeen patients received neoadjuvant radiation while 43 patients did not. There was a 41% overall wound complication rate. The most common complication was delayed wound healing followed by infection of the wound. Patients who had undergone neoadjuvant radiation therapy were found to be at a significantly greater risk of developing overall wound complications at 47% when compared with 23% in those who were not irradiated. Patients who had radiation were also more likely to have wound infections. In short, patients who had neoadjuvant radiation were found to have twice the risk of developing wound complications following primary closure. This increased risk of wound complications following primary closure stresses the importance for having alternate means to affect safe and satisfactory closures of these defects (Bullard et al. 2005).

While a comprehensive discussion of technical details of reconstructive procedures using tissue flaps is beyond the scope of this book, it is necessary that the colorectal surgeon has an appreciation for and an understanding of the options available for closure of the defects resulting after extirpative surgery. A variety of myocutaneous flaps have been devised for the purpose of closure of these large wounds. Use of such flaps provides healthy, well-vascularized tissue to previously irradiated sites. They also help in filling dead space within the pelvis and thereby alleviate the descent of abdominal organs into the deep pelvis. It is necessary that the colorectal surgeon and reconstructive surgeon collaborate closely when planning to perform such procedures. Achieving well-healed wounds with minimal morbidity as well as a good functional outcome are basic tenets that must be adhered to when flap closure is entertained. One must also take into account stoma locations and previous surgery, which may prevent the use of certain types of flaps.

Multiple options are available for flap closure; these range from the simple to the complex. When the extirpative procedure results in the removal of the pelvic organs without an associated perineal skin defect, the omentum can be used to fill the dead space in the pelvis and bring new vascular supply into that area. However, the omentum may be absent and as such other options may be utilized to gain closure of the perineum (Friedman et al. 2000). Another option for reconstruction may be the rectus abdominus myocutaneous flap, which is derived from the rectus abdominus muscle. This flap is based on the inferior epigastric artery and vein as the source of vascular supply. In making this flap, a skin island with underlying subcutaneous fat is raised supraumbilically. The rectus muscle is carefully dissected off the rectus abdominus sheath down to the insertion of the muscle in the pubis symphasis. It is then passed down transabdomanly where the bulk of the muscle is situated in the pelvis to help fill the dead space resulting from extirpative surgery while the skin island is used to bridge the gap in the perineum and thereby provide effective closure of the wound. The right rectus abdominis muscle is preferentially used over the left so as to allow for placement of a colostomy in the left lower quadrant across the left rectus abdominis muscle. In a study by Chessin, the use of RAM flap in 19 patients who had neoadjuvant radiation followed by APR was compared with outcomes of a similar group of 59 patients who also had APR but with primary wound closure. Perineal wound complications were found to be significantly lower relative to the control group. Patients who underwent RAM flaps had a 15.8% rate of wound complications when compared with the much higher incidence of 44% of wound complications in the control group (Chessin et al. 2005).

Another possible flap is the gracilis muscle or myocutaneous flap. This flap derives its blood supply from the medial circumflex branch of the profunda femoris artery. The muscle is used to fill the resulting pelvic dead space by introducing it into the cavity through rotating the muscle superiorly. A skin island could be fashioned as necessary to assist in the closure of the perineum. Shibata et al. compared the outcomes of closure using gracilis muscle flaps following APR and IORT for recurrent rectal cancer in 16 patients vs. primary closure in 24 patients with similar characteristics. Twelve percent of the patients

who had gracilis flap had major complications consisting of pelvic abscesses requiring further intervention, antibiotics, and prolonged hospitalization, whereas 46% of patients who had primary closure were noted to suffer from these complications. Minor complications including subcutaneous abscesses and persistent perineal sinuses all managed by local wound care were noted to be similar in both groups. One-third of the control group had minor complications when compared with 25% of the flap patients, thus showing no statistically significant difference. The gracilis muscle flap is another viable option, which could be utilized with satisfactory outcomes (Shibata et al. 1999).

The posterior thigh or gluteal fasciocutaneous or myocutaneous flap is another type of autologous tissue flap that could be utilized for closure of perineal defects (Fig. 10.5). The gluteal flap could also be de-epithilialized and positioned in such a way as to fill the cavities resulting from pelvic exenteration. This flap receives its blood supply from the inferior gluteal artery (Friedman et al. 2000). In a study evaluating 16 patients who underwent inferior gluteal myocutaneous flaps for closure of APR defects, there was an overall 50% complication rate. Those patients required only minor wound revisions or local wound care. All but one patient achieved complete wound healing of their flaps (Baird et al. 1990).

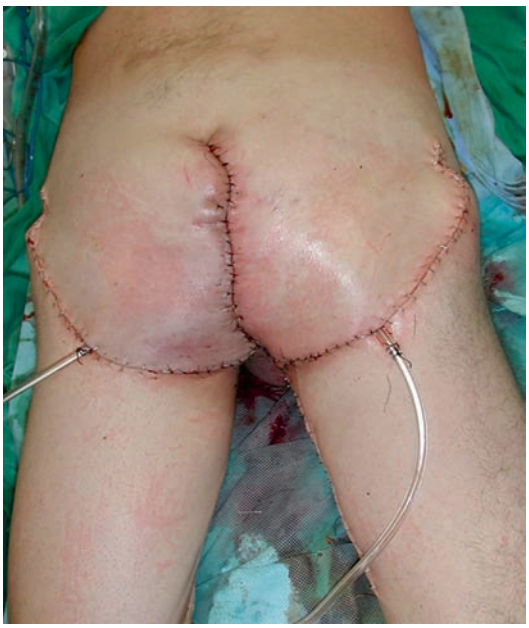

Figure 10.5. Bilateral gluteal flap reconstruction of perineal defect following sacral resection.

Other reconstructive options include the concomitant creation of a neovagina when a vaginectomy is necessary for complete resection of the recurrent rectal cancer. Just as in the reconstruction of perineal defects following rectal surgery, the goals for vaginal reconstruction are to promote wound healing and restore pelvic floor structure. Other secondary goals include restoration of the patient's body image and possibly normal sexual function. Similar to the perineal reconstruction, the same types of tissue flaps are utilized in a manner specific to the reconstruction of the vaginal defect. Omental flaps, skin grafts, and muscular or myocutaneous flaps using the rectus abdominis or gracilis muscles have been described (Small et al. 2000). In evaluation of the functional outcomes of such flaps, Ratliff et al. surveyed 40 patients who underwent pelvic exenteration and gracilis myocutaneous vaginal reconstruction regarding their sexual function. Twenty-one of the 40 patients had not resumed sexual activity since their surgery. Thirty-three percent cited vaginal dryness as the reason for not being able to resume sexual activity while 28% felt that their neovaginas had excessive secretions. Too small or too large neovaginal capacity was identified as another reason for lack of resumption of sexual activity in 20 and 5% of patients, respectively. Eighteen percent of patients complained of having painful intercourse and another 18% had flap prolapse. Self-consciousness relating to ostomies and donor site scarring was also noted in 40 and 13% of patients, respectively, thereby preventing normal sexual relations. Other issues that prevented return to sexual activity were lack of pleasure and the sensation that the patients' thighs were being touched during coitus (Ratliff et al. 1996).

D'Souza and his colleagues evaluated 12 patients who underwent vaginal reconstruction following surgical resection of locally advanced and recurrent rectal cancer. All these women underwent extirpative surgery followed by reconstruction of a neovagina using vertical rectus abdominis myocutaneous flaps. The procedure involved the raising of the flap in the usual manner, then tubularizing the cutaneous portion of the flap onto a stent or mold. The graft was then delivered into the perineal defect

where it was sewn in place. The average operative time was more than 9 h and all patients required a blood transfusion. Two patients had a superficial necrosis of their flaps while four had mild wound infections. All patients eventually healed their grafts. Five patients resumed sexual intercourse; however, the quality of their sex lives was not assessed (D'Souza et al. 2003). A study evaluating the complications and the sexual function after such reconstruction evaluated a group of patients who underwent different procedures such as primary closure, unilateral or bilateral gracilis myocutaneous, or VRAM myocutaneous flap. The overall complication rate was 83% in 54 patients who underwent these procedures. The complications included perineal wound problems in 33% and vaginal wound problems in 41%. While many patients were not willing to answer questions regarding sexual function after reconstruction, nine living patients who had flap reconstruction of the vagina never resumed regular sexual intercourse citing inadequate vaginal capacity, chronic wounds, and pain as the reason for their inability to resume sexual activity. Only 20% of the women who participated in the survey ever recalled having a preoperative discussion regarding the effects of surgery on sexual function. This underscores the importance of extensive counseling regarding these issues prior to surgery (Hendren et al. 2007).

While such flap reconstruction of the vagina after radical surgery may offer the patient the possibility of return of sexual function, this should not be a primary objective when treating recurrent rectal cancer. One must not compromise the possibility of a cure that could be accomplished by radical oncologic procedures for the sparing of sexual function. Moreover, the benefits gained from the functional outcomes of these reconstructions do not seem to warrant subjecting these patients to lengthy operations with excessive blood loss requiring blood transfusions and the inherent risks of immunosuppression associated with these transfusions. In essence, one must evaluate each woman individually to determine who may be best served by vaginal reconstruction. The patient must have a thorough understanding of the likely impairment in sexual function resulting from radical surgery and the less than optimal functional results following reconstruction; she must also have the motivation to pursue the return to sexual activity and the psychosocial support network necessary for enduring the lengthy recovery process.

Nonoperative Management

Nonoperative management of recurrent rectal cancer may be employed for palliative measures only. Such means include pain management services such as various NSAIDS, narcotics, or intrathecal injections with narcotic, phenol, or alcohol and possibly external beam radiation. Wanebo and his colleagues investigated using isolated chemo-therapeutic infusions of cisplatinum and mitomycin C of the pelvis in patients with advanced and previously irradiated rectal cancer. They were able to achieve pain relief in 11 of these patients while an additional 8 patients were considered potentially resectable at the conclusion of this therapy (Wanebo et al. 2003). Re-irradiation with combined 5-FU therapy after initial failed radiation has been used by Mohiuddin and his colleagues. Long-term complications with re-irradiation may include small bowel obstruction, fistula formation, persistent diarrhea, and long-term use of total parenteral nutrition. The 5-year survival with re-irradiation alone was 15% (Mohiuddin et al. 2002).

Summary

In conclusion, the best means of treating recurrent rectal cancer is to prevent it in the first place. It is imperative to closely follow the patients postoperatively to detect recurrence early in the hope that they can be salvaged with more radical treatments including surgery. Surgical options are associated with considerable morbidity and mortality and as such careful patient selection must be used. A team of experts and specialists is often required to assist these difficult patients. This team will need to include enterostomal therapists, nutritionists, psychologists, and social workers.

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11

The Surgical Management of Evacutory Dysfunction

Brooke H. Gurland

Introduction

Evacuatory Dysfunction refers to a constellation of symptoms such as prolonged repeated straining at bowel movements, sensation of incomplete evacuation, and the need for digital manipulation. Evacuatory dysfunction is used interchangeably with obstructed defecation syndrome (ODS), outlet constipation, and pelvic outlet obstruction and is a common complaint of women. In a cohort of 2,000 women ages 40–69 years 60% of respondents self-reported symptoms of ODS over a 12-month period while 12% reported symptoms of ODS weekly (Varma et al. 2008).

Evacuatory dysfunction may be due to mechanical obstructive or functional etiologies or impaired rectal sensation (Table 11.1). In women, childbirth, hysterectomy, and chronic straining can damage the pelvic diaphragm and rectal vaginal supports resulting in abnormal descent of the distal rectum (leading to rectocele, intussusception, rectal prolapse (RP)), sigmoid colon (sigmoidocele), or small bowel (enterocele) causing mechanical outlet obstruction or difficulties with expulsion of stool (D' Hoore and Penninckx 2003; Wald 2001). Functional etiologies of evacuatory dysfunction include inefficient relaxation of striated pelvic floor muscles (multiple sclerosis, spinal cord lesions, nonrelaxing puboretalis), or inefficient inhibition of the internal sphincter muscle (short-segment Hirschsprungs, Chagas, hereditary internal sphincter myopathy). Abnormal rectal sensation refers to diminished perception of fecal contents and can lead to megarectum and fecal impaction.

Patient Evaluation

A systematic and complete pelvic floor history should be elicited on all patients with constipation. Stool consistency and frequency needs to be reported even on patients who report "normal" bowel habits. The Rome Criteria are useful to define constipation but do not help to identify etiology (Table 11.2) (Drossman et al. 2000). Obstructing colon lesions and inflammatory conditions such as IBD or diverticulitis must be excluded by colonoscopy or GI contrast studies before considering functional etiologies. Colonic motility disorders can coexist with ODS but are more commonly associated with less than two spontaneous bowel movements per week or laxative dependence. Whereas fecal symptoms associated with ODS include incomplete or unsuccessful attempts to evacuate, prolonged episodes on the toilet, rectal pain, posturing, digitations or perineal massage, or enema dependency. Fecal incontinence to gas, liquid, solid stool, or mucus alerts the provider to possible occult RP, anal sphincter dysfunction, or descending perineal syndrome.

Medical conditions such as diabetes, hypothyroidism, hypercalcemia, connective tissue diseases, and central or peripheral neurologic

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Table 11.1. Pathophysiologic mechanisms with ODS

Mechanical outlet obstruction (intussusception or enterocele)
Dissipation of force vector (rectocele, descending perineum, rectal prolapse (RP)
Impaired rectal sensation (megarectum/rectal hyposensitivity)
Functional outlet obstruction secondary to
Inefficient inhibition of the internal anal sphincter (short-segment Hirshsprungs, Chagas, hereditary internal sphincter myopathy)
Inefficient relaxation of the striated pelvic floor muscles (multiple sclerosis, spinal cord lesions, puborectalis syndrome)

disorders may be associated with constipation. Poor diet, obesity, and sedentary lifestyle are treatable etiologies for constipation. Medication history should include prescription over the counter, and herbal remedies which may have constipating or laxative properties.

Inquires into urinary symptoms, feelings of prolapse, and sexual dysfunction should be made. We believe that it is very important to identify multicompartment problems and to collaborate with urologic and gynecologic colleagues preferably those subspecialized in pelvic floor disorders. Multicompartment surgery may be offered to selected patients and therapies can be chosen which have an impact on both bladder and bowel. Furthermore, it is best to investigate complex pelvic floor problems prior to surgical intervention in order to provide the patient with realistic expectations and to avoid treatment failures.

Table 11.2. The Rome criteria (Drossman et al. 2000)

The presence of at least two of the following complaints in without the use of laxatives for at least 12 months
Straining during >25% of bowel movements
Sensation of incomplete evacuation with >25% of bowel movements
Hard or pellet-like stools with >25% of bowel movements
Less than three bowel movements per week
Fewer than two stools per week on a regular basis

Physical Examination

Perineal, vaginal, anal, and rectal evaluations are important components of the physical examination. Bulging of the posterior vaginal wall beyond the hiatus is consistent with advanced prolapse and may represent a rectocele, enterocele, or sigmoidocele. Examination in the standing position with a finger in the rectum and vagina may be performed to elicit the maximal prolapse of the pelvic organs as they descend through the pouch of Douglas and genital hiatus. A gaping patulous anus may indicate neurological injury, intra-anal intussusception or full-thickness RP. Flattening of the perineum during valsalva beyond the ischial tuberosities is suggestive of excessive perineal descent. Valsalva maneuver or simulated defecation on a commode is useful to elicit full-thickness RP. Sphincter coordination is noted on anorectal examination when patients are asked to squeeze, relax, and push. Digital examination reveals resting and squeeze anal tone and a large rectocele or sphincter defect may be palpated. Anoscopy is performed to evaluate patients for mucosal abnormalities and rectoanal intussusception. Colonoscopy is recommended in patients who have not undergone appropriate cancer screening to rule out anatomic lesions and inflammatory conditions.

During gynecologic evaluation, evaluation of the posterior vaginal wall is performed using single blade speculum to retract the anterior wall and allow direct visualization of the posterior wall and fornix during rest and Valsalva maneuver. The Pelvic Organ Prolapse Quantification (POP-Q) is a validated score used to report the stage of prolapse (Bump et al. 1996).

Diagnostic Testing

Laboratory testing with thyroid studies and calcium levels are useful to rule out metabolic etiologies of constipation. Colonoscopy is necessary to exclude malignancy or inflammatory bowel disease. Before considering further evaluation we advocate diet modifications, exercise, and medication adjustments. A trial of a fiber supplement may be beneficial in some patients with simple constipation but can exacerbate symptoms in others.

Additional testing is reserved for patients who fail medical therapy. Anorectal and radiologic studies are very useful to determine different pathologic mechanisms. Anal manometry evaluates resting and squeeze anal pressures and rectal sensory deficits. The presence of the rectal anal inhibitory reflex (RAIR) is useful to exclude Hirschsprungs disease. Electromyography (EMG) aids in the diagnosis of puborectalis syndrome. Balloon expulsion is an inexpensive method to assess ability to evacuate. Defecography is the gold standard to confirm evacuatory dysfunction due to intussusception, RP, enterocele, sigmoidocele, rectocele, and perineal descent. Discrepancies exist in the colorectal and gynecologic literature as to the role of defecography for diagnosis of pelvic organ prolapse. Most colorectal surgeons and urogynecologists find it very useful to identify mulitfactorial etiologies for ODS especially when there is a discrepancy between symptoms and physical examination. Defecating MRI has advantages over traditional defecography because it involves less radiation and provides multicompartment images. However, the sitting MRI is not universally available and defecating in the supine position is not physiologic. At this time we feel that both studies have a role in diagnosing complex pelvic floor disorders. Transit marker studies or nuclear medicine transit studies (when available) are recommended for selected patients who have infrequent BMs or laxative dependency to identify patients with gut dysmotility in conjunction with outlet dysfunction constipation.

For patients with refractory constipation who fail medical therapy or biofeedback, surgery can be an option. However, surgical outcomes vary and incremental symptom improvements are more realistic than cure. Many patients will continue to need fiber, stool softeners or intermittent laxatives. Communication and setting patient expectations are an important part of the preoperative assessment.

Rectocele

A rectocle is defined as herniation of the rectum into the posterior vaginal wall due to a defect in the rectal vaginal septum. Bulging of the rectum into the posterior vaginal wall can lead to accumulation of stool in the rectocele rather than propulsion of the stool out of the anal canal. The exact mechanism is unknown but risk factors include childbirth and chronic straining which causes stretching and tearing of the rectovaginal support structures. A rectocele can be classified on degree of protrusion relative to the hymen on clinical examination or radiographically based on size at maximal straining. The most common surgical approaches for rectocele repair are transvaginal, transanal, or transperineal. The transvaginal approaches, namely posterior colporrhaphy or defect-specific posterior repair, are routinely performed by gynecologists while the transanal or transperineal approaches are preferred by colorectal surgeons. Gynecologic indications for rectocele repair include bowel symptoms (manipulation of the vagina or perineum to defecate, incomplete rectal evacuation, and straining to defecate), lower pelvic pressure or heaviness, prolapse of posterior vaginal wall, and pelvic relaxation with enlarged vaginal hiatus. Posterior colporrhaphy or defect-specific posterior repair is frequently performed in conjunction with other vaginal prolapse and anti-incontinence procedures (Figs. 11.1 and 11.2). Involvement of the colorectal surgeon is reserved for patients with complaints of OD unresponsive

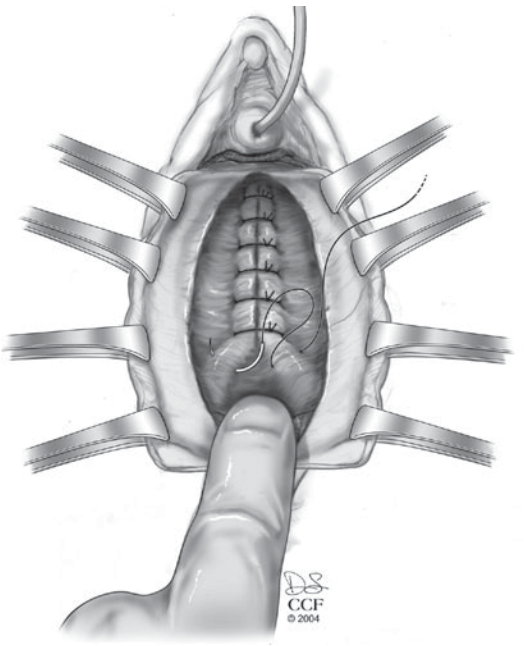

Figure 11.1. Plication of the rectal vaginal fascia in the midline.

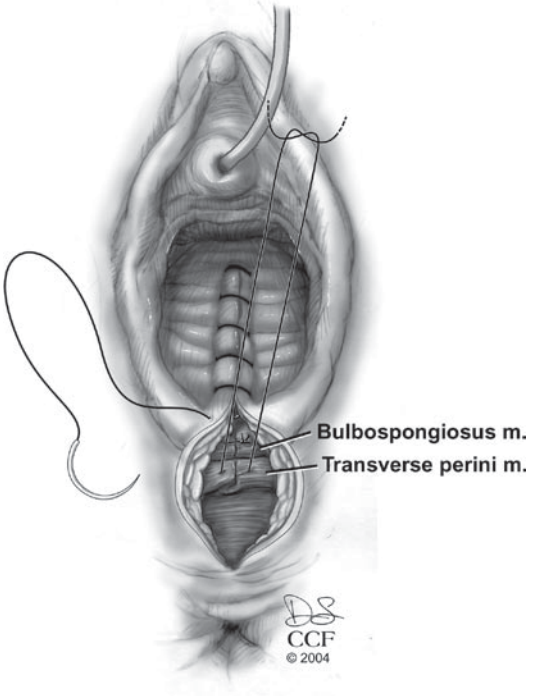

Figure 11.2. Transvaginal rectocele repair.

to medical therapy. In the colorectal surgical literature indications for rectocele repair include complaints of difficult evacuation, manual digitation, rectocele >4 cm and residual contrast in the rectocele by defecography. Evidence of nonrelaxing puborectalis has been associated with poor functional results (Tjandra et al. 1999). Rectocele repair regardless of the technique reports mean improvement of 75–80% for bowels symptoms. However, there is level I evidence that transvaginal is superior to transanal because of better anatomic outcomes (Nieminen et al. 2003; Kahn et al. 1999). Biologic and synthetic graft placement in the posterior vaginal wall is depicted in Fig. 11.3 but there are no data to support its routine use. There is level I evidence that demonstrates superior anatomic outcomes with traditional posterior colporrhaphy and defect-specific posterior repair over defect-specific posterior repair with implantation of a cross-linked porcine, small intestinal submucosa graft. Bowel and sexual function improved in all groups with no difference between groups (Paraiso et al. 2006; Gustilo-Ashby et al. 2007).

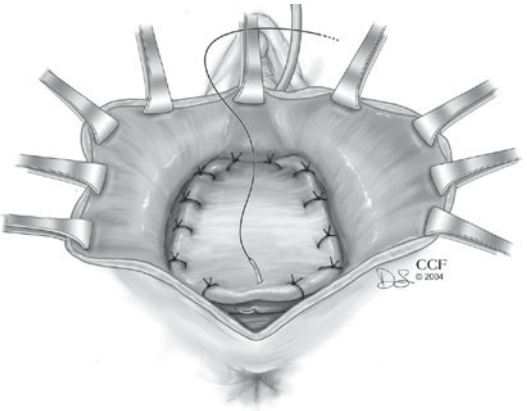

Figure 11.3. Transvaginal rectocele rapair with graft.

Enterocele

An enterocele refers to small bowel descent into the lower pelvic cavity leading to mechanical obstruction of the rectum. Enterocele results from a defect in the integrity of the endopelvic fascia at the vaginal apex (a defect between the pubercervical and rectovaginal endopelvic fascia where peritoneum and vaginal epithelium are opposed without any intervening fascia) and repair can be performed transandominally, laparoscopically, or vaginally. Older techniques involve obliteration of the posterior cul-de-sac or Pouch of Douglas by approximating the peritoneum in a vertical or purse string fashion or plicating the uterosacral ligaments. Newer techniques involve reestablishing the pericervical ring by suturing the pubocervical and rectovaginal endopelvic fascia together and reattaching them to the uterosacral ligaments. However, it is impossible to analyze the contribution of the enterocele resection to the final anatomical or functional success because enterocele repair is usually performed in conjunction with other prolapse procedures.

Sigmoidocele

A sigmoidocele refers to descent of the sigmoid colon into the lower pelvic cavity leading to compression and mechanical obstruction of the rectum. A break in the fascial supports of the upper vagina – the uterosacral cardinal ligament complex and rectal vaginal septum allows for descent of a redundant sigmoid colon.

Sigmoidoceles are uncommon and cannot be distinguished from a rectocele during clinical examination of posterior vaginal wall prolapse. Sigmoidocele is identified in 4–5% of defecography studies for obstructed defecation (Fenner 1996; Jorge et al. 1994). Sigmoid resection or sigmoidopexy in conjunction with posterior compartment repair has been shown to be effective in relieving symptoms of obstructed defecation in a limited number of patients.

Rectal Anal Intussusceptions and Rectal Prolapse

Rectal intussusception (RI) or occult RP is an infolding of the rectal wall that can occur during defecation. The bowel wall may descend varying degrees in the rectum and anus and is thought to cause obstructive symptoms and pain by blocking the rectal ampulla or by triggering the desire to defecate. The true incidence of RI is unknown but has been demonstrated in 31–40% of patients undergoing defecography for OD (Mellgren et al. 1994). When the full thickness of the rectum extends beyond the anal verge it is known as RP but only a few patients with internal prolapse will progress to external prolapse (Mellgren et al. 1997). RP is usually associated with abnormal defecation and both symptoms of fecal incontinence and constipation are reported. The underlying pathophysiologic mechanism is unknown but prolonged straining may lead to advanced RP and RP can act as a functional obstruction.

The surgical principles for RI and RP are based on suspension of the rectum or resection of redundant tissue to restore anatomic normality. Surgery is the primary treatment option for patients with RP and successful outcome involves correction of the prolapse and avoidance of worsening or new-onset constipation or fecal incontinence. Any surgical procedure that involves extensive mobilization and fixation is likely to correct the RP with low recurrence rates, and technical differences have been shown to contribute to functional success (Kuijupers 1992). In randomized controlled trials, division of the lateral stalks have been implicated as an etiology for postoperative constipation but have been associated with less prolapse recurrence (Speakman et al. 1991). Decreased constipation is reported after open resection rectopexy compared to rectopexy alone (McKee et al. 1992). Laparoscopic approaches to RP surgery are associated with equivalent results in terms of recurrence but with the well-reported advantages of laparoscopic surgery (Solomon et al. 2002; Kariv et al. 2006). Laparoscopic ventral rectopexy and colpopexy with mesh involves limited rectal dissection and fixation of the anterior rectal wall to the sacrum. Ventral rectopexy claims to avoid constipation without increasing prolapse recurrence (Portier et al. 2006).

Unlike the data reported for patients with RP, treatment of internal intussusception reveals conflicting functional results. Several authors have identified worsening constipation and evacuation disorders following resection rectopexy. Schultz et al. compared the results of Marlex rectopexy in 46 patients with a full-thickness RP to 29 patients with intussusception. A much higher proportion of patients with intussusception developed a deteriorating constipation compared with the prolapse group (Schultz et al. 2000). Retrospective reviews comparing patients with RP and RI treated by abdominal suture rectopexy also reveal inferior functional results (Graf et al. 1996; Brown et al. 2004) Other authors advocate rectopexy for intussusception and report a significant reduction in symptoms severity scores and overall improvement (Johnson et al. 2003; Papen et al. 2006; Tsiaoussis et al. 2005). Perineal procedures for intussusception such as Delorme mucosectomy, sarles mucosal stripping, and transanal prolpasectomy reveal variable results (Liberman et al. 2000; Dippolito et al. 2005; Renzi et al. 2006; Pescatori et al. 2006).

Stapled transanal rectal resection (STARR) has elicited substantial interest in the last several years. It is indicated specifically for patients with ODS and clinical findings of RI, rectocele, and mucosal prolapse. It employs a double-stapled circumferential full-thickness resection of the lower rectum using specialized stapling guns (Endosurgery, Cincinnati, OH). There have been several modifications to the design of the staples and the device since its initial reports. The first staple line placed anteriorly reduces the intussusception and the bulging rectocele, correcting the anterior wall defect while the second staple line placed posteriorly is aimed at correcting the intussusception. Prospective multicenter trials of patients who underwent

Table 11.3. STARR: stapled transrectal resection results of various series

Author/year	*N*	Study design	Outcomes/constipation scores (Renzi et al. 2008)
(Boccasanta et al. 2004)	90	Prospective multicenter trial	Decreased constipation scores 13–4.5
(Ommer et al. 2006)	14	Prospective	Decreased constipation scores 13–4
(Arroyo et al. 2008)	104	Prospective multicenter trial	Decreased in constipation score from 13.5 to 5.1
(Lehur et al. 2008)	119	RCT STARR vs. Biofeedback	Successful treatment 81.5% STARR vs. 33% BF
(Frascio Frascio et al. 2008)	25	Prospective	Decrease constipation scores 14.4–9.5

the STARR reveal initial and long-term symptom improvement of obstructed defecation (Boccasanta et al. 2004; Ommer et al. 2006; Arroyo et al. 2008; Lehur et al. 2008; Frascio Frascio et al. 2008; Renzi et al. 2008) (Table 11.3). A randomized controlled trial of STARR vs. biofeedback reveals that STARR is more effective for treatment of evacuatory dysfunction (Lehur et al. 2008).

Puborectalis syndrome

During normal evacuation, distention of the rectum with fecal matter induces relaxation of the internal sphincter muscle followed by contraction of the external anal sphincter. At the time of defecation the external anal sphincter and puborectalis muscles relax. The failure of this muscle to relax, results in maintenance of the anorectal angle and the difficulty with initiating and completing bowel movements. Paradoxical contractions of the puborectalis are also known as puborectalis dysnergia, nonrelaxing puborectalis, paradoxical puborectalis syndrome, dyssnergic defecation, or anismus and can be diagnosed on physical examination and confirmed by EMG or defecography. Randomized controlled trials show that biofeedback is superior to laxatives, sham treatments, and alternative therapies for treatment of dysnergic defecation (Rao et al. 2007; Heyman et al. 2007). Injection of botulinum toxin A into the pelvic floor muscle can chemically relax the muscles and has been shown to give short-term symptoms improvement (Maria et al. 2006). In some patients, marked hypertrophy of the puborectalis muscle fibers may occur. The etiology is unclear but may be related to inflammation and the puborectalis loses it elasticity and its ability to contract and to relax (Yu et al. 1989). Daily anal dilation with increasing sized anal dilators has been shown to be effective (Maria et al. 1997). Some surgeons advocate partial resection of the puborectalis for patients with puborectalis hypertrophy and report 90% success rates (Liu et al. 2001).

Megarectum

Nonobstructive constipation associated with rectal dilatation greater than 6.5 cm on a lateral view contrast enema is defined as megarectum (Preston et al. 1985). Elevated maximum tolerable volume on anorectal manometry may be identified in patients with a dilated rectum but can overestimate patients with megarectum due to inherent limitations with the equipment. Controlled (pressure-based) distention with the barostat allows accurate identification of patients with megarectum and may be useful in those patients with an elevated maximum tolerable volume on anorectal manometry when surgery is being contemplated (Gladman et al. 2007). Outcome data of surgery for idiopathic megarectum and megacolon need to be regarded with caution due to inherent limitations in the studies (Gladman et al. 2005). For patients with a dilated colon and rectum, restorative proctocolectomy has a reported

success rate of 70–80% (Hosie et al. 1990). In those patients with distal dilatation of the sigmoid colon and rectum, options include proctectomy with colo-anal anastomosis or vertical reduction rectoplasty (VRR) (Stabile et al. 1992; Stewart et al. 1994). VRR involves transection of the dilated rectum along its antimesenteric border in conjunction with sigmoid resection. VRR has been associated with increased frequency of defecation, reduction, or elimination of the need for manual evacuation and enemas (Gladman et al. 2005). VRR involves less pelvic dissection compared to proctectomy and may be a safer alternative for patients.

Sacral Nerve Stimulation for Constipation

Sacral nerve stimulation (SNS) involves low-level chronic electrical stimulation to the sacral plexus producing a physiologic effect on the end organs. As a coincidental finding in patients undergoing SNS for lower urinary tract dysfunction, many patients experienced improved fecal continence, an increase in bowel frequency, and improved defecation. The mechanism of SNS is poorly understood making it difficult to give precise indications for eligible patients; however, there is a potential to alter colonic motility, pelvic floor and anal sphincter function, and afferent sensation. Small series have investigated its efficacy in patients with slow transit constipation (STC) and evacuatory dysfunction refractory to medical therapy (Holzer et al. 2008; Kenefick 2006; Kenefick et al. 2002; Malouf et al. 2002; Ganio et al. 2001). In general, the number of weekly BM increased and difficulty with evacuation, unsuccessful visits to the toilet, and time necessary to evacuate decreased (Table 11.4).

Antegrade Colonic Enema

For the patient with severe bowel dysfunction who is contemplating a permanent colostomy, the antegrade colonic enema procedure may be a viable option. This procedure allows easy access to the colon through the abdominal wall with intermittent catheterization, irrigation of the colon, and rapid, controlled bowel purging (Fig. 11.4). The patient can avoid a stoma bag while independently managing their own bowel activities. The ACE technique was first described by Malone in 1990 using the appendix as the conduit but since then the cecum, ileum, and left colon have been utilized as the continence mechanism (Malone 1990; Monti et al. 1997; Willams et al. 1994; Kiely et al. 1994).

Table 11.4. Sacral nerve stimulation (SNS) for constipation results of various series

Author/year	Study design	Indications	# test phases	# permanent implants	Post treatments findings
(Gladman et al. 2005)	Prospective	9 ODS 8 Slow transit 2 ODS + STC	19	8(42%) 4: ODS 4: slow transit	No need for further digital manipulation or irrigation Increased number of defecations decreased laxative use
(Kenefick 2006)	Prospective	STC	8	2	Increased BM
(Malouf et al. 2002)	Double blinded placebo cross over study	Idiopathic constipation (<2Bm/week and evacuation >25% BM)	4	4	Increased number of defecations benefit was lost with blinded removal of stimulation
(Kenefick et al. 2002)	Prospective	4 STC 8 ODS	12	10	Improved rectal evacuation increased number of BM's

ODS obstructed defecation syndrome; *STC* slow transit constipation.

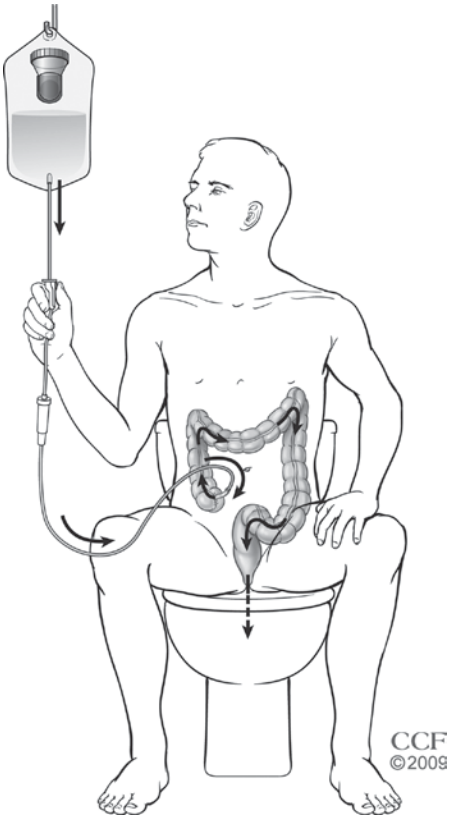

Figure 11.4. Antegrade colonic enema.

Malone adapted this concept from Mitranoff, a urologist who introduced the continent cutaneous appendicovesicostomy in 1980 that used a flap valve principle to maintain urinary continence (Mitrofanoff 1980). These procedures have become an increasingly popular treatment option for children with spinal dysraphism and anorectal malformations and are well-reported in the pediatric literature (Sinha et al. 2008). The ACE procedure is gaining recognition in the adult population for patients who would like to avoid a colostomy bag. Success has been reported in adults with neurologic dysfunction, obstructed defecation, and fecal incontinence (Gerharz et al. 1997; Lees et al. 2004; Hirst et al. 2005; Poirier et al. 2007; Worsoe et al. 2008; Teichman et al. 1998) (Table 11.5).

Fecal Diversion

Fecal diversion with a permanent stoma is a last resort for patients who fail other modalities. There is little published data to guide choice of ileostomy or colostomy and symptoms such as distention and abdominal pain may persist (Woodward et al. 2004; Scarpa et al. 2005).

Table 11.5. Antegrade colonic enema: results of various series

Author/year	*N*	Indication	Conduit	Follow-up months	Satisfaction/ use
(Sinha et al. 2008)	16	Constipation 16 Soiling 8	Appendicostomy 9 Ileacecostomy7	3–79	50%
(Gerharz et al. 1997)	32	Constipation	Appendicostomy 20 Ilealcecostomy 10 Cecal tube 5	13–140	47%
(Lees et al. 2004)	20	ODS + FI 13 ODS 7	Appendicostomy 13 Cecostomy 7	3–51	65%
(Hirst et al. 2005)	18	Constipation 12 FI 5 Both 1	Appendicostomy 17 Cecostomy 1	3–67	78%
(Poirier et al. 2007)	80	FI (20) Constipation (48) Both (12)	Appendicostomy 39 Ilealcecostomy 13 Cecal tube 3 25 appendicostomy/ilealcecostomy + colostomy	3–183	74%

ODS obstructed defecation syndrome; *FI* fecal incontinence..

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12

New Approaches in Perineal Crohn's Disease

Scott A. Strong

Introduction

Crohn's disease is a chronic, unremitting inflammatory disorder of unknown etiology that may affect a person of any age, involve all segments of the alimentary tract, and manifest itself in extra-intestinal sites. The treatment of this disease focuses on safely and effectively alleviating associated symptoms using a combination of medical and operative therapy predicated upon the site and nature of the disease involvement.

The incidence of perineal involvement in patients with Crohn's disease ranges from 8 to 90%, (McClane and Rombeau 2001) and the abnormalities can manifest themselves at any time in the disease course, but intestinal symptoms usually antedate the perineal findings (Williams et al. 1981; Sangwan et al. 1996). Although the perineal component can be completely asymptomatic in some fortunate patients, it is a major source of disability in others.

Classification

A variety of perineal manifestations can complicate Crohn's disease including perineal skin lesions, anal canal lesions, anoperineal abscesses or fistulas, anovaginal fistulas, and neoplasia. The skin lesions can be further described as skin tags or hemorrhoids, and the canal lesions can be categorized as fissures, ulcers, or strictures/stenoses. The abscesses and fistulas are typically labeled according to their anatomic location and relationship to the internal and external sphincters. The fissures and ulcers are considered primary disorders whereas the others are secondary abnormalities (Hughes 1978).

Skin tags and hemorrhoids: External skin tags are commonly observed as edematous and cyanotic swellings caused by lymphatic obstruction that occasionally suggest concomitant intestinal inflammation. Conversely, symptomatic internal hemorrhoids are rarely seen prolapsing out the anal canal (Wolff et al. 1985).

Fissures and ulcers: Anal canal fissures occur with considerable frequency (Fleshner et al. 1995), appear broad-based with cyanotic overhanging edges, and cause no or minimal pain. These fissures are often multiple and eccentrically positioned around the perimeter of the anal canal (Linares et al. 1988). Cavitating ulcers, on the other hand, are much more uncommon and cause considerable pain as they erode the underlying anal sphincter, which can lead to anoperineal abscesses and fistulas.

Strictures and stenosis: The strictures of perineal Crohn's disease can be short, web-like,

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intra-luminal diaphragms positioned near the dentate line or long, indurated, extra-luminal areas of stenosis located just above the anorectal ring and often associated with canal ulcers or proctitis (Hughes 1992; Bergstrand et al. 1980).

Abscesses and fistulas: Anorectal abscesses and anoperineal fistulas are common findings in patients with perineal Crohn's disease, and their incidence is increased with rectal involvement (Makowiec et al. 1997). The abscesses are commonly painful and often present with coexisting fistulas (Radcliffe et al. 1988). The fistulas can either evolve from infection originating in the cryptoglandular area (Figs. 12.1 and 12.2) or arise from an anal canal fissure or cavitating ulcer.

Anovaginal and rectovaginal fistulas can target any level of the vagina and they vary in diameter ranging from <5 mm to >25 mm. The majority of these fistulas are trans-sphincteric in nature and originate from the anterior anal canal at the level of the dentate line (Sjodahl et al. 2003).

Neoplasia: Invasive cancer can affect areas associated with Crohn's disease of the perianum (Laurent et al. 2005; Smith et al. 2008; Singh et al. 2004), and the incidence is approximately 0.7% with adenocarcinoma and squamous cell carcinoma occurring in equal frequency (Francois et al. 1993). However, the incidence is likely underestimated as it may be difficult to diagnose cancer in the presence of active proctitis where worsening symptoms are often attributed to the underlying Crohn's disease. The exact etiology of these malignancies is unclear, but may be secondary to chronic inflammation, fistula epithelialization, underlying anorectal neoplasia, or anal duct carcinoma (Singh et al. 2004).

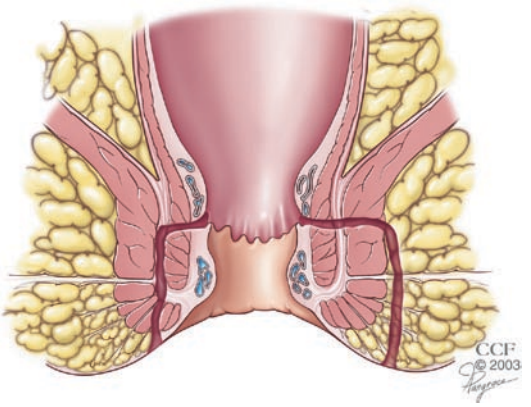

Figure 12.1. Intersphincteric (*left*) and trans-sphincteric (*right*) fistulas are the most common fistulas of cryptoglandular origin complicating Crohn's disease.

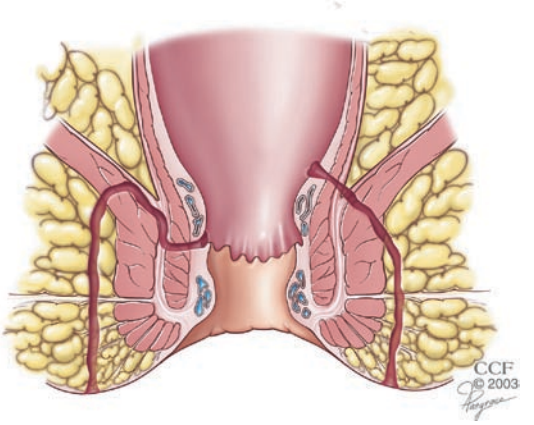

Figure 12.2. Supra-sphincteric (*left*) fistulas can originate from cryptoglandular disease or cavitating ulcers, whereas extra-sphincteric (*right*) fistulas are more commonly associated with significant proctitis or iatrogenic injury.

Classification and scoring schemata: The Cardiff classification schema was initially proposed (Hughes 1978) and later revised (Bergstrand et al. 1980) to accurately describe the type and objectively score the degree of perineal involvement. The system records each of the major perineal manifestations, assesses the presence and severity of proximal intestinal disease, and grades the global activity of the anal disease. The classification scheme is accurate and comprehensive (Enriquez-Navascues et al. 1997; Pikarsky et al. 2002), but it has not been prospectively validated.

An alternative scoring system was previously proposed by Markowitz and colleagues (Markowitz et al. 1990) that calculates a disease activity index based on points assigned for the presence and severity of discharge, pain, and restriction of activity as well as type of perineal disease and degree of induration.

Most recently, Pikarsky and associates (Pikarsky et al. 2002) proposed and validated a scoring system against surgical outcome. The

system is based upon physical findings (i.e., abscess, fistula, fissure/ulcer, stenosis, incontinence) as well as other weighted factors such as de novo or recurrent disease, chronicity, and concomitant intestinal disease. This scoring scheme appears to correlate with the short-term outcome of patients undergoing surgical management of their perineal Crohn's disease.

Unfortunately, none of these classification or scoring schemata has been universally adopted for usage in clinical trials.

Diagnosis

Perineal Crohn's disease can be diagnosed through an examination in the office setting or in the operating room with the patient under a regional or general anesthetic. Imaging modalities such as endoanal ultrasound (EUS) and pelvic magnetic resonance imaging (MRI) can further aid in the diagnosis and management of the disease without exposing the patient to radiation. The presence and extent of concomitant intestinal disease must also be determined through a variety of endoscopic and imaging tests.

Examination: Perineal involvement in patients with known intestinal Crohn's disease is generally obvious on inspection accompanied by digital examination, anoscopy, and rigid proctoscopy. If the patient is too uncomfortable or uncooperative for an adequate evaluation, a well-conducted examination under anesthesia is mandated. Alternatively, individuals without a history of Crohn's disease can present a diagnostic challenge as many of the findings are seen in normal individuals or patients with other gastrointestinal maladies. Crohn's disease is the more likely diagnosis if multiple abnormalities (e.g., laterally located fissures, cavitating anal canal ulcers, anorectal ring stenosis) are noted. Occasionally, biopsies of the perianal lesions or affected perineum will be required to obtain an accurate diagnosis.

Imaging modalities: EUS can be an extremely useful tool for the diagnosis of anorectal abscesses and anoperineal fistulas (Hussain et al. 1996; Buchanan et al. 2004a; Spradlin et al. 2008), especially using hydrogen peroxide enhancement (Moscowitz et al. 2003; Cheong et al. 1993; Buchanan et al. 2005) and the newer generation 3-dimensional machines (Morris et al. 2000; Maier et al. 2001). Moreover, a recent randomized trial reported that endoanal ultrasonography can guide the usage of combination medical and operative therapy to significantly improve outcome defined as cessation of fistula drainage and time to cessation (Spradlin et al. 2008). Pelvic MRI is a similarly valuable, yet expensive, means of identifying abscesses and classifying primary and secondary fistulas (Hussain et al. 1996; Moscowitz et al. 2003; Cheong et al. 1993; Buchanan et al. 2005; Morris et al. 2000; Maier et al. 2001; Schaefer et al. 2004). These secondary fistulas originate from intestinal sites located proximal to the anal canal and may be seen with segmental colitis or ileocolic disease.

In patients with perineal Crohn's disease, direct comparison of EUS, MRI, and examination under anesthesia has suggested that ultrasound might be most accurate (Orsoni et al. 1999), but ultrasound and MRI used together or separately in combination with examination under anesthesia are 100% accurate (Schwartz et al. 2001).

Medical Management

For many perineal conditions, local measures can provide some degree of symptomatic relief, and these actions include warm sitz baths and control of the causative bowel dysfunction with fiber products or antidiarrheals. Many of the prescription medications traditionally used to control intestinal Crohn's disease (i.e., 5-aminosalicylates, corticosteroids) are largely ineffective in the management of perineal Crohn's disease (Lichtenstein 2000; Gelbmann et al. 2002; Sandborn et al. 2003; Rutgeerts 2004; Griggs and Schwartz 2007). Conversely, antibiotics, immunomodulators, and biologic agents have been found to be beneficial in these patients. Newer approaches to fistula disease using autologous fibroblast (Ascanelli et al. 2007) or adipose-derived stem cell (Garcia-Olmo et al. 2008) transplantation have demonstrated promising results, but are not yet ready for routine implementation. Thus, a management algorithm for perineal Crohn's disease should ideally include

early and optimal treatment with an appropriate combination of hygiene measures, bowel regulation, antibiotics, immunomodulators, and biologics.

Antibiotics: Uncontrolled studies have shown a reduction in fistula-associated pain and drainage in adults with Crohn's disease treated with metronidazole or ciprofloxacin after 6–8 weeks of therapy, but symptoms typically recur immediately after antibiotic discontinuation (Sandborn et al. 2003; Rutgeerts 2004; Wise and Schwartz 2006). Accordingly, therapy is usually continued for 3–4 months (Griggs and Schwartz 2007). Adverse side effects are more commonly seen with the metronidazole therapy, and include metallic taste, glossitis, nausea, and neuropathy; metronidazole should be discontinued with any signs of neuropathy. Conversely, ciprofloxacin usage can be associated with untoward effects such as headache, diarrhea, nausea, and rash.

Immunomodulators: Immunomodulation with optimized azathioprine (2.5 mg/kg per day) or 6-mercaptopurine (1.5 mg/kg per day) is effective as de novo therapy in nearly one-half of patients (Pearson et al. 1995), but response is often slow or incomplete (Sandborn et al. 2003; Rutgeerts 2004; Wise and Schwartz 2006). Immunomodulators have also been found to successfully delay fistula recurrence following antibiotic discontinuation in patients initially responding to antibiotic treatment (Dejaco et al. 2003). Patients managed with these medications should have regular monitoring of their leukocyte counts and liver transaminase levels because associated adverse events include leukopenia and drug-induced hepatitis. For patients intolerant of these agents or affected by disease that is refractory to these therapies, cyclosporine, tacrolimus, and methotrexate have been used to provide rescue therapy (Sandborn et al. 2003; Wise and Schwartz 2006; Mahadevan et al. 2003).

Biologic agents: The management of perianal fistulizing disease has been improved with the development of an antitumor necrosis factor (TNF)-alpha antibody, infliximab, which is a chimeric monoclonal antibody. The complete arrest of the fistula drainage is obtained in nearly one-half of adults 10 weeks after the administration of 5–10 mg/kg of infliximab at weeks 0, 2, and 6, and usually persists for 12 weeks (Present et al. 1999). Additionally, more than one-third of initial responders will maintain cessation of drainage with ongoing therapy delivered over the ensuing year (Sands et al. 2004). An alternative anti-TNF-alpha medication, adalimumab, is a fully human monoclonal antibody that has been approved for patients with moderate to severe Crohn's disease unresponsive to or intolerant of infliximab. Adalimumab has been shown in an unpublished open-label extension trial to be more effective than placebo for inducing fistula healing, and complete healing is sustained for up to 2 years in most patients (Colombel et al. 2009).

Surgical Management

The appropriate treatment of perineal Crohn's disease must be individualized to the specific patient with adherence to certain management tenets. As Crohn's disease is incurable, the primary treatment goals are the amelioration of symptoms and prevention of future complications. Then again, the realization of these goals is not to be at the expense of harmful adverse effects, impaired fecal continence, or increased risk of complications necessitating a permanent stoma. In general, a conservative surgical approach is adopted because a more aggressive attitude will often result in outcomes that are worse than the disease itself.

Skin tags and hemorrhoids: Surgical treatment of skin tags, whether conservative or aggressive, is often associated with prohibitive morbidity. Excision of simple skin tags is commonly complicated by chronic, nonhealing ulcers, and excisional hemorrhoidectomy may have disastrous results as supported by Jeffery and colleagues (Jeffery et al. 1977). A study of 21 adults treated for hemorrhoids on a background of Crohn's disease, included 12 patients who presented prior to the diagnosis and nine who presented after, reported that postoperative complications occurred in seven and three patients, respectively. Moreover, of the ten patients with complications, six ultimately required proctectomy (Jeffery et al. 1977). This traditional view has been challenged by others who reported healing in 15 of 17 patients where hemorrhoidectomy was performed at the time of quiescent or absent Crohn's proctitis (Wolkomir and Luchtefeld 1993). Moreover, the effects of the newer immunomodulators and biologic agents have not been assessed in the context of their impact, if any, on posthemorroidectomy results. Regardless, patients with Crohn's disease and symptomatic skin tags or hemorrhoids are

best treated by local measures unless hemorrhage occurs or malignancy is suspected.

Fissures and ulcers: Fissures in patients with Crohn's disease should be relatively asymptomatic and nearly one-half will heal with medical treatment, especially those that are painless or acute in nature. However, a painful fissure might also imply a component of underlying sepsis and thus a careful, yet thorough, examination is warranted. Symptoms from an uncomplicated fissure that do not improve with nonoperative measures may be an indication for a lateral internal sphincterotomy, especially if the rectum is spared of involvement and manometry studies indicate an increased anal canal resting pressure. The majority (88%) of fissures treated by fissurectomy or sphincterotomy will heal in appropriately select individuals (Linares et al. 1988; Wolkomir and Luchtefeld 1993). Fortunately, fissures in people with Crohn's disease typically display a self-limiting course with only ten of 53 patients (19%) in one series still afflicted after 10 years of follow-up (Buchmann et al. 1980).

Symptoms secondary to large and cavitating ulcers can often be controlled with debridement of overhanging edges and intra-lesional steroid injection. Nevertheless, some of these patients will eventually require proctectomy or diversion because of unrelenting pain, sepsis, or fecal incontinence.

Abscesses and fistulas: An anorectal abscess, regardless of its etiology, will typically manifest itself as a painful, indurated area with or without associated fluctuance. Any suspected abscess of the perineum mandates careful inspection and the principles applied to the treatment of abscesses in the general population, also apply to the patient with Crohn's disease. Unless perineal sepsis complicates the presentation, simple incision and drainage of the abscess will adequately relieve the acute symptoms and allow resolution of the inflammation. A stab incision is made into the medial aspect of the overlying skin, penetrating into the abscess. A small-caliber mushroom-tipped catheter is then passed to the apex of the cavity and trimmed 3–4 cm beyond the skin level to allow egress of pus over the ensuing days. Further inspection for a potential fistula is rarely performed in the acute setting because the cumulative 2-year recurrence rate after the initial abscess is only 54% (Radcliffe et al. 1988). Contrarily, a thorough search is suggested for a recurrent abscess because of the significant likelihood of a third abscess due to an underlying fistula. In addition, oral antibiotics are prescribed only in instances with accompanying cellulitis, diabetes mellitus, immunosuppression, prosthetic implants, or valvular heart disease.

The management of anal fistulas represents one of the most challenging dilemmas in the treatment of Crohn's disease. As in most components of this disease, therapy is directed at alleviating symptoms while avoiding untoward side effects. This view does not imply that treatment should be delayed or withheld, but conservative medical and operative treatments should be initiated in a timely manner. At the extreme, aggressive surgical procedures are practical in only the occasional patient.

The treatment of this perineal manifestation is based upon the patient's presentation considering the fistula's location and complexity, the presence or absence of concomitant proctitis, and the severity of accompanying anal canal disease. In addition, the surgeon should be cognizant of the known potential for malignant degeneration of the chronic fistula tract and the patient should be counseled regarding this risk (Laurent et al. 2005; Smith et al. 2008; Singh et al. 2004; Roe and Mortensen 1989). Medical therapy to optimize control of disease-related inflammation is typically recommended to increase the likelihood of healing (Griggs and Schwartz 2007; Talbot et al. 2005; van der Hagen et al. 2005; Kamm and Ng 2008) without adversely impacting surgical outcomes (Hyder et al. 2006a, b; Gaertner et al. 2007). Local injection of infliximab adjacent to the fistula tract has been safely used to treat perineal Crohn's disease at two centers with both series reporting responsive improvement in more than two-thirds of patients (Poggioli et al. 2005; Asteria et al. 2006).

Most low-lying, simple fistulas without concomitant proctitis can be appropriately managed by fistulotomy (Sohn et al. 1980; Fry et al. 1989; Levien et al. 1989; Halme and Sainio 1995). Many institutions have reported good success with fistulotomy for the Crohn's disease patient with normal continence and a straightforward intersphincteric or low trans-sphincteric fistula. Fry and associates (Fry et al. 1989) reported complete healing in all 13 Crohn's disease patients within 4 months of undergoing intersphincteric fistulotomy. Levien, Surrell, and

Mazier (Levien et al. 1989) also reported excellent results in 18 of 21 patients following an intersphincteric or low trans-sphincteric fistulotomy. Sohn and colleagues (Sohn et al. 1980) and Fuhrman and Larach (1989) reported similar results when fistulotomy was combined with the postoperative use of sulfasalazine and metronidazole, respectively. Despite careful patient selection, an occasional fistulotomy will fail to heal and result in a chronic, relatively asymptomatic ulcer. Further operative treatment should be avoided and previously mentioned medical management is recommended. If an overly generous fistulotomy results in fecal incontinence, an overlapping sphincteroplasty has been successful in select patients (Scott et al. 1989).

If partial sphincter division would compromise fecal continence, a noncutting seton or rectal mucosal advancement flap is indicated for low-lying simple fistulas without significant proctitis. Noncutting setons adequately satisfy the goals of therapy by reducing perianal drainage and pain without worsening fecal continence or risking proctectomy. The soft, nonreactive nature of vessel loops makes them an ideal seton material for long-term fistula management. The seton is passed through the curetted fistula tract and then loosely tied on itself, encircling the perianal tissue. The seton establishes drainage of the fistula, minimizes the risk for future abscesses arising from the fistula tract, rarely causes discomfort, and does not interfere with personal hygiene.

Alternatively, the rectal advancement flap is a versatile procedure that can be used when rectal inflammation is limited and no cavitating ulceration or anal stenosis is present because the flap procedure does not significantly jeopardize continence or unduly increase the risk of proctectomy (Fig. 12.3). The procedure is performed under general anesthesia following mechanical and antibiotic bowel preparation. The patient is positioned with the internal opening of the fistula dependent and the anal canal is everted. The fistula tracts are carefully identified and curetted clean of granulation tissue. Normal saline with or without epinephrine is then injected into the submucosal plane to help identify the level of dissection. A rhomboid-shaped trapdoor or a curvilinear incision is made in the rectal mucosa to include the internal opening in its most distal aspect; the base of the rhomboid flap should be twice the width of the apex and the curvilinear incision should occupy a 120°–180° arc. Taking care to maintain meticulous hemostasis, the flap is then elevated with a small portion of the underlying internal sphincter. After the flap has been widely mobilized, the sphincteric portion of the fistula tract is debrided and sutured closed, and the mucosal site of the fistula is excised. The flap is drawn distally over the now-closed muscular opening and secured without tension to the distal mucosal margin, which typically lies caudad to the dentate line. The external fistula sinuses are drained with mushroom-tipped catheters until the flap has healed and the tracts have collapsed. Temporary fecal diversion is not necessary unless the patient is undergoing a repeat advancement flap procedure or an excessive amount of fibrosis was encountered during flap mobilization.

A report of 36 advancement flaps performed on 32 adults who were prospectively followed for 20 months, noted that four repairs primarily failed, 11 fistulas recurred, and a new fistula

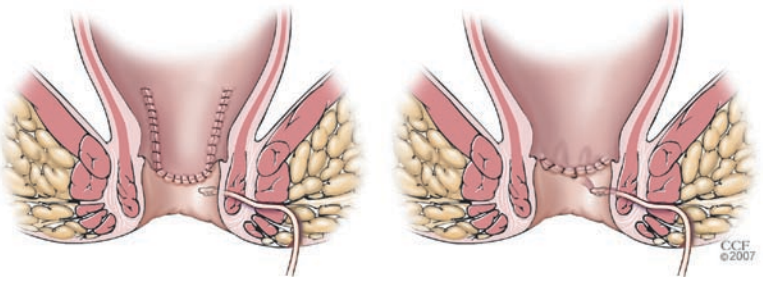

Figure 12.3. The rhomboid-shaped (*left panel*) and curvilinear (*right panel*) rectal mucosal flaps are advanced to permit a tension-free anastomosis to the epithelium situated distal to the prior internal opening. A small-caliber catheter is placed through the external opening to drain the associated tract during the postoperative period.

developed in another six patients (Makowiec et al. 1995). The operation was most successful if the rectum was not diseased and the fistula did not extend into the vagina. Even in those patients who experienced recurrent fistulas, the short-term improvement of symptoms justified the relatively simple procedure. In a separate report, a history of small bowel Crohn's disease, but not prior failed repair, was associated with a lower probability of success following an attempt at fistula repair using the rectal mucosal advancement flap procedure (Joo et al. 1998). Fecal diversion might increase the likelihood of successful repair, but studies are lacking regarding the indications for and impact of diversion at the time of repair. In general, a temporary stoma should be considered in patients undergoing a flap repair for fistulas presenting with mild proctitis, significant sphincter involvement, or history of multiple failed repairs.

In the event that the above scenario is complicated by anal canal ulceration or stricturing, a rectal sleeve advancement with temporary fecal diversion can be performed in select patients (Marchesa et al. 1998). This operation is a more extensive version of the rectal mucosal advancement flap whereby the full thickness of the rectum is circumferentially mobilized after excision of the ulcerated or strictured area. A formal proctoanal anastomosis is performed in combination with diverting loop ileostomy. Although the mobilization can be transanally completed in the majority of cases, trans-abdominal mobilization is sometimes necessary.

If moderate or severe proctitis complicates a low-lying simple fistula, an examination under anesthesia or imaging studies are performed to exclude concomitant sepsis (Hyder et al. 2006; Regueiro and Mardini 2003). Medical therapy is then employed with (Regueiro and Mardini 2003; Topstad et al 2003) or without a noncutting seton, thereby avoiding fistulotomy. Contrary to this approach, Williams and colleagues occasionally performed fistulotomies in this setting with nine of 12 study patients demonstrating healed fistulas within 3 months of surgery (Williams et al. 1991).

In a patient with a high, complex fistula and no evidence of Crohn's proctitis, a rectal mucosal advancement flap can be performed. One-third of complex fistulas treated in this fashion completely heal. If the anal canal is diseased, rectal sleeve advancement may be attempted (Marchesa et al. 1998).

The presence of proctitis with a high, complex fistula prevents the successful use of an advancement flap and relegates the patient with Crohn's disease to medical therapy in combination with seton drainage, temporary fecal diversion, or proctectomy. White and associates (White et al. 1990) reported a series of ten patients with complex fistulas and proctitis treated by noncutting seton, and excellent palliation was noted after 4 months to 7 years of follow-up. Despite severe proctitis in six, none had required proctectomy. The experience of Williams and colleagues (Topstad et al. 2003) was similarly encouraging with only three of 16 patients (19%) ultimately losing their rectum after seton management of a high, complex fistula.

A group of surgeons at St. Antoine Hospital in Paris conducted a long-term study of 41 patients treated with chronic draining setons for high fistulas (Faucheron et al. 1996). Eleven of the 18 adults who had their seton removed after an average interval of 12 months, remained in remission and seven suffered recurrence of fistula symptoms 10 months later. Eleven other patients had their seton in place at the time of last follow-up (37 months); none of these patients developed a recurrent abscess or fecal incontinence. In a separate study (Buchanan et al. 2004a, b), the success rate associated with noncutting setons falls over time (>10 years) and many patients develop further sepsis that usually requires surgery. Nevertheless, under appropriate conditions, seton drainage is a clearly attractive alternative to more complex reconstructive surgery.

More recently described procedures for the management of fistulas in adults with Crohn's disease and perineal fistulas entails occlusion of the fistula tract with fibrin sealant (Sentovich 2001; Lindsey et al. 2002; Loungnarath et al. 2004; Vitton et al. 2005) or collagen plug (O'Connor et al. 2006; Ky et al. 2008; Schwandner 2008; Safar et al. 2009).

The fibrin sealant procedure commences with gentle tract debridement using a curette, gauze sponge, cytology brush, or string of knots on a silk suture to remove any pus, stool, or granulation tissue present within the tract. The flexible tip of the fibrin sealant applicator is subsequently passed through the fistula from the external opening toward the internal os. The tip is maneuvered all the way through so that the catheter can be easily seen within the anal canal.

The fibrin sealant is then slowly injected through the catheter until a bead of sealant forms at the internal opening; the catheter is typically left in this position until a bead of clotted sealant forms. The catheter is then slowly withdrawn as the sealant is injected to fill the entire fistula tract, and a second bead is left at the external opening. Additional fistulas or side branches are also injected so as to obliterate all tracts. The sealant is allowed to cure for 5 min and then the internal and external openings are dressed with a nonadherent dressing.

The fibrin plug operation is similar in some ways, but differs in others. Specifically, no curettage or mechanical debridement is performed, but after irrigation of the fistula tract, the anal fistula plug is inserted in a pull-through technique from the internal opening to the external opening after soaking the plug in a normal saline solution. The plug is then secured with 00 polyglycolic acid suture, which is inserted deep into the underlying internal sphincter muscle. The excess plug material is trimmed flush with the anal canal wall taking care to avoid the fixation sutures, and the internal opening is covered with mucosa. Finally, the excess plug material is trimmed at skin level without further fixation.

Results with fibrin sealant for fistulas related to Crohn's disease have been inconsistent partially because complex fistulas tend to be less responsive to treatment (Swinscoe et al. 2005), but the largest series to date revealed more than one-half of treated fistulas remained drainage-free after nearly 2 years of follow-up (Vitton et al. 2005). The use of intra-adhesive antibiotic solution or primary closure of the internal os has not increased the healing rate for the procedure in fistulas related to cryptoglandular disease (Singer et al. 2005). However, Garcia-Olmo and associates (Garcia-Olmo et al. 2008) reported that 20 million adipose-derived stem cells added to the sealant significantly increased the likelihood of healing to 71% compared to 16% for patients treated using fibrin glue alone.

Similar to the fibrin sealant experience, some centers (O'Connor et al. 2006; Schwandner 2008) have reported high success rates (>80%) in patients with fistula tracts treated by collagen plug occlusion, while others (Ky et al. 2008; Safar et al. 2009) have encountered somewhat discouraging outcomes. Once again, the mixed results may partially result from bias in patient selection because closure rates are higher with single tracts than those seen with complex fistulas originating from multiple primary openings (O'Connor et al. 2006). Ascanelli and colleagues (Ascanelli et al. 2007) recently used a tissue-engineered skin substitute in the form of human autologous fibroblasts previously harvested from a skin biopsy to successfully treat a patient with Crohn's disease complicated by a trans-sphincteric fistula-in-ano.

In select patients with severe perineal disease, fecal diversion is required. While patients undergoing temporary diversion will enjoy an improved quality of life (Kasparek et al. 2007), a temporary ileostomy does not generally influence the long-term outcome of perineal Crohn's disease because less than one-quarter of individuals will have intestinal continuity restored (van Donegn and Lubbers 1986; Yamamoto et al. 2000). The majority of patients who undergo successful closure of their stoma require a secondary procedure (e.g., rectal mucosal advancement flap) to achieve stoma closure.

Therefore, a loop ileostomy for severe perineal disease may acclimate the patient to life with a stoma and, in some instances, provide control of perineal sepsis or proctitis prior to mucosal advancement flap or proctocolectomy. However, the creation of a loop ileostomy as a planned definitive procedure is rarely indicated. Instead, an endoanal proctectomy is necessary in approximately 5% of Crohn's disease patients solely to control anal or perineal disease, especially if high, complex fistulas (van Donegn and Lubbers 1986), deep ulcerations (Keighley and Allan 1986), colonic disease (Galandiuk et al. 2005), or anal canal stenosis (Galandiuk et al. 2005) are present.

Anovaginal fistula: Symptoms of gas or stool passing through the vagina are typical of an anovaginal fistula, but dyspareunia and perineal pain are also common. A careful examination under anesthesia with vaginoscopy and rectal insufflation while the vagina is filled with saline will usually identify an anovaginal or rectovaginal fistula. As with all Crohn's disease perianal fistulas, several factors influence the appropriate therapeutic choice. Assessment of the anal sphincters is an important aspect of the evaluation to exclude a sphincter defect that might hinder successful operative treatment.

Initial treatment with catheter drainage is directed at control of any associated sepsis, possibly in combination with oral antibiotics. If the

rectum is free or relatively spared of involvement and the anterior canal is intact, local repair with either a rectal mucosal advancement flap or rectal sleeve advancement is performed depending on the condition of the anal canal. The advancement flap is generally preferred because no sphincter division is necessary, and 68–80% of women ultimately heal their anovaginal or rectovaginal fistula (Fry et al. 1989; Hull and Fazio 1997; O'Leary et al. 1998; Penninckx et al. 2001). Rectal sleeve advancement is rarely performed, but is indicated when anal canal inflammation, ulceration, or stricture accompanies the anovaginal fistula. In these select patients, 60% of fistulas will heal following successful operation (Marchesa et al. 1998). Transvaginal repair is advocated by some as a routine approach to anovaginal fistulas, but this modality is successful in only 40–60% of cases regardless whether fecal diversion is also employed (Hannaway and Hull 2008). An episioproctomy repair is utilized only when mucosal inflammation is absent and concomitant overlapping sphincter reconstruction is warranted.

Although significant rectal or anal disease often relegates the patient to nonoperative treatment or proctectomy, an anocutaneous flap can be alternatively used with reasonable (70%) healing after 18 months of follow-up (Fig. 12.4) (Hesterberg et al. 1993). The anocutaneous flap has been also championed by some centers for patients without anorectal inflammation, because the procedure has high success rates without significant changes in continence or manometric outcomes (Athanasiadis et al. 2007).

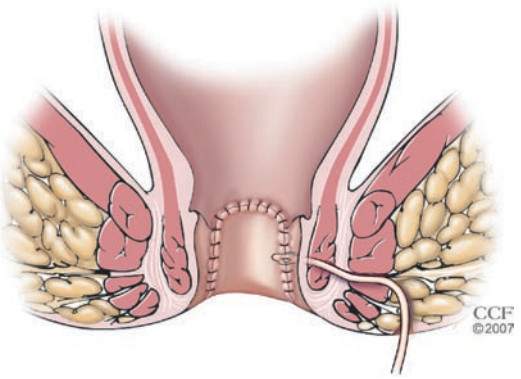

Figure 12.4. An anocutaneous flap is utilized for anoperineal and anovaginal fistulas complicated by proctitis that prohibits usage of a rectal mucosal advancement flap.

Once successful repair is accomplished, durable closure of the fistula is not guaranteed. In one series that typifies the anticipated disease course, 58% of successfully repaired anovaginal or rectovaginal fistulas had recurred at a median follow-up of less than 1 year (Makowiec et al. 1995). An attempt to repair recurrent fistulas is plausible, but an acceptable amount of time (>3 months) must lapse between the two attempts (Halverson et al. 2001). Gracilis interposition is often an especially attractive option in this cohort of patients (Wexner et al. 2008) because it successfully repairs the fistula in most patients (92%) and reconstructs the perineum with little risk (9%) for recurrence with 3.4 years of follow-up (Fürst et al. 2008).

Conclusion

Perineal Crohn's disease can vary in its presentation because it is associated with a constellation of clinical symptoms and findings. Appropriate management potentially requires employment of multiple diagnostic modalities to discern which of the many medical therapies and surgical options should be used in isolation or combination to achieve timely, yet sustainable symptom amelioration.

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13

Complex Anal Fistula

Avraham Belizon and Eric G. Weiss

Introduction

Complex fistula-in-ano is a frequent source of concern for both patients and surgeons because of its high rate of recurrence and potential for postoperative anal incontinence. There remains a balance between total sphincter-preserving surgery that may result in a high rate of fecal continence and the more radical approaches.

Historically anal fistula was recognized as a difficult surgical problem as well. In the fifth century BC Hippocrates argued for the laying open of an anal fistula, and that those who remain untreated die. In the fourteenth century, John of Ardene advised his students not to do much at one sitting on complex anal fistula, because it was a troublesome condition and required long and patient treatment. Lowe in 1,612 wrote that it is better not to operate on the very complicated fistula because of the risk of causing incontinence. The eighteenth-century Parisian surgeon Felix, rediscovered anal fistulotomy and cured King Louis XIV after experimenting on the inmates of Parisian jails. Understanding this to be a great accomplishment the King granted Felix an honorarium, an estate, and a title. In 1929, Lockhart Mummery noted that more reputations had been damaged by failed fistula surgery than by excision of the rectum or colon.

More recently, much has been written and debated about the treatment of anal fistula especially complex fistulae and the ailment continues to be a difficult clinical entity for both surgeons and patients. This chapter highlights various types of fistula, reviews the management options, and discusses certain types of problems that may be encountered in the treatment of this difficult condition with focus on the complex or more difficult types of fistulas.

Definitions and Classifications

Anal fistula, as defined by Marks and Ritchie (1977), is a track or cavity communicating with the anal canal or rectum by an identifiable internal opening. Simple fistulas usually have a single, readily identifiable external opening on the perineal skin. Anal fistulas can be defined as complex for a variety of reasons. Any fistula that cannot be adequately treated by simple fistulotomy may be considered complex. Situations can occur in wide range of circumstances including patients with Crohn's disease, otherwise low fistula in the presence of poor sphincter function, as well as high fistula with fistulous involvement of significant sphincter muscle such as those extending to the anorectal ring and extrasphincteric areas. Parks along with the contribution of others (Parks et al. 1976; Eisenhammer 1958; Lilius 1968) developed the most widely accepted classification of anal fistula. The classification is based on the course of the fistulous tract with special reference to the anorectal ring. This classification system divides fistulas into four types, intersphincteric, trans-sphincteric, suprasphincteric, and extrasphinteric, based on

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the anatomy of the fistula tract in relation to the sphincter mechanism.

Intersphincteric Fistula (Fig. 13.1a)

When the fistula tract courses through the intersphincteric plane it is termed an intersphinteric fistula. This tract represents the most common type of fistula (45–56%) (Marks and Ritchie 1977; Parks et al. 1976), and usually presents to a physician as a perianal abscess. Other tracts may be present which can extend in a cephalad direction cranially beyond the rectal wall which can result in a supralevator abscess.

Trans-sphincteric Fistula (Fig. 13.1b)

A trans-sphincteric fistula tract passes from an internal opening at the dentate line through the internal and external sphincter into the ischiorectal space. These fistulae account for approximately 20–30% of fistulae and most pass directly to the perineal skin. If the tract is located deeper in the external sphincter they become more complicated to treat and more of the external sphincter will need to be divided for cure. In addition the tract can extend superiorly up to or through the levators, demanding a more complicated treatment as well.

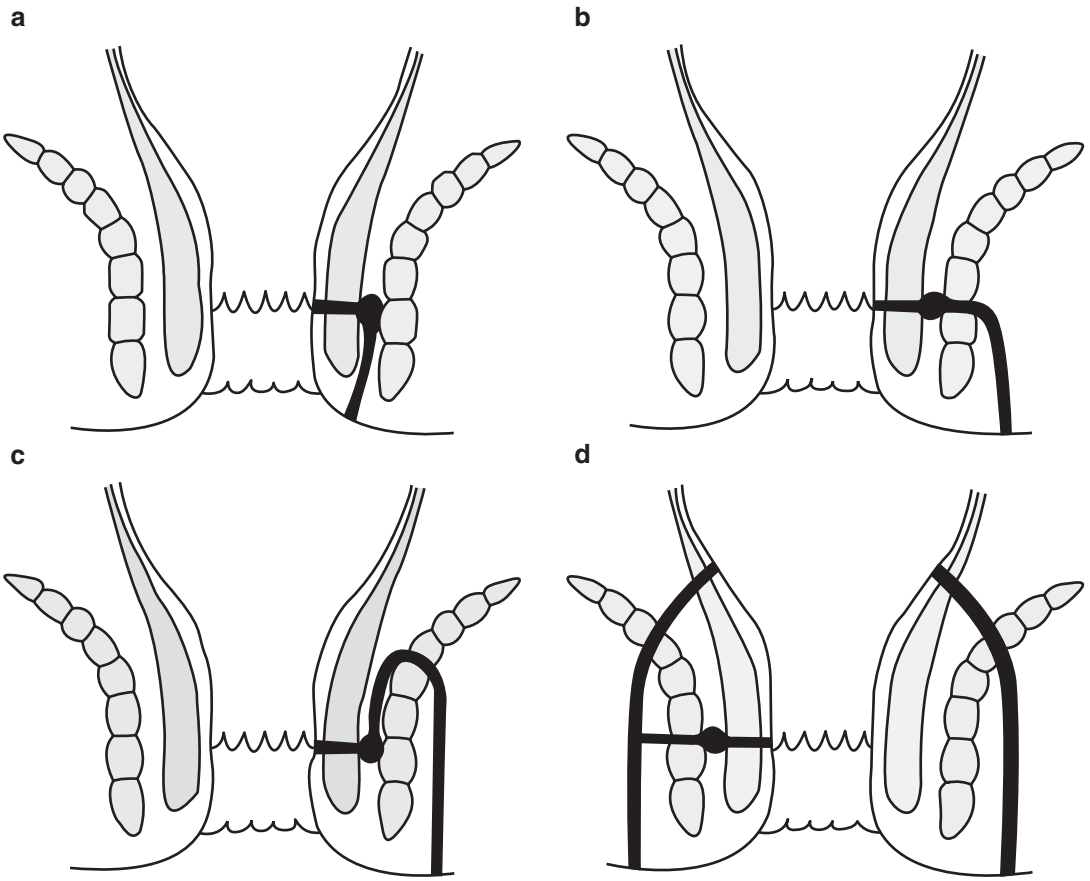

Figure 13.1. (**a**) Intersphincteric fistula; (**b**) trans-sphincteric fistula; (**c**) suprasphincteric fistula; (**d**) extrasphincteric fistula.

Suprasphincteric Fistula (Fig. 13.1c)

In this fistula the tract passes through the intersphicteric plane and then extends above the puborectalis muscle. The tract then turns downward through the ischiorectal space to the perineal skin; situations which occurs rarely in about 3.3% of patients (Marks and Ritchie 1977). Supralevator abscesses can rarely form as a result of cephalad extension and can sometimes be palpated during digital rectal examination.

Extrasphincteric Fistula (Fig. 13.1d)

A fistulous tract that passes from the rectum above the levators, through the levator muscle to the perineal skin via the ischiorectal space is defined as an extrasphincteric fistula. Most commonly, these tracts result from iatrogenic trauma as a result of the vigorous use of a probe in the presence of high trans-sphincteric or suprasphincteric fistula. These tracts can also result from traumatic injury to the rectum, including foreign body perforation of the rectum (chicken bone, enema tip), or penetrating injury of the perineum. Crohn's disease and rectal cancer can be responsible for the development of this type of fistula as well. Rarely pelvic abscesses secondary to diverticulitis can present as an extrasphincteric fistula.

Based on this classification system further accessory or secondary tracts may develop and lead to more complex fistulas such as those associated with high blind tracts, multiple secondary openings, and tracts or horseshoe tracts.

Prevalence

The reported prevalence rate is 8.6 cases per 100,000 population; the male to female ratio is estimated to be 1.8–1 and the mean age of patients affected is 38.3 years (Hamalainen and Sainio 1998).

Etiology

Fistula-in-ano is nearly always caused by a previous anorectal abscess. The cryptoglandular hypothesis postulates that anal glandular infection is the primary cause of fistula and abscess. The anal canal glands situated at the dentate line afford a path for infecting organisms to reach the intramuscular spaces. Our understanding of the glands is limited and little is known about their function in humans. Chiari and Herrmann were the first to point out the relationship between anal intramuscular glands and anal fistula (Seow-Choen and Nicholls 1992). However, only Johnson, in 1914, identified these structures as glands and ducts extending downward and outward penetrating the internal sphincter (Johnson 1914). Since then, histologic and pathologic studies have confirmed that cryptoglandular sepsis is present in greater than 90% of patients with anal fistula (Eisenhammer 1956; Parks and Morson 1962). Multiple series have shown that the formation of a fistula tract following anorectal abscess occurs in 7–40% of cases. Morson and Dawson compared the anal glands to intestinal diverticula in being prone to stasis and secondary infection (Morson and Dawson 1972). Since the glands traverse the internal sphincter, muscle tone can compress the lumen resulting in stasis, cystic transformation, secondary infection, with external discharge on the perianal skin producing a fistula. Most fistulas do arise in the posterior midline where the largest number of anal glands is located in adults. Nevertheless, the reason complex anal fistulas that take a course through external sphincter muscle and develop multiple secondary tracts in all different planes still remains unclear.

Clinical Presentation and Evaluation

Patients present in the acute setting with symptoms of a perianal abscess, complaining of perineal pain, swelling, and fever. Typically an external manifestation of an abscess with obvious swelling, erythema, tenderness, and heat are noted. However, if these signs are not present and a patient has such severe pain that digital rectal examination cannot be performed urgent examination under anesthesia is necessary. In these situations either a postanal space abscess or intersphincteric abscess should be suspected. Following the drainage of a perianal or ischiorectal abscess 60% of the time the abscess will fully heal without further manifestations or symptoms but 40% of the time a chronic fistula will occur.

Patients with a chronic anal fistula will usually relate a history of initial perianal drainage or discharge either spontaneous in nature or following surgical intervention. Accurate preoperative delineation of the anatomy although ideal and ultimately important to avoid recurrence and incontinence is not always possible. There are five essential elements to be obtained when evaluating an anal fistula. These elements are the location of the internal opening, the location of the external opening(s), the site and anatomy of the primary fistula tract and if present the site and anatomy of secondary tract(s) and the presence or absence of an underlying disease or undrained sepsis. Digital examination has been shown to be up to 84% accurate in defining the internal opening, primary tract, and secondary tract of anal fistula (Seow-Choen et al. 1991). It is important to take note of the patient's baseline resting anal sphincter tone when possible if a digital rectal examination can be performed in the office. Otherwise, reliance on a good history specifically questioning the patient regarding the status of their continence is required. Poor tone at baseline may mean that conservative surgery is necessary to avoid postoperative incontinence (Pescatori et al. 1989).

Systematic and careful examination with attention to detail is vital to the successful treatment of anal fistula. Intersphincteric tracks tend to have an external opening close to the anal verge, while trans-sphincteric and more complex fistulae will tend to open further away (Sainio and Husa 1985). The more difficult challenge is locating the internal opening. Internal openings may be felt as indurated nodules or pits leading to an indurated tract. The opening may exude purulent drainage when the tract or abscess is palpated and gently massaged. Gentle use of probes through the external opening can be very useful in locating the internal opening. However, many more complex fistulas have been created by surgeons probing unjudiscially forming false passages and false secondary tracts than would otherwise occur naturally. Goodsall's rule states that external openings located anterior to the trans-anal line (the coronal plane of the anus) have a fistula track usually runs radially into the anal canal. For external openings posterior to this line, the track is usually curvilinear, entering the anal canal in the posterior midline. However, any external openings 3 cm or more from the anal verge, horseshoe fistula, and fistulas associated with Crohn's disease or carcinoma of the anal glands are exceptions to Goodsall's rule and often will have a tract that enters the posterior midline even when the external opening is anterior. If an external opening is not apparent one must suspect an intersphincteric abscess or a fistula that is draining into the anal canal. If an anal fissure is found, careful inspection and probing is necessary at the time of operation because often there is a fistula orifice at its base.

Besides the use of probes, intraoperative injection of methylene blue, saline, or other solutions have been advocated (Chulani and Kulkarni 1982; Vasilevsky and Gordon 1984; Gingold 1983). Methylene blue is perhaps the most widely used but tends not to be very useful. It has been compared to pouring ink on a newspaper to facilitate reading (Phillips 1989; Dunphy and Pikula 1955). A small amount of hydrogen peroxide injected via a blunt-tip needle or angiocatheter into the external opening may produce a stream of white bubbles at the site of the internal opening. If the internal opening cannot be found but gentle probing reveals the tip close to the dentate line, an association to that point can be presumed. At times the use of smaller lacrimal duct probes as opposed to standard anal fistula probes will allow for negotiation of narrower tracts. If the probe tip is far from the dentate line it is better to defer the search for the internal opening to a different day and possibly control the external opening with a small mushroom catheter. In addition, a more vertical (cephelad) course is associated with a more complex anal fistula and can represent a high trans-sphincteric fistula with a high infralevator or supralevator extension, a suprasphincteric or extrasphinteric fistula. Probing should be performed gently and carefully to avoid both undue discomfort and the creation of a false track. If the probe passes easily into the anal canal one can then get a good idea as to how much sphincter muscle is involved which will dictate the type of treatment that will be employed.

Fistulography is notoriously unreliable having a 16% accuracy rate and is associated with a 12% incidence of false rectal openings and high extensions which could lead to harmful exploration (Kuijpers and Schulpen 1985). The only exception to this is in patients with recurrent fistula, where unexpected pathology may be revealed 48% of the time according to a previous report

(Weisman et al. 1991). More recently, anal endosonography has been showed to be an excellent evaluation tool of anal fistulous abscesses and should be part of the workup in complex anal fistula and recurrent fistula. This technique can be performed in the office in an ambulatory setting and can give significant information regarding the anatomy of the fistula tract. The addition of hydrogen peroxide via the external opening during endosonography can help outline the fistula tract, and may be useful to delineate missed internal openings (Seow-Choen et al. 1991).

MRI has been found to have an 80–90% concordance with operative findings. It has become a study of choice when evaluating complex anal fistulae. It has also been shown to improve recurrence rates by providing information on otherwise undetectable secondary extensions of the primary fistula tract (Buchanan et al. 2003a, b).

In certain cases the probe can be passed through a tract but does not pass freely into the anal, and injection techniques reveal no internal opening. In this case the luminal opening may have temporarily or permanently closed. Most surgeons would excise the crypt and complete the fistulotomy; however, when the end of the tract is above the dentate line, or very far from lumen (greater than 1 cm), there is a real risk of making a false tract and increasing the rate of recurrence. In this case it is advisable to curette the tract and possibly control the external opening with a small mushroom catheter and return at a subsequent time for further evaluation; the internal opening will usually be located at subsequent examinations.

Procedure Options

The principle in treating anal fistula is opening and draining the entire fistula tract. However, if the fistula does include significant amounts of muscle, other options need to be explored to maintain fecal continence and control.

Fistulotomy

Superficial fistulas allow for simple fistulotomy. Following passage of the probe along the entire tract, electrocautery is used to incise the tissue until the probe is exposed. Many surgeons will taper the tract edges, in order to ensure free drainage. It is advisable to biopsy the fistula edges when there is chronicity or any abnormal findings that are suspicious. Some surgeons will marsupulize the edges of the fistula tract to the fibrous tract to improve hemostasis and prevent early approximation of the edges. The tract is curetted along its entire course. Secondary tracks if present usually do not need to be unroofed, as healing is adequate when the primary track is opened and providing adequate drainage for the secondary tracts. Postoperatively a dressing is applied and the patient is given adequate analgesia. Patients can usually be discharged within a few hours of the procedure and should be seen in the office 4–6 weeks later.

Fistulectomy

This procedure is seldom used as it involves the excision of the entire fistula track and provides very little advantage over fistulotomy. There is a greater risk of injuring surrounding muscle and a higher incidence of severe bleeding. These wounds which are typically larger and wider, take longer to heal (Kronberg 1985) and recurrence rates are similar at 1 year.

Setons

Setons are very useful in the treatment of complex anal fistulas, either as definitive treatment or as an adjunct to partial fistulotomy. The basic principle involved in seton treatment as definitive therapy is that a fibrous tract will from around a foreign body. Culp described that the main indications to use a cutting seton are: a fistula that involves the puborectalis muscle, anatomic distortion that precludes fistulotomy, anterior fistulas in the female, or a very deep fistula that reveals no fibrosis of the overlying sphincter muscle. Our feeling is that this procedure is mainly indicated for recurrent fistulas that have severe distortion to the sphincter anatomy and that have failed most other more conservative treatments. Materials that are commonly used include penrose drains, rubber bands, vessel loops, nylon, and silk. Through continuous and slow tightening, the seton will cut through the track and underlying sphincter muscle. As the seton advances, the divided muscle begins to heal with fibrous scarring. In theory the sphincter completes the fistulotomy while retaining the muscle function and fecal control. Limitations to seton use include patient discomfort and prolonged process. In addition

secondary tracts may be incompletely drained as a result of fibrous scarring occluding the track. The seton does not need to be excessively tight as even a loosely applied seton will work its way out, with considerably less pain to the patient.

Draining setons can also be used as an adjunct to partial fistulotomy. This has been applied to extrasphincteric, suprasphincteric, and trans-sphincteric fistulas. The principle being that combined with a partial unroofing and division of the fistula tract, the placement of a seton will allow for faster healing of the fistula, preventing the premature closing of the portion that was not unroofed all the while providing minimal disturbance to continence. The seton allows for drainage and promotes fibrosis. In 1983 the Cook County group (Ramanujan et al. 1983) used a staged fistulotomy technique. They divided the deep external sphincter and placed the seton around the caudad component of the tract. This was the opposite of Parks description which involves passing the seton around the deep external sphincter muscle. In the Cook County group, among 45 patients with suprasphincteric fistulas only one patient reported incontinence to flatus. In Parks series 39% of patients complained of partial incontinence. Hanley (1965) described the use of a narrow penrose drain combined with a partial fistulotomy. This is especially useful with horseshoe fistula which would normally require extensive unroofing and large perianal skin wounds. The penrose is placed loosely and allows for drainage until the fistula heals.

Advancement Rectal Flaps

It is important to understand that the control or eradication of the internal fistulous opening is most important in determining the resolution vs. persistence of an anal fistula. One method developed was to address the internal opening by advancement of a flap of rectal wall or rectal mucosa over the internal opening. This was first described in the treatment of rectovaginal fistulas by Noble in (1902), and was then applied to the treatment of anal fistulas by Elting (1912). The principle applied included excision of the internal opening, curettage (or excision) of the main tract, and advancement of a flap of viable mucosa and submucosa to a point distal to the original internal opening. Many differences in practice exist in this procedure. Specifically with regard to thickness of the flap (full thickness vs. mucosa/submucosa), closure of the defect in the internal sphincter, drainage deep to the mobilized flap, advancement close to the dentate line vs. suturing the flap to a point in the upper anorectum, and the use of temporary fecal diversion in select cases.

There are many advantages to the flap advancement: no sphincter division is required and no deformity or contour defect of the anal verge occurs. In addition, there is less pain associated with this procedure as there is no perianal wound. However, fistulas with high internal openings are difficult to treat in this manner, as the cephalad extent of the lateral edges of the flap can be no greater than twice the width of the base. In select cases this procedure has been found to be very successful. In one series of 189 patients, a recurrent fistula rate was found to be 1.5%. The study had 80% follow-up rate, and no incontinence to solid stool was reported (Fazio 1987). In six patients with suprasphincteric fistula treated with advancement flap at Cleveland Clinic Ohio, no recurrence or incontinence was reported. Other studies have demonstrated recurrence rates between 1–10% and incontinence rates up to 6%. The authors comment that these results are encouraging and demonstrate that this option is available in certain select cases, in the absence of stricture or abscess, in the absence of anorectal Crohn's disease, and in patients where simple fistulotomy will result in a higher likelihood of incontinence such as suprasphincteric, high trans-sphincteric, or anterior fistulas in women (Fazio 1987).

Island advancement flaps have also been used in the treatment of complex or high trans-sphincteric fistula. Unlike an endorectal advancement flap this technique uses skin and subcutaneous tissue advanced into the anal canal to cover and control the internal opening. This was first described in 1996 by Del Pino et al. (1996), where 11 patients, three with Crohn's disease were treated by this technique. Although the follow-up was short, 8 of 11 patients and 7 of 8 without Crohn's disease had healed fistulas. A follow-up series from the same institution 4 years later (Nelson et al. 2000) with the technique being used in 65 patients revealed a success rate of 80%. Failure was more common in males, those who had previous repairs, those requiring multiple flaps, and those who had concomitant fibrin glue placement.

Fibrin Glue Injection and Fistula Plug

Recent advances in biotechnology have led to the development of many new tissue adhesive materials. Early reports of fibrin glue treatment had 1 year success rates approaching 60%, with little or no postoperative morbidity. However, longer-term follow-up reports were less encouraging (Buchanan et al. 2003a, b; Loungnarath et al. 2004). More recently, Cook Surgisis® developed an anal fistula plug for the management of more complex anal fistula involving a significant amount of sphincter muscle. It is an acellular naturally derived extracellular matrix that acts as a scaffold for the epithelialization of the tract itself. It is engineered to be resistant to infection, and early trials reported success rates approaching 80% (Champagne et al. 2006). However, more recently, reports have been showing significantly lower success rates with the fistula plug. We conducted a retrospective review of all our patients undergoing fistula plug placement for complex anal fistula between July 2005 and July 2006. The majority of these patients had already undergone at least one prior procedure for the treatment of their anal fistula. Our success rate was 13.9% overall. Interestingly patients with perianal Crohn's had a higher success rate when compared to patients with a crypoglandular etiology (25 vs. 12.5%) (Safar et al. 2008). Despite our low success rate we continue to perform the procedure since the morbidity associated with it is minimal and the potential benefit although small does exist, especially in patients in whom other procedures could cause significant incontinence and morbidity. Multicentered prospective trials are necessary to determine the true outcome of the anal fistula plug.

Recently, our institution performed a Meta analysis looking at the existing literature on the use and success of the anal fistula plug. There were four retrospective studies which included 115 patients in which a success rate of 31.3% (36 out of 115) and failure rate of 68.7% (79 of 115 patients) were obtained. There were eight prospective studies with 196 patients in total; a success rate of 67.4% (132 out of 196 patients) and a failure rate of 32.6% (64 out of 196 patients) were calculated. Overall then, the success rate for the anal fistula plug in healing fistulas was 54% (168 out of 311 patients) and the failure rate was 46% (143 out of 311 patients) (Table 13.1).

Table 13.1. Success and failure rates of anal fistula plug

Study type	No. Success	No. Failure	No. Total
Retrospective	79	36	115
	25.4%	11.6%	37%
Prospective	64	132	196
	20.6%	42.4%	63%
Total	143	168	311
	46%	54%	100%

The duration of the studies varied from a mean follow-up of 3.5–10.4 months, with a range of 0.5–24 months, but not all studies published the length of follow-up. Eleven studies included information on subsequent abscess formation; the overall rate of abscess formation was 6.7% (21/311). Nine of the 12 studies discussed the fistula plug falling out; the overall rate of plug fallout was 14.1% (44/311) (Shih et al.).

Colostomy

Temporary fecal diversion either through a colostomy or ileostomy may be necessary as an adjunct to the repair of a difficult and complex recurrent fistula. This is very uncommon except in those fistulas related to inflammatory bowel disease such as Crohn's Disease. In addition, certain patients that have undergone multiple failed procedures for complex fistulous disease may prefer permanent fecal diversion in rare cases.

Crohn's Disease

Crohn's disease of the anorectum can present with multiple and often complex fistulae. They require careful surgical treatment usually in the form of seton placement. Acute perianal abscess requires incision and drainage as it does in the patient without Crohn's disease. Special attention should be made to minimize the required incision and dissection as more aggressive intervention can lead to more extensive disease and substantial morbidity. Definitive repair of fistulae in these patients requires that the intra-abdominal disease be under control with medical therapy. Recurrent fistulous disease with persistent anorectal sepsis is an indication for proctectomy in select patients. Recent studies have identified a

role for medical therapy with infliximab, a monoclonal antibody to tumor necrosis factor, with reported response rates between 50 and 60% in patients with Crohn's associated perianal fistula (Topstad et al. 2003). These fistulae are addressed in more depth in chapter 12.

Summary

Complex anal fistulas represent one of the most challenging clinical problems in colon and rectal surgery. It demands a high level of familiarity with anorectal anatomy, and significant attention to detail on clinical examination in order to prevent both recurrence as well as postoperative incontinence. Even with excellent clinical skills fistula can prove to be persistent and require long patient treatment involving repeat surgical procedures. Although much has been written about anal fistula, a great deal remains uncertain and controversial. Further research is necessary to provide better treatment options for complex anal fistula that are associated with lower recurrence rates and do not put the patient at risk for fecal incontinence.

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14

Rectovaginal and Rectourethral Fistula

Daniel Lawes and Jonathan Efron

Introduction

A comprehensive review of the literature for recto-urethral and recto-vaginal fistulas was performed. Etiology, diagnosis, and management techniques are described. Management recommendations are made containing descriptions of both abdominal and perineal surgical repairs as well as the success rates for the various procedures listed

Rectovaginal Fistula

Rectovaginal fistulas are abnormal, epithelial lined connections between the vagina and rectum which may be congenital or acquired. They account for around 5% of all anorectal fistulas (Rothenberger and Goldberg 1983) and are severely debilitating for the patient, often resulting in rejection by partners, family, friends, and leading to social isolation particularly in the underdeveloped world. Rectovaginal fistulas have been described as the "most distressing surgical condition … that a woman can experience" (Casadesus et al. 2006). Management may be highly problematic, particularly if they result from radiation damage or inflammatory bowel disease with high recurrence rates following surgical repair. Although fistulas arising below the dentate line and connecting with the vagina should technically be classified as anovaginal fistulas, they can be managed in a similar fashion as those arising from more proximal in the rectum and will be considered as a single entity.

Presentation and Investigation

Rectovaginal fistulas may be entirely asymptomatic, but usually present with the passage of stool per vagina. Such passage may be prominent when the patient is suffering with diarrhea; although presentation is often more subtle with complaints of passing a fecal smelling vaginal discharge, flatus, or recurrent vaginitis, and such symptoms should be taken seriously. Following a careful history, many fistulas can be identified by simple clinical examination in the office and may be palpable on digital vaginal examination either as an obvious defect in the recovaginal septum or a small pit; in some series around three-fourths arise within 1 cm of the dentate line (Baig et al. 2000). Rectovaginal fistulas can often be visualized with a sigmoidoscope or speculum; however, some may be impossible to identify in this way. In such a case, there are several ways in which to confirm its presence. The patient may be asked to insert a tampon into the vagina; methylene blue dye is introduced into the rectum and the anus plugged for 15–20 min, following which the tampon is removed and inspected with the presence of dye confirming a fistula. Alternatively, with the patient under general anesthesia in the lithotomy position, the posterior wall of the vagina is covered with water and the rectum is gently insuflated

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with air, the presence of a fistula being identified by bubbles of air.

Radiological imaging techniques using contrast such as proctography or vaginography are unreliable since the fistula tract is often collapsed (Stoker et al. 2000). Proctography identifies the fistula in only 34% of cases (Bird et al. 1993), although the sensitivity of vaginography may reach up to 79% when a balloon is used to occlude the vagina; (Giordano et al. 1996; Baliga and Cooper 1982) this may also occlude the opening of a low fistula giving rise to false negative results. In addition, information regarding the relation of the tract to the anal sphincters is difficult to establish and the presence and severity of an anal sphincter defect cannot be appreciated. Fistulography has become obsolete in evaluating all perianal fistulas, the opening of the tract in the vagina or anal canal may be impossible to identify and has been shown to be of value in only 16% of cases with anal fistula (Kuijpers and Schulpen 1985). Visualization of ano- and rectovaginal fistulas with high resolution imaging is more challenging than the more commonly encountered perianal fistula. Fistula tracts are much shorter, rarely contain fluid, are collapsed down, and are often thin-walled without ongoing chronic inflammation when compared to other perianal fistulas; however, the presence of gas in the rectovaginal septum is an important positive predictive finding (Stoker et al. 1999). Endoluminal ultrasound has been used to delineate rectovaginal fistula with variable success; one study found that the tract could be identified in only 28% of cases, although an anterior sphincter defect was identified in 92%, leading to an important change in the surgical approach (Yee et al. 1999). Others have found ultrasound to be highly sensitive and comparisons with endoluminal magnetic resonance imaging (MRI) have demonstrated a sensitivity of 100% for ultrasound and 92% for MRI with a similar success in identifying sphincter defects (Stoker et al. 2002). Others have confirmed the usefulness of MRI in assessing anorectal fistula detecting additional abnormalities such as an abscess, an unsuspected fistula tract, and sphincter defects in up to 35% of cases (Dwarkasing et al. 2004). This suggests that either endorectal ultrasound or MRI should be employed if there is any doubt as to the diagnosis, and should probably be undertaken in all cases to assess the integrity of the anal sphincter, particularly when the fistula may be related to childbirth.

Classification

There are various ways of classifying rectovaginal fistulas, according to size, location, or etiology. The size of fistulas may vary greatly but a rudimentary classification of small (<0.5 cm), medium (0.5–2.5 cm), and large (>2.5 cm), has been employed. Fistulas can also be classified as low if the rectal opening is located below or at the level of the dentate line and the vaginal opening just inside the vaginal fourchette, or high if they are located at the level of the cervix, and middle if they arise at any site between. Classification may be related to etiology: congenital, traumatic, inflammatory bowel disease, infectious, radiation damage, or neoplastic. A more widely used classification is into simple or complex. Simple fistulas are benign, located in the low or mid-vaginal septum, less than 2.5 cm in diameter and are secondary to trauma or sepsis; complex fistulas are greater than 2.5 cm in diameter, persist after one or more attempts at repair, and are caused by other factors such as Crohn's disease, radiation damage, or malignancy (Lowry et al. 1988).

Etiology

Rectovaginal fistulas may be congenital or acquired. Congenital fistulas tend to arise from fetal malformations. Their management lies predominantly within the practice of pediatric surgeons; it is a highly specialized field and very different to that of acquired fistulas and as such they will not be discussed further. Acquired fistulas result from a variety of factors and published series suggest they are caused by obstetric injury in 20–81%, operative trauma in 2–7%, radiation injury in 1–50%, inflammatory bowel disease in 4–34%, infection in 6–38%, and from miscellaneous causes in up to 19% (Baig et al. 2000; Yee et al. 1999; Lowry et al. 1988; Bandy et al. 1983; Halverson et al. 2001; Mazier et al. 1995; Shieh and Gennaro 1984; Soriano et al. 2001; Watson and Phillips 1995; Wise et al. 1991; Zimmerman et al. 2002).

Trauma

Obstetric injury remains one of the primary causes of rectovaginal fistula with a reported incidence of 0.1% of all vaginal deliveries

(Venkatesh et al. 1989; Homsi et al. 1994). The condition may be underreported and thus the incidence may actually be much higher. The use of episiotomy is controversial; although it may reduce the incidence of fistula formation to 0.06% in those having midline episiotomy (Beynon 1974), there is also strong evidence to suggest that performing an episiotomy predisposes to third and fourth degree lacerations (Homsi et al. 1994). Symptoms of the fistula at presentation may be overshadowed by the fecal incontinence caused by underlying sphincter disruption and the possibility of a fistula should be considered when evaluating women presenting with incontinence following childbirth (Leigh and Turnberg 1982). Up to 28% of primiparous women will have an occult sphincter injury following vaginal delivery (Sultan et al. 1993) and careful evaluation of the sphincter integrity is essential.

Complications of operative procedures may lead to the development of rectovaginal fistula. Care must be exercised when performing anal, perineal, or vaginal procedures. The use of circular stapling devices for anastomosis of the colon to the rectum can be hazardous because of the possibility of including the posterior vaginal wall in the staple line. A report of 57 rectovaginal fistulas following low anterior resection demonstrated 53 were following circular stapling techniques (Rex and Khubchandani 1992) whilst others have reported an incidence of 4% (Antonsen and Kronborg 1987). A variety of other traumatic causes such as retained pessaries, vaginal foreign bodies, forceful intercourse, and following removal of rectal foreign bodies have all been described as case reports (Anderson and Anderson 1993; Hanavadi et al. 2004; Kouraklis et al. 1997; Singhal et al. 2007).

Inflammatory Bowel Disease

Inflammatory bowel disease is an important cause of rectovaginal fistula being responsible for between 4 and 34% in published series (Yee et al. 1999; Bandy et al. 1983; Shieh and Gennaro 1984; Soriano et al. 2001; Zimmerman et al. 2002). Although fistulas have been reported to be associated with ulcerative colitis (Faulconer and Muldoon 1975), such a situation is rare in the absence of an ileal pouch and is far more likely to be caused by Crohn's disease, due to the nature of the transmural inflammation seen in that condition. In a study of 886 women with Crohn's disease and an intact distal large bowel, the incidence of fistula was recorded as 10% (Radcliffe et al. 1988). The presence of a rectovaginal fistula in the absence of a history of trauma should alert the physician to the possibility of Crohn's disease and investigation should be aimed at excluding this as a diagnosis.

Malignant Fistulas

Malignant lesions may lead to rectovaginal fistulas which may be primary or recurrent and can arise from advanced rectal or gynecological malignancy although leukemias and endometriosis have been implicated in their development in some cases (Anderson and Anderson 1993). Recently, use of the chemotherapeutic agent Bevacizumab has been associated with a delayed rectovaginal fistula 3 years following anterior resection (Ley et al. 2007), with bowel perforations and entero-vaginal fistula also noted following treatment (Sparano et al. 2004). Appropriate management of a malignant rectovaginal fistula depends greatly on the stage of the cancer, general health of the patient, and the possibility of a curative or palliative approach. In these cases a defunctioning stoma performed as the primary procedure can be of great benefit either as a palliative procedure or prior to first-line chemotherapy or radiotherapy and a subsequent definitive surgical procedure with curative intent.

Pelvic Radiation

Radiation therapy is the mainstay of treating a wide variety of pelvic malignancies, most notably cervical and endometrial cancer. Whilst late fistulas arise from progressive obliterative enarteritis leading to tissue ischemia, early fistulas may occur as a result if destruction of a tumor which has invaded both structures. Fistulas usually develop between 6 and 24 months after treatment ceases and follow the onset of radiation proctitis with the development of an ulcerated area on the anterior rectal wall which in up to 50% of cases go on to become fistulas. Although rectal stricture, predominantly located in the proximal rectum, is the most common late manifestation of pelvic radiation damage (Hatcher et al. 1985; Anseline et al. 1981; Kimose et al. 1989), it is often associated with a fistula. These tend to be situated more distally and are generally located in the mid-

rectum (Kimose et al. 1989) The incidence of fistula formation following pelvic radiotherapy has been reported as 1–22% (Alert et al. 1980; Anseline et al. 1981; len-Mersh et al. 1987; Kimose et al. 1989; Alert et al. 1980; len-Mersh et al. 1987; Boronow 1986) and, as with all radiation-related tissue injury, the total dose is directly related to the incidence and severity of complications (Sandeman 1980). When presented with a case in which previous radiotherapy may be the cause of a rectovaginal fistula, it is essential to exclude the presence of recurrent malignancy.

Management

Up to half of small, simple obstetric-related fistulas spontaneously heal and waiting 6 months after presentation to assess the outcome in these cases is recommended (Homsi et al. 1994). Spontaneous healing of complex fistulas seldom occurs and the management should be guided by its position and etiology, but the principles of good surgical practice such as sepsis control, meticulous dissection, removal of diseased tissue, and a repair incorporating healthy tissue remain paramount. A wide variety of approaches has been advocated but may essentially be broken down into local repairs and trans-abdominal repairs (Table 14.1). Care should be taken to manage the patient's expectation. Studies suggest that healing can be expected in all simple fistulas with 77% occurring at the first attempt; however, this drops to 60% for complex fistulas with only 38% occurring at the first attempt (Devesa et al. 2007). Recurrence of a simple fistula following a first repair renders it by definition a complex fistula and the success rate of closure decreases with the number of previous procedures performed (Lowry et al. 1988; Wise et al. 1991).

Table 14.1. Common operations for rectovaginal fistula

Local repair	*Trans-abdominal repair*
Conversion to a perineal laceration with layered closure	Mobilisation, division and omental interposition+/− bowel resection
Excision of fistula with closure in layers	Low anterior resection with colo-anal anastamosis
Endo-anal advancement flap	Sleeve (pull-through) anastamosis
Endorectal advancement flap+/- sphicteroplasty	
Trans-perineal approach	
York-Mason approach	
Interposition grafts	*Miscellaneous*
Bulbocavernosus (Martius) graft	Colostomy or ileostomy
Gracilis interposition	

Local Repairs

Simple Fistulas

Simple fistulotomy has a limited place in the management of rectovaginal fistula since it would lead to the destruction of substantial amounts of the anterior sphincter complex. Although of some use in treating low anovaginal fistula caused by cryptoglandular sepsis, a more standard technique is to use an anal advancement flap. Advancement of the anterior rectal wall in the management of fistulas was first described in 1902 by Noble, the aim being to obliterate the internal opening by sliding a flap of healthy rectal wall consisting of mucosa, submucosa, and circular muscle from proximal to cover the opening and suturing it into place. It is particularly beneficial since it does not cause any surgical division of the external sphincter leading to preservation of continence in 98% of patients (Kodner et al. 1993). The use of this technique in the management of rectovaginal fistulas has been widely reported (Ozuner et al. 1996; Jones et al. 1987; Makowiec et al. 1995; Joo et al. 1998; Wise et al. 1991; Macrae et al. 1995; Rothenberger and Goldberg 1983; Casadesus et al. 2006; Baig et al. 2000; Stoker et al. 2000; Bird et al. 1993; Giordano et al. 1996; Baliga and Cooper 1982; Kuijpers and Schulpen 1985; Stoker et al. 1999; Yee et al. 1999; Stoker et al. 2002; Dwarkasing et al. 2004; Lowry et al. 1988; Hilsabeck 1980; Sonoda et al. 2002) (Table 14.2). The results of treating specific types of rectovaginal fistula with advancement flap alone are unclear; many studies are heterogeneous and include those with complex fistula including Crohn's disease and those with simple fistulas. In addition, the technique used for repair is not uniform even in within the same study, often including a group of obstetric patients in whom an

Table 14.2. Local techniques in the treatment of rectovaginal fistula

Author	Condition	Type of repair	No. Patients	Overall healing rate (%)
Athanasiades et al. 2007	Crohn's	Various	37	73
Bauer et al. 1991	Crohn's	Trans-vaginal	13	92
Casadesus et al. 2006	Simple	Trans-vaginal	12	75
Hilsabeck et al. 1980		Trans-anal	9	100
Hoexter et al. 1985	Simple	Trans-anal	35	100
Hull and Fazio 1997	Crohn's	Trans-anal	35	68
Khanduja et al. 1999	Simple	Trans-anal	20	100
Lowry et al. 1988	Simple	Trans-anal	56	78
Macrae et al. 1995	Recurrent	Trans-anal	17	29
Makowiec et al. 1995	Crohn's	Trans-anal	12	75
Mizrahi et al. 2002	Crohn's	Trans-anal	14	43
Penninckx et al. 2001	Crohn's	Various	34	78
Rahman et al. 2003	Simple	Trans-vaginal	47	100
Rothenberger et al. 1982	Simple	Trans-anal	35	91
Sonoda et al. 2002	Crohn's	Trans-anal	32	50
Zimmerman et al. 2002	Simple	Various	21	48

advancement flap was performed alone or in conjunction with a sphincter repair. Wise et al. suggested success rates of 95% in those treated with an advancement flap alone (Wise et al. 1991), Lowry and Rothenberger reported success rates of 83 and 91% respectively, although both included significant numbers of patients who underwent concomitant sphincter repair (Lowry et al. 1988; Bandy et al. 1983; Halverson et al. 2001; Mazier et al. 1995; Shieh and Gennaro 1984; Soriano et al. 2001; Watson and Phillips 1995; Wise et al. 1991; Zimmerman et al. 2002; Venkatesh et al. 1989; Homsi et al. 1994; Beynon 1974; Leigh and Turnberg 1982; Sultan et al. 1993; Rex and Khubchandani 1992; Antonsen and Kronborg 1987; Anderson and Anderson 1993; Hanavadi et al. 2004; Kouraklis et al. 1997; Singhal et al. 2007; Faulconer and Muldoon 1975; Radcliffe et al. 1988; Ley et al. 2007; Sparano et al. 2004; Hatcher et al. 1985; Anseline et al. 1981; Kimose et al. 1989; Alert et al. 1980; len-Mersh et al. 1987; Boronow 1986; Sandeman 1980; Devesa et al. 2007; Kodner et al. 1993; Ozuner et al. 1996; Jones et al. 1987; Makowiec et al. 1995; Joo et al. 1998; Macrae et al. 1995; Hilsabeck 1980; Sonoda et al. 2002; Rothenberger et al. 1982). A technique particularly suited to obstetric-related fistula in which the sphincter has been damaged, is to convert the fistula into a complete perineal laceration and perform a layered closure (Goligher 1984). The vaginal wall is dissected from the perineal body, the rectal mucosa closed, followed by approximation of the internal and external sphincters, perineal body reconstruction, and closure of the vaginal mucosa. Tsang et al. found that the presence of a sphincter injury reduced the likelihood of successfully healing the fistula with an endorectal advancement flap alone in the absence of a concurrent sphincteroplasty (Tsang et al. 1998). Only 58% of those with a healed fistula were satisfied with the results of their surgery, 19% were partially satisfied, and 23% not satisfied; all of these patients were incontinent postoperatively, emphasizing the importance of recognizing sphincter injury and attempting to improve continence (Tsang et al. 1998). The combination of rectal mucosal advancement flap in conjunction with sphincteroplasty has also been demonstrated to be successful in 100% of women with rectovaginal fistula following obstetric trauma with restoration of perfect continence in 70% (Khanduja

et al.1999) with good functional results achieved in 75% (Tancer et al. 1990; Soriano et al. 2001). All women with an obstetric-related rectovaginal fistula should undergo evaluation for occult sphincter injury. A retrospectively review compared those who underwent advancement flap alone with those in whom a concomitant sphincteroplasty was performed (Tsang et al. 1998) and identified an improvement in success rates from 41 to 80% when sphincteroplasty was included.

In a review of 105 patients with anorectal and rectovaginal fistulas treated with advancement flap, overall healing rates of 64% were noted although these were only 43% when subgroup analysis of the rectovaginal fistulas was performed (Sonoda et al. 2002), again suggesting a benefit for additional sphincter repair.

A trans-perineal approach, in which the rectovaginal septum is dissected, the fistula tract divided, and the rectal and vaginal openings both closed, has been described by Goligher (1984). This approach avoids excessive tension on suture lines and prevents the rectal and vaginal suture lines being in direct contact. Although limited to a small series of patients, success rates of 100% have been reported (Wiskind and Thompson 1992).

Vaginal mucosal advancement flaps have been advocated by some as a technically simpler way to close the opening of the fistula owing to easier access than the trans-anal approach. The transvaginal approach has a number of potential advantages; there is no perineal wound or deformity as seen with endoanal flap or conversion to a perineal laceration, a wide well-vascularized flap can be raised and closure without tension can be easily achieved. Despite these benefits it has been less commonly used than endorectal advancement flap. This relates to the rectum being both infected and at higher pressure (25–85 cm H_2O) than the vagina. A vaginal advancement flap would, theoretically, leave the fistula open to ongoing sepsis and may be pushed away by the increased rectal pressure (Devesa et al. 2007). This, however, may not be the case and healing in 9/12 traumatic fistulas has been achieved with vaginal advancement flap (Casadesus et al. 2006), whilst others favor a trans-vaginal purse-string repair for obstetric-induced fistulas with a 100% success rate (Rahman et al. 2003). Vaginal advancement flap may be particularly appropriate when a rectal advancement flap has previously failed or the rectal mucosa is diseased, such as in Crohn's disease and eradication of the fistula in 12/13 patients treated in this manner at 50-month follow-up has been reported (Bauer et al. 1991). In addition it has been suggested that any risk of incontinence in those with chronic diarrhea caused by internal sphincter damage during mobilization of a trans-anal advancement flap is eliminated by using a vaginal flap (Sher et al. 1991).

Crohn's Disease

The management of these fistulas can be particularly difficult resulting in proctectomy in between 6 and 53% (Radcliffe et al. 1988; Ley et al. 2007; Sparano et al. 2004; Hatcher et al. 1985; Anseline et al. 1981; Kimose et al. 1989; Alert et al. 1980; len-Mersh et al. 1987; Boronow 1986; Sandeman 1980; Devesa et al. 2007; Kodner et al. 1993; Ozuner et al. 1996; Jones et al. 1987; Makowiec et al. 1995; Joo et al. 1998; Macrae et al. 1995; Hilsabeck 1980; Sonoda et al. 2002; Rothenberger et al. 1982; Goligher 1984; Tsang et al. 1998; Khanduja et al. 1999; Tancer et al. 1990; Wiskind and Thompson 1992; Rahman et al. 2003; Bauer et al. 1991; Sher et al. 1991; Penninckx et al. 2001; Scott et al. 1992; Morrison et al. 1989; Michelassi et al. 2000; Athanasiadis et al. 2007; Hull and Fazio 1997) This figure may be misleading since many patients included in the studies have severe proctitis in addition, which may have been the symptom which necessitated proctectomy. Although the success rates for treating Crohn's related fistulas remains considerably lower than crypto glandular fistula, the contention by Hellers et al. in 1980 that "the combination of rectal Crohn's disease and anal fistulae invariably leads to proctocolectomy" (Hellers et al. 1980) is a nihilistic view. Even by the late 1980s Radcliffe et al. demonstrated that laying open of the fistula resulted in resolution of symptoms in 56% and local repair in 75% (Radcliffe et al. 1988). In a patient with quiescent disease and an asymptomatic fistula, management should be conservative; (Buchmann et al. 1980a, b) however, in those patients with symptomatic fistula the approach should initially be as for any perianal fistula related to Crohn's disease; sepsis should be drained and medical therapy optimized before surgical intervention is considered. Immunosuppressive therapy has been used to treat Crohn's related fistulas and outcomes such as "lessening fistulation" is seen in up to 63% (O'Brien et al. 1991). Complete closure rates, when recorded, are disappointingly

low at around 25%, with high recurrence rates reported when therapy is been stopped (Dejaco et al. 2003; Present et al. 1980; Present and Lichtiger 1994; Korelitz and Present 1985). Newer biological agents such as the anti-tumor necrosis factor α monoclonal antibody, infliximab have been demonstrated in placebo controlled trials to decrease the incidence of draining fistulas at 54 weeks from 81% in the placebo group to 64% in the treatment group (Sands et al. 2004a, b). Subgroup analysis of 25 patients with rectovaginal fistulas demonstrated response to infliximab in 60 and 45% of patients at 10 and 14 weeks (Sands et al. 2004a, b) and of those who responded, 72% had no drainage of their fistulas at 14 weeks (Sands et al. 2004a, b). Despite this situation the fistula tract continues to be present in around one-third of those with "healed" fistulas and the incidence of closure of rectovaginal fistulas is lower than that of perineal fistulas being 14 vs. 63% at week 6 and 28 vs. 59% at week 10 (Ardizzone et al. 2004). MRI confirmed the presence of perineal fistula tracts in 8/11 patients who had clinically responded to infliximab suggesting a high possibility that symptoms may return on cessation of the treatment (Van et al. 2003). Phase I trials evaluating the feasibility of treating Crohn's fistulas with mesenchymal stem cells has demonstrated that this may be feasible and although experimental, further work is ongoing (Garcia-Olmo et al. 2005). The treatment of rectovaginal fistula resulting from Crohn's disease with local advancement flaps has been widely reported, with primary success rates of 42–100%; although recurrence rates are high varying between 25 and 72% (Makowiec et al. 1995; Sonoda et al. 2002; Penninckx et al. 2001; Hull and Fazio 1997; Mizrahi et al. 2002). A variety of specific technical modifications have been described including using a layered closure of the attenuated rectovaginal septum, closure of the rectal opening by advancement flap and leaving the vaginal side open for drainage (Greenwald and Hoexter 1978), and use of vaginal mucosal advancement flaps. An advancement flap incorporating mucosa, submucosa, and internal sphincter has been reported in which the two edges of the internal sphincter are mobilized and brought together with the flap advanced and sutured to the anal verge (Rothenberger et al. 1982). A literature review evaluated all types of local repair in those with Crohn's disease (rectal, vaginal, anocutaneous advancement, or perineoproctotomy with fistula closure) and concluded that they are all similarly successful. Healing rates after the first repair are 46–71% (average 58%), with healing in subsequent repairs 40–71% (average 62%), and an overall healing rate of 75% (Penninckx et al. 2001). It does not appear that attempting local repair adversely affected the final outcome of the patient with an average proctectomy rate of 6% following attempted repair. Univariate analysis identified the number of Crohn's sites, the presence of extraintestinal manifestations and previous proctitis as adverse prognostic features, whilst multivariate analysis confirmed only the number of Crohn's sites as an adverse prognostic feature. Late recurrence of the fistula was also noted to occur after 3 or more years in 16%; however, the presence of marked proctitis failure of a local technique in a symptomatic individual may result in a defunction stoma for symptomatic control or a proctectomy.

Trans-Abdominal Approaches

Local repairs are generally unsuccessful for high rectovaginal fistulas and are inappropriate for those caused by radiation damage or malignancy. High fistula usually results from obstetric or surgical trauma. The simplest method generally reserved for benign fistulas involves mobilization of the rectovaginal septum, division of the fistula, and closure of the rectum and vagina with interposition of healthy tissue such as omentum. Alternatively, this approach may be performed in conjunction with resection of the diseased segment of bowel with a low anterior resection and colo-anal anastamosis to ensure that normal healthy bowel is brought down into the pelvis, again where possible healthy tissue should be placed between the vagina and neorectum. Hysterectomy may improve access to the fistula, and patients should be consented for this procedure, although preservation of the ovaries should be possible. Cases of laparoscopic repair of high rectovaginal fistula with omental interposition have been reported (Palanivelu et al. 2007), whilst others have reported laparoscopic rectovaginal mobilization to facilitate trans-vaginal repair (Pelosi and Pelosi 1997).

Radiation-Induced Fistula

The management of radiation-related fistula is problematic; local repairs are contraindicated due to the unhealthy nature of the tissues. The

use of a defunctioning colostomy as the principle way of managing these patients has been reported in the literature with the suggestion that fistulas represent a more severe manifestation of radiation damage (Bricker et al. 1986), often associated with a frozen pelvis making proctectomy technically difficult. The results from defunctioning are often satisfactory, local symptoms are controlled an acceptable level in 60%; however, 15–33% have stomal complications such as necrosis, fistulation, stenosis, prolapse, and hernia, some of which may result from existing radiation damage (Kimose et al. 1989; Hatcher et al. 1985) and irradiated colon or small bowel should not be used to fashion the stoma. When possible, resection gives the optimal outcome; (Hatcher et al. 1985) however, operating in the presence of extensive radiation injury can be hazardous and overall radiation-induced mortality rates of 20–33% have been reported with the predominant cause being peritoneal sepsis following injury to the intestine or urinary tract (Kimose et al. 1989; Alert et al. 1980; len-Mersh et al. 1987; Boronow 1986; Sandeman 1980; Devesa et al. 2007; Kodner et al. 1993; Ozuner et al. 1996; Jones et al. 1987; Makowiec et al. 1995; Joo et al. 1998; Macrae et al. 1995; Hilsabeck 1980; Sonoda et al. 2002; Rothenberger et al. 1982; Goligher 1984; Tsang et al. 1998; Khanduja et al. 1999; Tancer et al. 1990; Wiskind and Thompson 1992; Rahman et al. 2003; Bauer et al. 1991; Sher et al. 1991; Penninckx et al. 2001; Scott et al. 1992; Morrison et al. 1989; Michelassi et al. 2000; Athanasiadis et al. 2007; Hull and Fazio 1997; Hellers et al. 1980; Buchmann et al. 1980a, b; O'Brien et al. 1991; Dejaco et al. 2003; Present et al. 1980; Present and Lichtiger 1994; Korelitz and Present 1985; Sands et al. 2004a, b; Ardizzone et al. 2004; Van et al. 2003; Garcia-Olmo et al. 2005; Mizrahi et al. 2002; Greenwald and Hoexter 1978; Palanivelu et al. 2007; Pelosi and Pelosi 1997; Bricker et al. 1986; DeCosse et al. 1969; Deitel and Vasic 1979; Galland and Spencer 1985). It is important to ensure that prior to undertaking such challenging and hazardous surgery the patient is cancer-free and has been fully counseled regarding the risks of surgery.

An alternative procedure, although no less difficult than anterior resection, is a "sleeve" or pull-through anastamosis of healthy non-irradiated proximal colon to the anal canal as initially reported (Parks et al. 1978). This approach involves performing a proctectomy to a level just distal to fistula and resecting the irradiated bowel. The colon is fully mobilized and a transanal mucosectomy performed all the way up to the level of the rectal division. The colon is then drawn through the muscular rectal tube and anastamosed to the anal canal. Technical success has been reported in up to 93% with full continence rates of 77% at a mean of 5-year follow-up (Cooke and Wellsted 1986). Functionally good results in 18/23 patients have been reported (Nowacki 1991), but others have reported reduction in compliance of the neorectum (Varma and Smith 1986), and suggested improvements in function may be obtained from the addition of a colonic J pouch (Cuthbertson 1986).

Malignant Fistula

In the case of malignant fistula management should be dictated by the potential chance of cure. If the patient has a terminal diagnosis, palliation with a stoma may be most appropriate. When there is a chance of cure a combined approach with an oncologist and radiotherapist should be undertaken; neo-adjuvant therapy should be implemented, if appropriate, usually under the cover of a diverting stoma. On cessation of treatment, or if not appropriate, an extensive resection should be considered, with en-bloc removal of the rectum, uterus, and vagina. The involvement of gynecologists and plastic surgeons (who may be required to reconstruct the vaginal and/or perineum) both prior to and during the surgical procedure should be encouraged. Restoration of gastrointestinal integrity may be achieved by a colo-anal anastamosis but the aim of surgery should be complete eradication of malignant tissue from the pelvis, this should not be compromised and an abdominoperineal excision with an end stoma should be performed if necessary.

Bulbocavernosus (Martius) Graft

The Martius flap was first described in 1928 (Martius 1928) and is a pedicled, bulbocavernosus, muscular fat pad graft taken from either labia majora based on the perineal branch of the pudendal artery (cadaveric studies suggest that the graft consists of fibroadipose tissue rather than bulbocavernosus muscle (Elkins et al. 1990). It has long been used by urologists and gynecologists for repair of urethero-vaginal fistulas (Flisser and Blaivas 2003; Rangnekar et al. 2000) but has more recently become used by colorectal

surgeons for the management of low, complex rectovaginal fistula (Pinedo and Phillips 1998; Chitrathara et al. 2001). The patient is positioned in lithotomy, a transverse incision is made in the perineum, and the rectovaginal septum opened. The fistula is identified, divided, and dissection continued cephalad into normal healthy tissue. The rectal side of the fistula is closed in two layers and if the external sphincter is disrupted a standard overlapping sphincteroplasty may be performed. A longitudinal incision is made over the labia (usually the left labium if the surgeon is right-handed) and the bulbocavernosus muscle is mobilized from the labia ensuring the posterolateral vascular pedicle is preserved. A subcutaneous tunnel is created up to the rectovaginal septum and the graft placed into the septum and loosely fixed in place with absorbable sutures, ensuring the vascular pedicle is not twisted. The labial and perineal incisions are then closed.

Data regarding the outcome of this procedure are limited to small series and case reports and results appear mixed. Aartsen et al. demonstrated excellent results with healing in 13/14; however, follow-up demonstrated a reduction in healing over a 10-year period to 6/14 with dyspareunia and vaginal stenosis being a significant complication (Aartsen and Sindram 1988). Others report good success with recurrence noted in only 1/16 (6%) of patients and an improvement in fecal incontinence; although dysparunia increased from a preoperative level of 7–31% it did not appear to significantly limit sexual function (McNevin et al. 2007). Pinedo and Phillips reported a 75% success rate in eight patients with complex peri-anal fistulas, six of whom had rectovaginal fistula (Pinedo and Phillips 1998). The use of Martius grafts in those with radiation-induced rectovaginal fistula has been successful in 11/14 patients with minimal complications (White et al. 1982) and others have also reported success in 84% also with radiation-induced fistula; (Boronow 1986) however, Zimmerman et al. have failed to demonstrate the benefit of interposition of a labial fat pad when compared to a standard local advancement flap repair (Zimmerman et al. 2002). Alternative techniques using interposition of gracilis muscle have also been used in the management of rectovaginal fistula, although they are more commonly used in the treatment of rectourethral fistula in males (see below), success rates of 62% have been reported (Oom et al. 2007) and the incidence of dyspareunia in women who undergo muscle interposition for rectovaginal fistulas may be as high as 57%.

Diverting Stoma

Controversy exists as to the benefit of a diverting stoma when repairing a rectovaginal fistula. Although a disappointment to the patient, stomas may be the optimal management for some patients such as those unfit for surgery or those with a fistula related to incurable malignant disease, thus avoiding the need for extensive surgery whilst offering satisfactory palliation. In addition, they may be used as a bridge to surgery, allowing healing of infected tissues and may improve the outcome of definitive surgery at a later stage; however, prospective randomized trials are lacking. Some advocate its liberal use (Watson and Phillips 1995), whilst others have found it to be unnecessary and failed to demonstrate any difference in healing rates for those who undergo a diverting stoma (Macrae et al. 1995; Khanduja et al. 1999) It is possible that stomas tend to be used in the management of the more complex or difficult fistulas (Sonoda et al. 2002), with Devesa et al. demonstrating healing rates of 11/13 with simple fistulas without the use of a covering stoma and 18/20 complex fistulas in whom a stoma was formed (Devesa et al. 2007). In those with Crohn's disease, the use of a diverting stoma alone rarely results in fistula healing; although it may result in an improvement in symptoms it does not seem to alter the long-term course of the disease with restoration of intestinal continuity uncommon (Grant et al. 1986). Of 12 patients with rectovaginal fistula, 7 healed following ileostomy although they recurred in all patients with rectal disease (Harper et al. 1982). Literature review including multivariate analysis demonstrated that a defunctioning stoma was not related to improved healing and carried with it intrinsic morbidity, increasing hospitalization by over 9 days (Penninckx et al. 2001).

Recurrent Fistulas

Recurrent fistulas present a particular challenge, but again the choice of operation should be tailored to the patient's symptoms, underlying condition and general health. A report of 35 women with recurrent rectovaginal fistulas identified 15 with obstetric injury, 12 with Crohn's disease, 5 following ileal pouch anal anastamosis, 2 with crypto-glandular disease and 1 following low anterior resection (Halverson et al. 2001). The overall healing rate was 79% with a

median of two operations performed per patient. Mucosal advancement was attempted on 30 occasions, fistulotomy with sphincter repair in 14, rectal sleeve advancement in three, fibrin glue in one, proctectomy and colonic pull-through in two, and ileal pouch revision in six. In patients with Crohn's disease, the presence of a diverting stoma and a decreased time between repairs were associated with a poorer prognosis. Others confirm that local repair may be effective in treating recurrent fistula, however the rate for healing falls from 85% after 1 previous attempt to 55% when 2 previous attempts have been made (Lowry et al. 1988), suggesting that alternative approaches are required such as vaginal advancement flaps, Martius grafts, gracilis interposition, or proctectomy with coloanal anastamosis be employed following recurrent failed attempts at local repair.

Rectourethral Fistula

Rectourethral fistula is an uncommon yet challenging surgical condition. They may be congenital which are accompanied by a variety of pelvic floor malformations or acquired which are predominantly seen in elderly men following treatment for prostatic disease.

Presentation and Investigation

The common presenting features are recturia in 73%, hematuria in 54%, pneumaturia in 34%, and rectorrhagia in 17% with 68% having urinary tract infections (Munoz et al. 1998). Even in highly symptomatic individuals, direct or radiological identification of the fistula may prove difficult. Cystoscopy and proctoscopy should be performed; if these fail to identify the fistula, traditionally retrograde urinary or rectal contrast studies have been employed but these have a poor record in identifying fistulas. Imaging such as CT scanning may be of use and although accurate in only 60% of cases (Munoz et al. 1998), it does provide useful information regarding pelvic sepsis or the extent of tumor. More recently, MRI or endorectal ultrasound scanning have been employed for the identification of fistula with great success; although data specific to the evaluation of rectourethral fistula are lacking it should be safe to assume that they will be of benefit. Although differentiation of the exact location of the fistula such as between a low vesical and uretheral fistula may prove problematic, it is less important in determining management than the underlying cause (Munoz et al. 1998). Examination under anesthesia is very useful and patients may have severe parianal pain and sphincter spasm precluding satisfactory clinical evaluation in the office.

In a retrospective series between 1980 and 1995 Mayo Clinic identified 22 rectourethral fistulas; nine were from benign disease (three Crohn's disease, three following pelvic fracture, two following perianal sepsis, and one following trans-rectal biopsy). Thirteen were related to malignant conditions, five following prostatectomy (four retropubis and one trans-perineal), four following combined radiotherapy and surgery (three post-cystoprostatectomy and one post-cystostomy tube placement), three presented after radiotherapy and one was secondary to tumor growth (Munoz et al. 1998). The increased use of brachyterapy, external beam radiotherapy, or a combination in the treatment of prostate cancer has led to increased numbers of men presenting with rectouretheral fistula secondary to radiation damage. Prior to 1997 only 3.8% of cases reported in the literature were as a result of radiotherapy (Vidal et al. 1985; Jordan et al. 1985; Lang and Meister 1990; Buchmann et al. 1980a, b; Wallner et al. 1994), whilst after this 49% are related to radiotherapy (Nyam and Pemberton 1999; Dinges et al. 1998; Izawa et al. 2000; Garofalo et al. 2003; Zmora et al. 2003; Moreira et al. 2004; Shah et al. 2004; Chrouser et al. 2005). This group is particularly difficult to treat; the possibility of recurrent malignancy may be difficult to exclude with certainty, biopsies of the area, prostate specific antigen studies, bone scans and imaging with CT, MRI and positron emission tomography (PET) should all be considered. In addition, local tissues are severely damaged often with extensive necrosis, fibrosis, and more likely to be associated complex abscess cavities when compared to other iatrogenic, inflammatory, or traumatic fistulas. The median time from last radiation treatment to the development of the fistula is 29 months; although patients may present up to 20 years later (Lane et al. 2006).

Management

Rectourerthral fistulas seldom spontaneously heal (Nyam and Pemberton 1999) and although

the ultimate treatment goal is to achieve healing of the fistula and restore the patient to normal bladder and bowel function a more pragmatic approach should be employed, based on the etiology of the fistula; simple, benign, Crohn's disease; radiotherapy or malignancy; and the age and general health of the patient. Benign fistulas can often be managed with local procedures such as local advancement flaps, whilst those related to radiation damage or direct malignant invasion may require extensive resection such as pelvic exenteration with stoma formation which may not be appropriate for the old, infirm, or terminally ill. In patients with a history of malignant disease, such as prostate cancer, a biopsy of the fistula should be undertaken to ensure that it is not malignant and best treated with an extended resection or palliation.

As with rectovaginal fistula a wide variety of surgical procedures have been described to manage these patients (Vidal et al. 1985; Nyam and Pemberton 1999; Boushey et al. 1998; Tiptaft et al. 1983; Martelli et al. 1984; Wilbert et al. 1996) but can be broadly divided into local repair via the rectal lumen, such as a simple advancement flap, trans-abdominal/abdominoperineal approaches, and a combination of either with the use of tissue interposition in which healthy tissue is transposed to separate the urethra and rectum. The use of initial fecal and urinary diversion by means of a catheter is widely advocated particularly in those following radiation damage; although some suggest this should be reserved for those patients with septic complications at presentation and then performed following definitive surgery (Nyam and Pemberton 1999) whilst others advocate this as the first step in management in all cases (Lane et al. 2006). Even in series in which rectal advancement flaps have been the therapy of choice, 34% had undergone either fecal or urinary diversion and 52% underwent both (Garofalo et al. 2003).

Local Techniques

It has been suggested that local rectal advancement flaps may be less useful in managing rectourethral than rectovaginal fistula since the high-pressure side of the fistula is the urinary tract rather than the rectum (Zmora et al. 2006). Published series tend to be small; Parks reported healing in five cases with a rectal advancement flap (Parks and Motson 1983). Garofalo et al. reported rectal advancement flap in 12 cases with primary closure achieved in 67% and overall closure following a repeat procedure of 83% (Garofalo et al. 2003). The posterior midline approach as described by York-Mason (1970) allows bloodless exposure through unscarred tissue and has been shown to be effective in healing rectoprostatic fistulas in three cases (Prasad et al. 1983). Trans-anal endoscopic microsurgery (TEM) has also been reported to be effective in two patients with rectourethral fistula (Wilbert et al. 1996). Perineal approaches have been advocated often with the use of interposition with Dartos muscle, or more commonly, gracilis muscle (see below).

Abdominal Approaches

Local advancement flaps have minimal role in those with radiation-induced rectourethral fistula or malignancy due to the poor quality of the surrounding tissues. In a retrospective review of 22 patients with radiotherapy-induced rectourethral fistula, three patients were treated with fecal and urinary diversion by means of a suprapubic catheter due to severe co-morbid condition, four patients underwent APER and cystectomy and permanent fecal and urinary diversion. Six patients were deemed to have adequate urinary and anal sphincter function to allow reconstruction and underwent proctectomy with a colonic pull-through and colo-anal anastamosis and a buccal mucosa reconstruction of the urethra. Interposition of healthy tissue such as gracilis may be of great benefit in this group.

Omental and Muscle Interposition

A variety of tissues have been used for interposition of rectouretheral and rectovaginal fistula including greater omentum; (Trippitelli et al. 1985) however, this requires a laparotomy and may not be feasible in thin patients or those who have undergone previous abdominal surgery. The most commonly used muscle however is the gracilis (Nyam and Pemberton 1999; Dinges et al. 1998; Izawa et al. 2000; Garofalo et al. 2003; Zmora et al. 2003; Moreira et al. 2004; Shah et al. 2004; Chrouser et al. 2005; Lane et al. 2006;

Boushey et al. 1998; Tiptaft et al. 1983; Martelli et al. 1984; Wilbert et al. 1996; Zmora et al. 2006; Parks and Motson 1983; York-Mason 1970; Prasad et al. 1983; Trippitelli et al. 1985; Ryan et al. 1979).

The patient is positioned in the modified lithotomy position and catheterized. Two to three 5 cms incisions are made along the medial border of the thigh overlying the gracilis muscle. The tendonous insertion into the tibial plateau is identified and divided. The muscle if then dissected free from surrounding connective tissue and delivered through the most proximal thigh incision, ensuring the neurovascular structures entering the muscle from the proximal end are preserved. A subcutaneous tunnel is created up to the perineum and the muscle brought up into this. The leg incisions are closed, the patient transferred to the prone jack-knife position, and a transverse perineal incision made and the rectouretheral plane opened. The fistula is identified, divided, and disection is continued cephalad into healthy uninflamed tissue. The rectal defect is closed with a rectal advancement flap, the uretheral defect is closed with absorbable sutures, and the gracilis muscle is delivered into the space between the rectum and urethra and secured to the top of the incision with nonabsorbable sutures. The perineal wound is closed over a suction drain (Ryan et al. 1979) Postoperatively the foley catheter is retained for 6 weeks. The use of a covering stoma is generally advocated in patients undergoing muscle interposition; (Zmora et al. 2003) although others have suggested it is not necessary (Oom et al. 2007) and data are limited. Whilst results from this technique appear to be good, they are based on small series or case reports. Zmora reported a success rate of 83% following the initial procedure with 100% overall following a second procedure in 11 patients with rectourethral fistula (Zmora et al. 2003) and Nyam reported 100% success in three cases (Nyam and Pemberton 1999). A more recent study by Wexner et al. demonstrated that use of the gracilis flap for rectourethral fistulas was successful 78% of the time with an initial repair attempt with an overall success rate of 97% after a second repair (Wexner et al. 2008). When used for rectovaginal fistulas the gracilis interposition had a success rate of 75% in patients without Crohn's disease. Only 33% of the patients with Crohn's disease had successful healing after the flap was placed. This to date is the largest series that clearly demonstrates the benefit of utilizing gracilis muscle as an interposition graft for rectourethral and rectovaginal fistulas.

Conclusion

Rectovaginal and rectourethral fistulas lead to a major detrimental impact on a patient's quality of life and present a significant problem for the surgeon to tackle. Cure should be expected in simple rectovaginal fistulas; however, more complex fistulas may be very difficult to eradicate and may necessitate extensive surgery to achieve this. The key in these more challenging cases is to have a realistic outcome goal and manage the patient's expectations appropriately. Those with extensive radiation damage to the pelvis may be better served by a defunctioning stoma as those with severe rectal Crohn's disease should be counseled that a stoma or proctectomy may be the eventual outcome. This should not preclude attempted cure and appropriate selection of a local advancement flap in conjunction with interposition of healthy tissue should be considered as the first step in managing these cases with subsequent procedures becoming more complex as necessary. Figures 14.1–14.3 give a simple algorithm for the management of simple and complex rectovaginal fistulas.

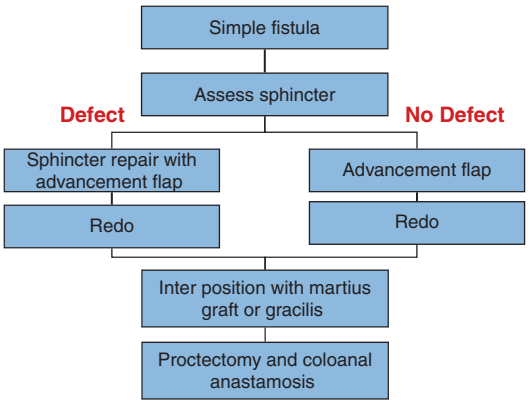

Figure 14.1. Management of simple rectovaginal fistulas.

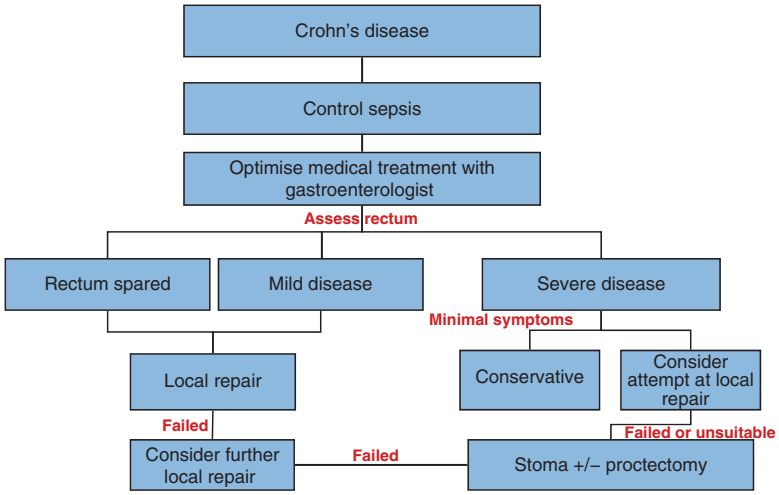

Figure 14.2. The management of Crohn's related colovaginal fistulas.

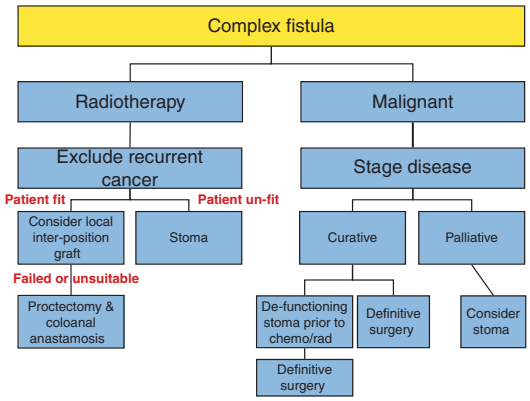

Figure 14.3. The management of complex rectovaginal fistulas.

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15

Surgeon-Performed Ultrasound in Proctologic Practice

Andrew P. Zbar and Marc Beer-Gabel

Introduction

Since the introduction of endoanal and endorectal ultrasound by Law and Bartram in 1989, (Law and Bartram 1989) there has been an accelerated use of this technique for the preoperative assessment and management of rectal and anal cancers, (Beynon et al. 1991; Garcia-Aguilar et al. 2002) delineation of the anatomy of complex cryptogenic and inflammatory bowel disease-related perirectal sepsis (Zbar and Armitage 2006; Regadas and Regadas 2008) and for the definition of potentially reparable or augmentable external and internal sphincter defects (Martinez Hernandez Magro et al. 2003; Gravanta and Giordano 2008). Modifications of this technique with hydrogen peroxide enhancement for assessment of fistula-in-ano, (Cheong et al. 1993) Duplex supplementation for detection of perirectal blood flow, (Mallouhi et al. 2004) contrast enhancement (Chew et al. 2003), and 3-dimensional reconstruction with stacked, close interval interpolation (Zimmerman 2003; West et al. 2003; Buchanan et al. 2004) have been recent developments as has been endorectal-guided biopsy of locally recurrent rectal and anal cancers and for perirectal lymph node biopsy particularly following radiotherapy (Gavioli et al. 2000; Liersch et al. 2003). Coronal reconstruction has attempted to resolve some of the limitations inherent in endoanal sonography to provide a multiplanar interpretation of complex fistulous disease and its relationship to the main sphincter complex (Gold et al. 1999; Williams et al. 2001) and has offered useful information about staging of anal cancers prior to definitive chemoradiation (Christensen et al. 2004).

Perineal sonography (both static and dynamic), has been described with selective advantage in delineation of trans-levator and lateral extrasphincteric fistula-in-ano, recto (and ano-) vaginal fistula, and in rectal and anal cancers where luminal distortion or pain prevent deployment of an endorectal assembly. In the dynamic mode it has proven sensitive for the diagnosis of the main conditions selectively associated with the "final common pathway" of evacuatory difficulty including rectocele, enterocele, and rectoanal intussusception (Beer-Gabel et al. 2002; Brusciano et al. 2007) providing comparative results with more complex technology such as defecating proctography (Beer-Gabel et al. 2004) and dynamic magnetic resonance (MR) imaging. Currently, formal comparisons between these two methdologies have so far not been published. The selective utilization by the practicing coloproctologist may be required in both benign and malignant colorectal and anorectal disease where these modalities are complementary rather than competitive, providing answers to specific anatomic or pathologic questions which are relevant to successful surgical management. The colorectal surgeon and trainee must be familiar with these imaging techniques and be able to perform them in order to interpret those cases referred to a tertiary coloproctological practice with complicated and recurrent perirectal sepsis, fecal incontinence, defecatory dysfunction, and rare

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perianal and retrorectal tumors. This view is illustrated in this chapter with examples, outlining the advantages and disadvantages in different clinical circumstances of these overlapping techniques.

Complex Perirectal Sepsis

At its simplest and most practical level, successful eradication of an anal fistula must be coupled with functional sphincter preservation. Although most perirectal infections do not require specialized imaging, (Sangwan et al. 1994) its use may in part lie in the delineation of the secondary destructive effects of unresolved or recurrent sepsis including horseshoeing in the anteroanal and/or retrorectal spaces, internal and/or external anal sphincter damage (either as a direct result of sepsis or of prior inadvertent sphincter injury), the presence of an ano- or rectovaginal fistula, or in the demonstration of a source of sepsis which primarily emanates from above the levator floor (Zbar et al. 1998). In each of these circumstances, the colorectal surgeon relies on preoperative imaging to answer specific questions. MR imaging, for example, will provide clues as to primary supralevator disease where ischiorectal drainage may result in a high extrasphincteric fistula. Here, the distinction must be made from a primary cryptogenic ischiorectal abscess which has a secondary trans-levator extension where ischiorectal drainage, fistula control (with either fistulotomy or seton deployment), and trans-levator drainage will result in successful therapy (Zbar and deSouza 1999; Zbar 2001).

In this setting, endorectal technology (either ultrasonographic or MR), will result in inadequate transducer probe coupling above the puborectalis and MR imaging is necessary to define disease extension above the pelvic floor. In those cases where there is attendant incontinence (often secondary to injudicious injury), endoluminal ultrasound (or if available endoluminal MR), will not only define the anatomic disposition of collections and tracks but has the added benefit of accurately demonstrating internal and external anal sphincter defects which may be reconstituted at a delayed stage by bioaugmentation and/or sphincteroplasty (Abbas et al. 2008; Kamm and Ng 2008). In this context, trans-perineal sonography will be able to trace more extensive soft-tissue tracks better than endoluminal techniques where anovaginal, anovestibular, and anoscrotal openings tend to lie well beyond the focal distance of an endoanal probe (Zbar et al. 2006). There appears to be little evidence that hydrogen peroxide enhancement in this circumstance is of any particular benefit (Zbar et al. 2006; Kleinübing et al. 2007), although it has established advantage for endoanal sonography and in situations where there is an extensive intersphincteric gas-containing abscess in these latter settings trans-perineal ultrasound has been relatively inaccurate (Zbar et al. 2006). This finding should be contrasted with endoanal ultrasound where large intersphincteric collections may be overstaged as trans-sphincteric because of excessive acoustic shadowing and where more sphincter muscle may be placed at risk of division if this imaging modality alone is relied upon for surgical decision making.

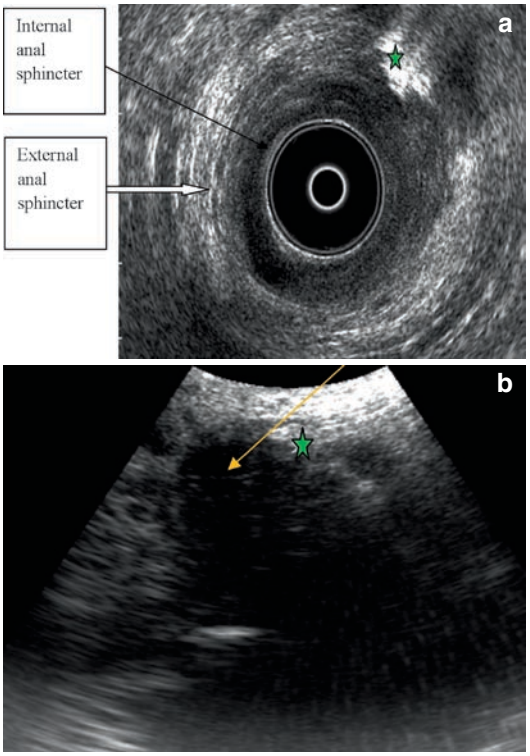

Figure 15.1. Endoanal (**a**) and axial trans-perineal (**b**) representation of chronic intersphincteric sepsis presenting as persistent anal pain. (**a**) *Arrow* internal anal sphincter, *Block arrow* external anal sphincter, *Star* hyperechoic intersphincteric abscess, (**b**) *Arrow* air-filled anal canal, *Star* intersphincteric abscess.

Both endoanal and trans-perineal ultrasound have been utilized with some success for the demonstration of occult intersphincteric sepsis in patients who present with chronic anal pain in whom there is no evidence of a perianal or ischiorectal sinus or fistula (Fig. 15.1; (Christiansen et al. 2001; Millan et al. 2006) as well as in the delineation between perineal sepsis and hidradenitis suppurativa (Fig. 15.2). Familiarity with trans-perineal sonography is of benefit in circumstances where endorectal probe deployment is either too painful or in perianal Crohn's disease where anal distortion prevents adequate positioning of an endoanal probe (Zbar 2006). The coloproctologist needs to gain from the selective and complementary use of such surface and endoanal imaging a preoperative

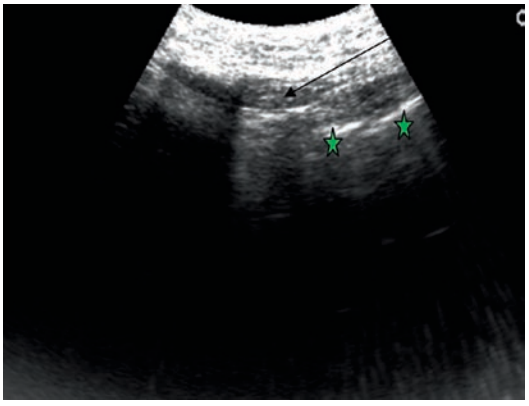

Figure 15.2. Axial trans-perineal image of perineal sepsis. *Arrow* anal canal, *Stars* hyperechoic areas of perineal sepsis separate from the anal canal.

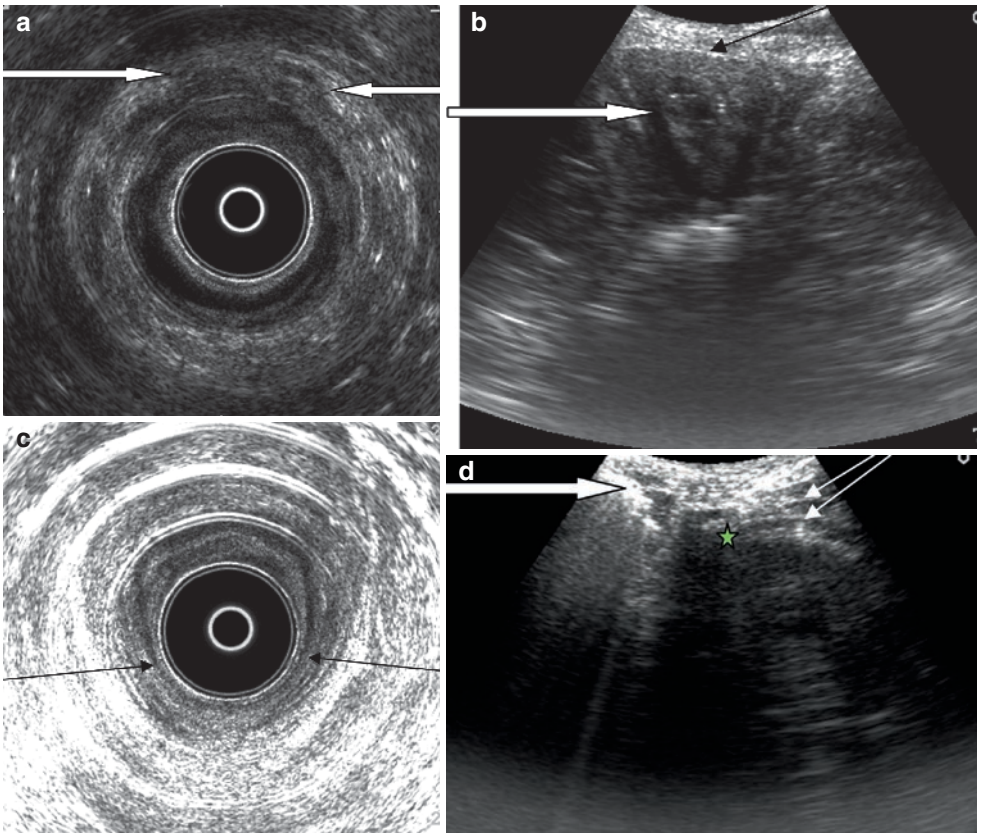

Figure 15.3. (**a**) Endoanal ultrasound confirming patchy external anal sphincter defect secondary to destructive perirectal sepsis (*arrows*), (**b**) Axial trans-perineal ultrasound showing thinned external anal sphincter (*arrows*). The internal anal sphincter is shown as the hypoechoic layer (*block arrow*), (**c**) Evidence of internal anal sphincter damage posteriorly (*arrows*) on endoanal ultrasound as part of previous fistulectomy. (**d**) Sagittal trans-perineal ultrasound showing the hypoechoic internal anal sphincter in profile (*arrows*) with a high trans-sphincteric secondary track (*bright echo: block arrow*) extending in the intersphincteric space to the level of the puborectalis (*star*) seen *en face*.

3-dimensional concept of the fistula and associated abscesses and their secondary destructive effects, utilizing and interpreting their specific additive roles for successful fistula eradication; an effect which can only be derived from direct surgical application (Fig. 15.3). This view may be assisted by the introduction of 3-dimensional endoanal and trans-perineal reconstructed sonography aiding in determination of the relationship of collections and tracks to the levator plate (Fig. 15.4). There are as yet no comparative studies of the value of trans-perineal sonography over endoanal ultrasound or Gadolinium-enhanced MR imaging in patients with perianal Crohn's disease (Wedemeyer et al. 2004; Bonatti et al. 2004). More recently, MR imaging has suggested that a more obtuse angulation of the primary fistula track at entry into the submucosa may be associated with a more rostral location of sepsis; forewarning of more potential functional disturbance by fistulectomy (Buchanan et al. 2003). These data should be viewed with caution considering the relatively poor definition of the sub-epithelial space utilizing MR technology and the assumption that the angle of luminal and intermuscular fistula entry necessarily correlate.

Fecal Incontinence

The surgical management of fecal incontinence has been revolutionized by the introduction of endoanal sonography which has been shown to correlate with anatomical external anal sphincter (EAS) defects (Sultan et al. 1994) and which has complimented the electromyography (Tjandra et al. 1993). Here, although there is still controversy concerning the overall incidence and significance of some anterior EAS defects (Bollard et al. 2002) as well as the relatively poor delineation of the structures of the perineal body either with endoanal or trans-vaginal ultrasound (Sultan et al. 1994; Oberwalder et al. 2004), there is good acceptance that endoanal ultrasound has separated EAS injuries from those injuries presenting with passive incontinence with attendant internal anal sphincter (IAS) damage where these patients have not benefited either from IAS plication at the time of EAS sphincteroplasty or biofeedback therapy (Leroi et al. 1997; Terra et al. 2008). The latter injury has responded with acceptable short- and medium-term functional improvement to bioaugmentation (Malouf et al. 2001; de la Portilla et al. 2008) and has provided an acceptable algorithm of management where ultrasound has directed surgical decision making. In this context, recent data have shown endoanal MR technology to accurately diagnose associated EAS atrophy which has correlated with overall worse short- and medium-term results following EAS sphincteroplasty (Briel et al. 1999) with this technology correlating well for the demonstration of EAS defects both with endoanal ultrasound (Cazemier et al. 2006) and with surface MR imaging (Terra et al. 2005; Stoker and Zbar 2008). Currently, there is, however, no histologic gold standard for EAS atrophy definition (Briel et al. 2000).

Three-dimensional endoanal ultrasound has suggested that there is a direct correlation between the angle of the EAS defect and its coronal extent (Gold et al. 1999) where it is known that relatively poor short-term functional outcomes following overlapping sphincteroplasty occur as a result of inadequate rostral repair (Pinedo et al. 1999). As yet, it is unclear whether prospective 3-dimensional endoanal imaging can direct attendant levatorplasty (Evans et al. 2006; Brown and Nelson 2007). More recently, trans-perineal sonography has shown uncontrolled benefit in intraoperative and immediate postoperative monitoring of the adequacy of EAS sphincteroplasty where concern has been raised about an endoanal probe stressing the integrity of the repair (Fig. 15.5). It is anticipated (although as yet unproven) that it will have a role in confirmation of deployment of bioaugmentables for IAS bolstering without the hazard of implant migration which has been a warning of its pioneers (Tjandra et al. 2004). Trans-perineal ultrasound may have an expanded role for assessment of postoperative anal incontinence due to IAS injury where it is expected that inadvertent IAS damage should substantially increase because of the expanded use of limited hemorrhoidectomy techniques such as Ligasure hemorrhoidectomy, Doppler-guided hemorrhoid artery ligation, and stapled PPH hemorrhoidopexy where the IAS is relatively unprotected from damage due to lack of its dissection from the submucosa (Zbar et al. 2001). This is more likely to ensue in those presenting primarily with significant hemorrhoidal prolapse and may also be a feature of older patients with preexisting unrecognized IAS degeneration (Waldron et al. 1989; Vaizey et al. 1997).

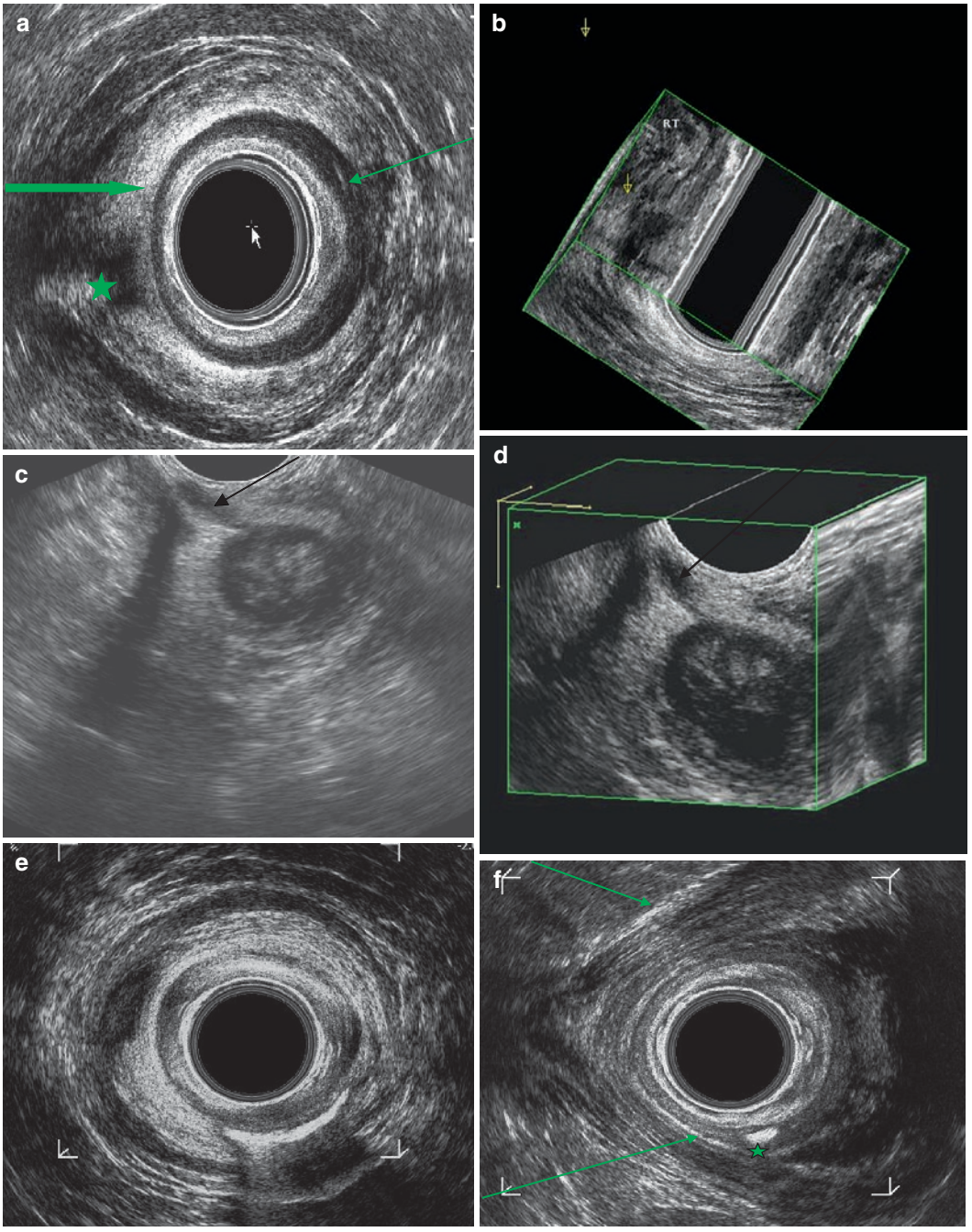

Figure 15.4. (**a**) Endoanal sonogram showing a trans-sphincteric collection (*star*). *Arrow* = internal anal sphincter, *block arrow* = external anal sphincter, (**b**) 3-dimensional endoanal reconstruction showing coronal extension of the abscess collection (*arrow*), (**c**) *Axial transperineal* ultrasound showing an anterior trans-sphincteric fistula-in-ano (*arrow*), (**d**) *3-D reconstructed* transperineal ultrasound demonstrating the *same* anterior transsphincteric fistula (arrow), (**e**) *Axial endoanal ultrasound* showing hyperchoic enhancement of an intersphincteric abscess between 4 *and* 6 *o'clock*, (**f**) *Endoanal ultrasound* showing the abscess cavity (*star*) extending to *the levator* plate (*arrows*).

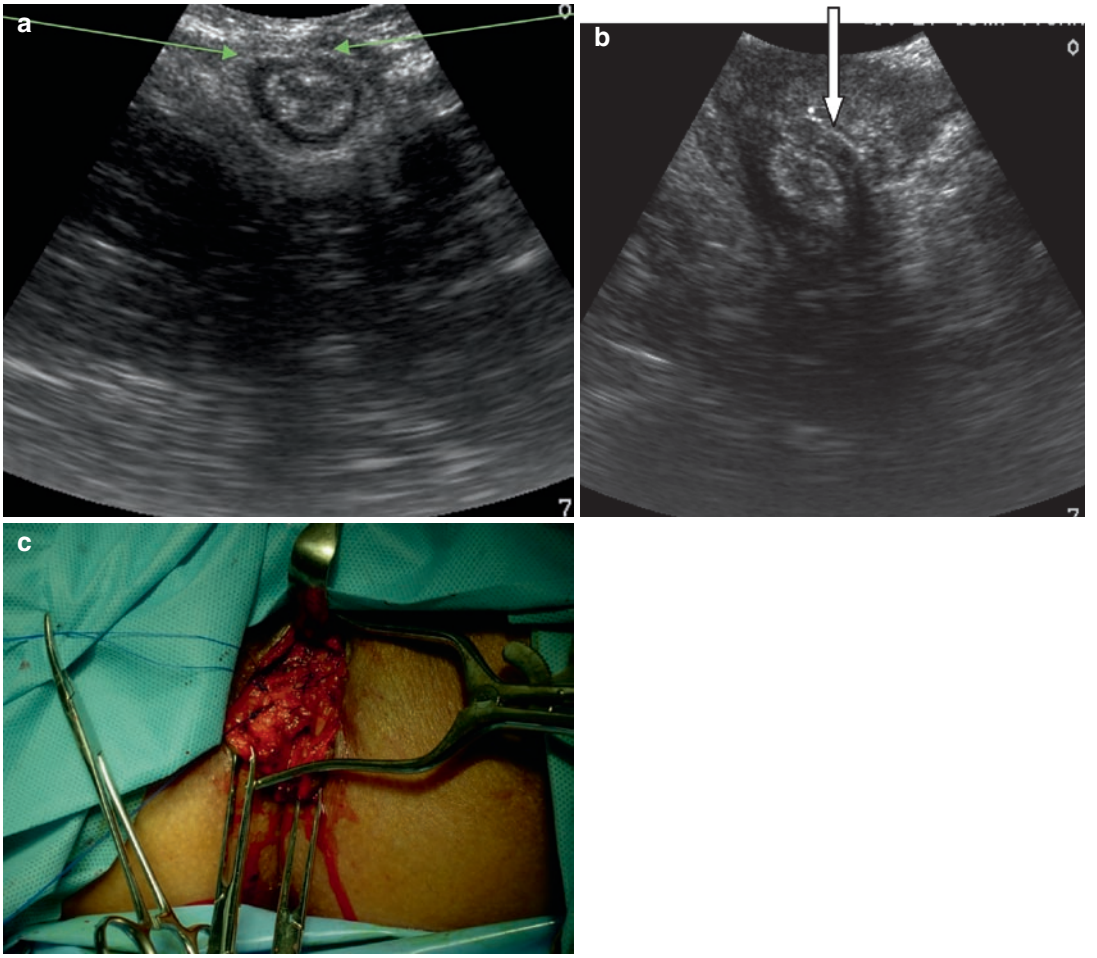

Figure 15.5. (**a**) *Intra*operative trans-perineal ultra**s**ound of an external anal sphincter defect (*arrows*), (**b**) Postoperative trans-perineal ultrasound of overlapping sphincteroplasty at 1 week (*block arrow*), (**c**) Intraoperative overlapping external anal sphincteroplasty.

Evacuatory Dysfunction and Other Functional Problems

The true incidence of evacuatory difficulty is unknown since directed imaging such as defecating proctography has defined abnormalities in an "abnormal" population (Shorvon et al. 1989). What is known, however, is that >90% of patients with specific pathologies (such as rectocele) have a multiplicity of pelvic floor and perineal soft-tissue abnormalities which transcend all compartments (Maglinte et al. 1999; Rotholtz et al. 2002). The use of modalities such as MR proctography and dynamic trans-perineal sonography to define the real-time complexity of pelvic floor interaction has arisen from a general dissatisfaction with complicated extended and often uncomfortable proctographic techniques (including defecoperitoneography) which are relatively poorly tolerated by patients (LeSaffer 1994; Bremmer et al. 1998) and an increasing understanding that the dynamic interaction of all organs during provocative maneuvers such as straining, simulated defecation/expulsion or withholding are required to fully outline pelvic floor pathology. This fact is particularly the case where surgery is used to correct one dominant pathology such as rectocele or enterocele despite the presence of other anomalies where it has been deemed that the complex of patient

symptomatology is attributable to one dominant condition. It is a testament to our lack of understanding of the etiopathogenesis of pelvic floor disorders that we still know relatively little about normal pelvic floor interaction, let alone distorted interaction as may occur following hysterectomy or colpoperineorrhaphy (Kahn and Stanton 1997; Kell et al. 1998).

Part of this poor understanding may go some way to explaining the dual dialogue in the literature concerning "good" or "bad" functional outcomes following novel procedures such as the STARR and TRANSTAR procedures (Schwandner et al. 2008; Renzi et al. 2008) or elaborate combined laparoscopic/perineal rectopexy and mesh deployments (D'Hoore et al. 2008; Slawik et al. 2008) where some have warned that new technology-related "syndromes" may occur postoperatively (Pescatori and Seow-Choen 2003; Pescatori and Zbar 2009). In this setting it needs to be understood that there is a relatively poor correlation between anatomical anomaly correction and symptom resolution (Oom et al. 2007). Although these matters lie further afield than our discussion in this chapter, the successful integrated use and interpretation of imaging designed to show the dynamic interaction between component parts of the pelvic floor must inevitably inform patient selection for reconstructive pelvic floor surgery in patients presenting with obstructed defecation.

Successful imaging in such circumstances relies on a visual interplay between organs and compartments. Such a feat has previously been lacking where considerable interpretation was required by orthograde and retrograde scrolling of videoproctography often opacifying the bladder, vagina, and sometimes the peritoneal cavity. This approach was improved by the work of Lienemann and colleagues in Munich who originally proposed dynamic MR proctography (Lienemann et al. 1997; Lienemann et al. 2000) using a variety of fast non-echo planar sequence techniques for image acquisition. This method was originally introduced as a gradient-echo sequenced protocol with fully refocused transverse magnetization [true-FIS sequence] combining speed (high bandwidth and very short TR) with mixed T1/T2 contrast to provide very high in-plane and temporal resolution. These images have now been upgraded and standardized for faster acquisition which is less sequence-related and which provides very low signal-to-noise ratios (Gufler et al. 1999). Image acquisition is obtained with single axial slices as well as a stack of coronal images and the occasional use of clarifying oblique and double-oblique slice orientations in areas of interest combining gadopentate dimeglumine (Magnevist, Schering Berlin) bladder opacification (Sprenger et al. 2000; Lienemann and Fischer 2005). This has further been supplemented by open-architecture systems for upright assessment of patients during straining and for diagnoses which present at the end of straining; most notably, descending perineum syndrome and rectal prolapse (Schoenenberger et al. 1998; Maglinte and Bartram 2007).

The introduction of dynamic trans-perineal ultrasound (DTP-US) by Beer-Gabel and colleagues heralded a new era of simpler, cheaper, noninvasive imaging to assess pelvic floor interaction for patients presenting with defecation difficulty and painful evacuation (Beer-Gabel et al. 2002; Beer-Gabel et al. 2004; Beer-Gabel and Zbar 2002) and has independently been assessed for clinical use in such patients by Piloni (Piloni 2001) and Kleinübing (Kleinübing et al. 2000; Kleinübing and Pinho 2008). Although the actual technique is quite simple, there is a considerable learning curve. Retrograde and orthograde video facility is advisable (as used in defecography) with utilization of a standard 7.5–10 MHz curvilinear transducer applying the probe axially over the perineal body for landmark registration. The procedure may be supplemented with administration 1 h prior to the examination of 100 mL of oral Gastrografin (Schering, UK) diluted 1:1 with tap water. The static axial images resemble those obtained with a standard endoanal probe (Fig. 15.6) with registration of the hypoechoic IAS and the hyperechoic sling of the puborectalis muscle. The transducer is then turned through 90° to demonstrate the mid-sagittal plane. For this view, the rectum and the vagina may be instilled (but not overfilled) either with saline or acoustic contrast gel delineating firstly the hypoechoic IAS in superior and inferior linear profile. The puborectalis is identified *en face* and the rectum and contrast filled vagina are then located (Fig. 15.7). These images may be supplemented in real time by forcible straining and simulated evacuation (Fig. 15.7). Anteriorly, the brightly echogenic pubis is evident as is the hypoechoic urethrovesical juntion in a partially filled bladder. Broad

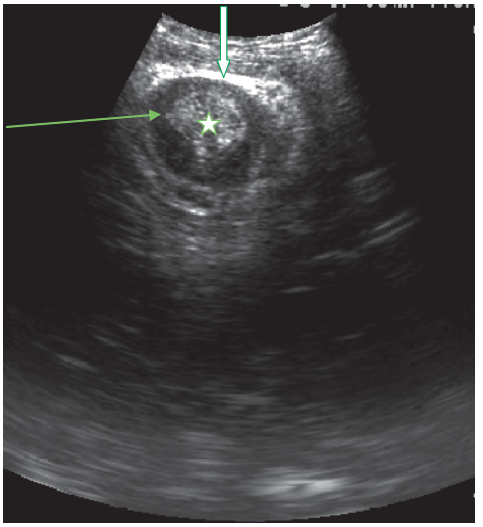

Figure 15.6. Axial transperineal ultrasound of the mid-anal canal showing images which resemble those obtained with endoanal sonography (*Arrow* internal anal sphincter, *block arrow* external anal sphincter). The anal mucosa is shown as a hyperechoic central region (*star*).

assessment of the depth and contents of the rectovaginal septum is readily demonstrable for determination of the presence of a perineocele (designated as a rectogenital septum exceeding 2 cm in maximal diameter; (Aigner et al. 2004; Eilber et al. 2006) or for peristaltic small bowel loops designating an enterocele (Beer-Gabel et al. 2008).

Comparative analysis of the anorectal angle (ARA) and descent during maximal straining in the left lateral position of the anorectal junction (ARJ) has shown high correlation with conventional proctography (Beer-Gabel et al. 2004; Zbar and Beer-Gabel 2006) with a slightly higher ARJ at rest during DTP-US and a greater degree of ARJ descent during defecography. The mean ARA during straining at proctography is higher than that measured with DTP-US (123.3° ± 4 vs. 116.4° ± 3.32, respectively). The limits of agreement between the two techniques at rest ranged from -65° to +26° and from -36° to +62° during straining where significant outliers yielded much higher proctographic than ultrasonographic

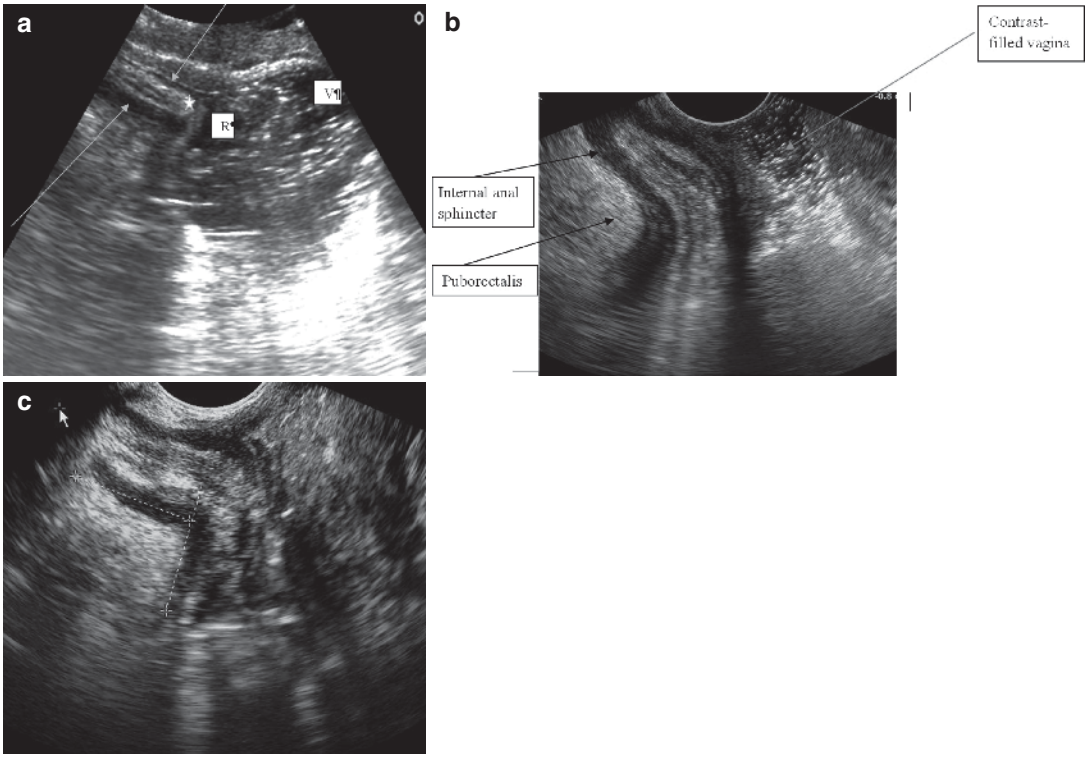

Figure 15.7. (**a**) Sagittal trans-perineal ultrasound with rectal and vaginal contrast. (R = rectum, V = vagina, star puborectalis *en face* and arrows = internal anal sphincter), (**b**) Sagittal trans-perineal ultrasound at rest, (**c**) Sagittal trans-perineal ultrasound during straining.

values. These effects are most likely a result of the differences in position during each examination (Dietz and Clarke 2001) with comparatively similar diagnoses being made with the two modalities and a greater diagnosis of enterocele with DTP-US in those patients presenting with a clinical rectocele. Given that currently DTP-US remains an essentially unvalidated technique against gold standards, its indications are somewhat controversial and are driven by both the experience and enthusiasm of the clinician. It provides a valid alternative in the absence of specialized MR imaging dedicated for functional GI use and, of course, avoids the irradiation required during proctography frequently in quite young patients (Goei and Kemerink 1990).

Its advantage is as a real-time rapid demonstration of interactive pelvic floor components without the need for complicated algorithms or irradiation which can be used in children with functional outlet problems. It defines enteroceles for which stapled trans-anal rectal resections are contraindicated (Corman et al. 2006). The technique has distinct pitfalls including the fact that it can be time consuming, a little messy, and is conducted in a relatively non-physiological position. The proximity of the operator's hand can create patient reticence during straining which may limit the diagnostic capacity; a phenomenon observed during patient scrutiny at proctography. It can be technically difficult to conduct in many men and in obese women because of prominent buttock fat.

Miscellaneous including Anal and Rectal Tumors

Endorectal and endoanal balloon sonography has proven of inestimable value in the staging of rectal and anal tumors (Low et al. 2008; Halefoglu et al. 2008; Giovannini et al. 2001; Martellucci et al. 2008). Here, there has been some disappointment in the uT1/uT2 distinction which might direct local excision as a definitive treatment (either endoanally or via TEMS) and there is a learning curve which is required in the uT2/uT3 separation where undercalling of T status provides risk to patients by denying them necessary preoperative therapy prior to a total mesorectal excision – TME (Kulig et al. 2006). Where available, although the data is somewhat uncontrolled and has been used on an intention to treat basis, preoperative thin-slice, high-resolution MR imaging has proven of benefit for decision making regarding preoperative short-course radiotherapy or neoadjuvant chemoradiation prior to surgery where it is anticipated that circumferential resection margins will compromise a TME specimen (Salerno et al. 2006; Taylor et al. 2008; Korkolis et al. 2007). Suffice to say that as up to one-third of perirectal lymph nodes are <5 mm in maximal diameter and up to one-quarter of involved nodes have micrometastases, the positive predictive value of endorectal ultrasound for metastatic lymph nodes will be less than its sensitivity for T status; an effect also evident in bulkier and circumferential tumors where metastatic nodal disease may lie beyond the focal distance of an endoluminal probe (Dworak 1991; Herrera-Ornelas et al. 1987; Smith et al. 2008).

As such, the utilization of 3-dimensional reconstructed endorectal ultrasound does not appear to enhance preoperative staging although there are some data suggesting an improved sensitivity for nodal status detection in anal cancer (Christensen et al. 2004; Giovannini et al. 2001; Berton et al. 2008). In any event, layer destruction following radiotherapy is observed restricting the role of this modality in such patients (Huh et al. 2008). Endorectal ultrasound is of proven value in the separation of villous adenomas from u/pT1 invasive tumors (Fig. 15.8; (Worrell et al. 2004)) and in postoperative recurrence (Fig. 15.9) where MR imaging and CT may be relatively misleading in their ability to distinguish recurrence

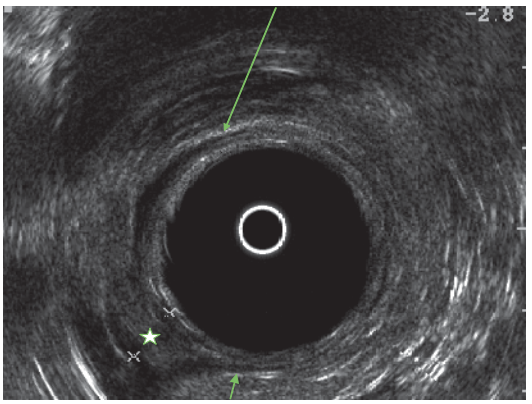

Figure 15.8. Endorectal ultrasound of a villous lesion (*star*) showing infiltration of the submucosa (*arrow*) confirming an early rectal carcinoma.

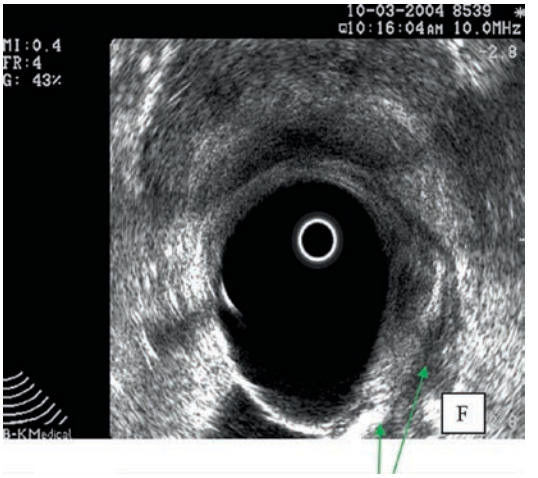

Figure 15.9. Endorectal ultrasonographic recurrent rectal cancer with finger-like projections (*arrows*) into extrarectal fat (hyperechoic area marked F).

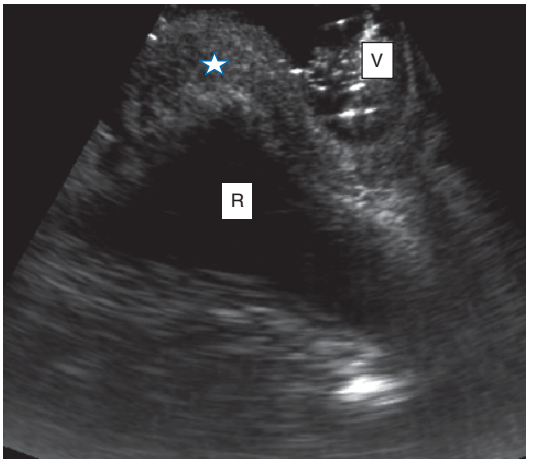

Figure 15.11. Sagittal transperineal ultrasound showing locoregional recurrence in the rectogenital septum (*star*). The vagina is filled with contrast (V) and the rectum is air-filled (R).

from a post-radiation effect. In this circumstance, PET scanning appears most useful with the clinician using ultrasound-guided pararectal and nodal biopsies where indicated (Hünerbein et al. 2001). Endorectal ultrasound may be of use in the diagnosis of presacral tumors (Wolpert et al. 2002) assisting in defining the upper limit of the tumor where low cases may be removed by a Kraske approach and higher lesions will require an abdominal or combined abdomino-trans-sacral (Localio) procedure (Fig. 15.10). An example is shown of a trans-perineal ultrasound which proved useful in showing a rectovaginal recurrence of anal cancer after definitive chemo-radiation (with its attendant MR image) and which permitted guided biopsy; the patient being successfully treated by posterior pelvic exenteration (Fig. 15.11).

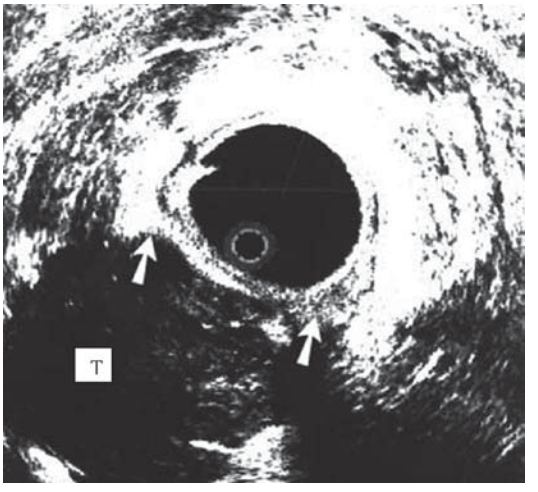

Figure 15.10. Endorectal ultrasound of a presacral tumor (*Arrows*; T).

Of late, Beer-Gabel and colleagues have begun staging of some rectal cancers by an end-fire frontal trans-rectal ultrasound probe in cases which have proven unsuitable for deployment of a traditional endorectal assembly. Here, the probe can lie at the distal end of the tumor and the field of examination lies in the axis of the tumor and not radially disposed. Its staging accuracy in early and soft villous lesions which may be distorted by an endoluminal probe remains to be determined; however, an initial report by Beer-Gabel et al. shows an 89% accuracy for T staging compared with 69% for conventional radial endorectal sonography ($P = 0.004$) with similar accuracy for lymph node staging (Beer-Gabel et al. 2010). This technique allows the staging of rectal cancer even in the case of rectal stenosis and/or proximal tumors which in both cases would not have been accessible to the radial probe. Other miscellaneous pelvic and pararectal masses are able to be diagnosed using a combination of endoanal and trans-perineal sonography. Figure 15.12 shows the endoanal sonographic and endoscopic appearance of a rectal duplication presenting with rectal bleeding and evacuatory

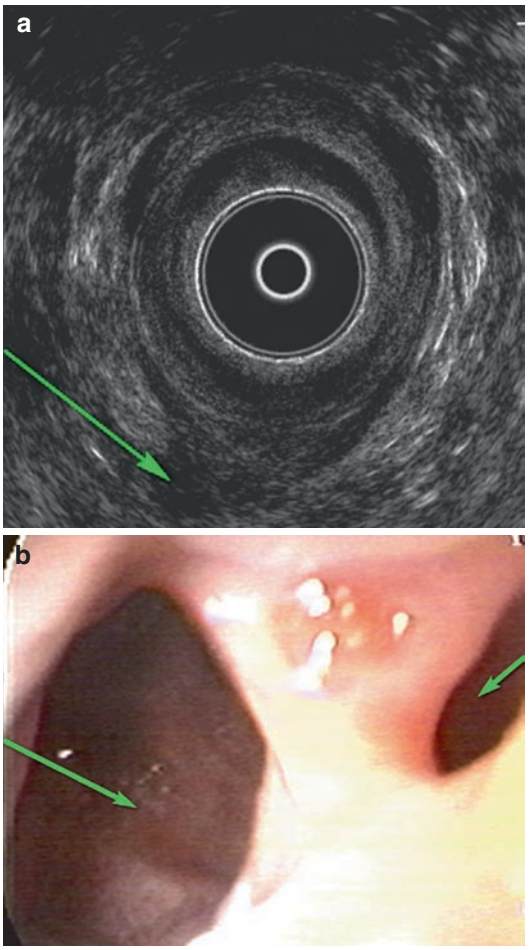

Figure 15.12. (**a**) Endorectal ultrasound of a rectal duplication (*arrow*), (**b**) endoscopic appearance of the duplication (*arrow*) with conventional lumen (*block arrow*).

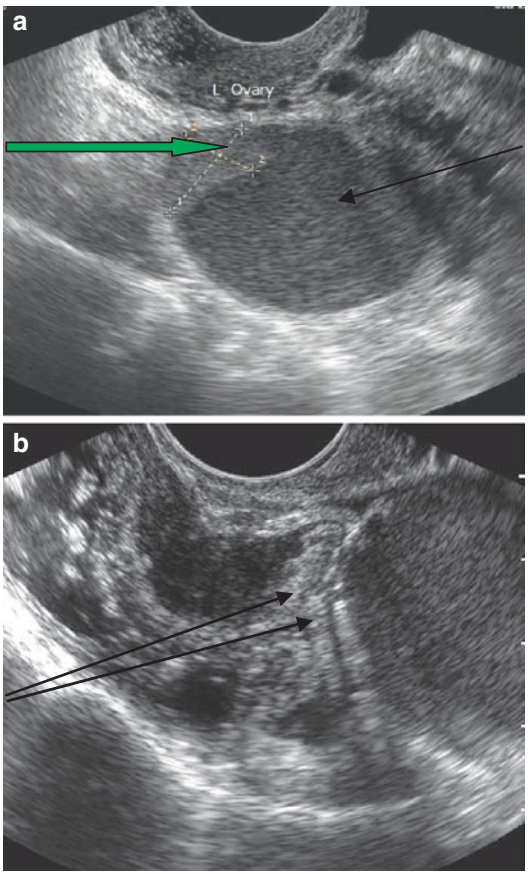

Figure 15.13. (**a**) Transperineal ultrasound showing an endometriotic ovarian cyst (*arrow*) showing a solid component (*block arrow*) thought to be secondary to bleeding, (**b**) trans-perineal ultrasound showing rectal wall infiltration by endo*metri*osis (*arrow*).

difficulty (treated by stapled spur division and mucosectomy) and Fig. 15.13 shows the transperineal ultrasonographic appearance of a complex ovarian endometriotic cyst with rectal wall infiltration in a patient presenting with chronic pelvic pain and obstructed defecation during menstruation.

In summary, the coloproctologist is best placed to conduct ultrasonography and its variants in patients presenting with complex and recurrent perirectal sepsis, in the assessment of tumor depth in rectal and some anal cancers, and in rare presacral tumors and rectal duplications. In the first situation, imaging is selective and should provide a reconstructed 3-dimensional concept which answers the basic questions regarding the site of the internal opening of a fistula and its relationship to the main sphincter complex in a way which can assist the surgical approach for fistula eradication and continence preservation. However, this 3-dimensional view is advanced (whether by coronally reconstructed and endosonographic images, by MR imaging, or by a transducer shift in static transperineal sonography), will depend on the circumstances of the case, the experience of the surgeon interpreting the images, and the expertise and availability of individual imaging modalities. Ancillary information with imaging will be obtained of the destructive effects of

perianal sepsis and prior surgery which will influence secondary reconstructive surgery in a tertiary coloproctological practice. Transperineal ultrasound will assist in two circumstances where there are limitations with any form of endoanal technology; notably where extrasphincteric fistulae will lie laterally beyond the focal distance of endoanal probes and where there is substantial, either primary or derivative, supralevator sepsis. The limitations in endoanal imaging for rectal and anal cancers, particularly where there has been prior adjuvant radiation or neoadjuvant therapy are mentioned; however, primarily endorectal ultrasound will assist in the T2/T3 definition of cases likely to benefit from preoperative short-course irradiation.

Clinician-led ultrasonography comes into its own in the complex group of patients presenting with functional anorectal disorders. In incontinence, trans-perineal sonography can be utilized intra- and immediately postoperatively to assess sphincter overlap without the concerns of endoanal repair distortion as well as a guide in the deployment of bioaugmentable material without the fear of implant migration. For those patients who present with the symptom complex of evacuatory difficulty, DTP-US shows an interactive interpretative interplay between the pelvic and

Table 15.1. Advantages and disadvantages of the different imaging modalities in perirectal sepsis

	Advantages	Disadvantages
Endoanal ultrasound	Delineation of internal opening	Poor definition of extrasphincteric fistulae
		Overcalling of intersphincteric abscesses
3-D Endoanal Ultrasound	Better coronal assessment	Limited in assessment of suprasphinhcteric disease
		Difficulty in deployment in some
Transperineal Ultrasound	Defines lateral extensions	Limited in gas-containing abscesses
	Coronal view advantage	Limited value of hydrogen peroxide instillation
	Assists in anovaginal/anovestibular and anoscrotal fistulae	
	May assist in supralevator disease	
MRI	Defines supralevator and pelvirectal disease	Selective contraindications
	Gadolinium enhancement in recurrence	Poorly defines subepithelial space
	May define proximal colonic Crohn's and diverticular disease	

Table 15.2. Advantages and disadvantages of the different imaging modalities in fecal incontinence

	Advantages	Disadvantages
Endoanal ultrasound	Accurately defines EAS and IAS defects	Poor definition of atrophy
		Relative contraindication in bioaugmentable deployment
3-D Endoanal ultrasound	Defines coronal extent of defect and predicts outcome after sphincteroplasty	
Trans-perineal	Simple	Limited ability to assess EAS and make measurements
	Can be used intraoperatively	
	Can assist in bioaugmentable deployment	
Pelvic phased-array MRI	Moderate accuracy in EAS defects	Limited accuracy in IAS defects
Endoanal MRI	High accuracy compared with endoanal ultrasound	
	Defines radiologic standard for EAS atrophy correlating with outcome	

perineal soft-tissue compartments during provocative maneuvers, although this modality is still somewhat in its infancy and requires a substantial learning curve. It is only though real-time clinical interpretation in this context that surgical decision making for perineal reconstructive surgery or an abdominal or abdominoperineal approach can be defined. This group of patients, (particularly those presenting with complex functional difficulties after prior pelvic or perineal surgery or following the construction of neorectal reservoirs), require collaborative multidisciplinary interpretation of ultrasonographic and complementary dynamic MR imaging to define more clearly the indications for surgery and the likely most beneficial surgical approach for relief of predominant symptoms. Tables 15.1–15.4 show the relative advantages and disadvantages of the

Table 15.3. Advantages and disadvantages of the different imaging modalities in evacuatory dysfunction

	Advantages	Disadvantages
Endoanal ultrasound	Defines sphincter defects in patients presenting with obstructed defecation and incontinence	Limited concept of perineal and pelvic floor soft-tissue interplay
Dynamic Trans-perineal	Defines compartmental interaction	Substantial learning curve
	Accurately reflects defecography and proctographic measurements	Time consuming
		Somewhat messy
Dynamic MR	Excellent pelvic floor definition	Expensive
Proctography		Limited availability
		Limited in maximal straining requiring open architecture MRI
Defecography	Shows complex interaction of small bowel, rectum bladder, and vagina	Invasive for extended techniques
	Excellent definition of enteroceles	High radiation dose
	Defines rectocele emptying	Patient embarrassment

Table 15.4. Advantages and disadvantages of the different imaging modalities in rectal and anal tumors

	Advantages	Disadvantages
Endoanal ultrasound	Relatively accurate T status	Limited N status
		Limitations after radiotherapy
3-D Endoanal Ultrasound	More accurate N status in anal cancer	
	Defines coronal sphincter involvement to assist in decision for colo-anal anastomosis	
CT	Widely available	
	Accurate in definition of mesorectal nodes	
	Enhanced presacral definition with coronal reconstruction	
MRI	Enhanced T status	Limited availability
	Assessment of circumferential radial resection margin status	Limited definition of recurrence after radiotherapy
	Defines role of preoperative therapies prior to total mesorectal excision	
	Assists in decision for exenteration	
	Better delineation of hepatic, pulmonary, and intraperitoneal disease	

different available imaging modalities for a range of important proctological problems.

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16

Changing Paradigms in the Treatment of Sigmoid Diverticulitis

Patricia L. Roberts

Introduction

Diverticulitis is a common condition in industrialized countries. The past decade has seen a paradigm shift in the management and treatment of sigmoid diverticulitis based on critical review of the literature and refinement of surgical techniques. The clinical manifestations of disease are defined by the first attack. Patients who present with uncomplicated disease remain with uncomplicated disease. Free perforation is rare and virtually always occurs on the first attack. Increasing numbers of patients may be treated safely with primary resection and anastomosis. Laparoscopic washout without resection may have an increasing role in management. This chapter examines the changing recommendations for treatment of this common problem.

Diverticular disease is a common condition in industrialized societies. An increasing prevalence of diverticular disease has been noted with increased processing of food and with a diet relatively low in fiber. The pervasive assumption that diverticulitis is caused by ingestion of nuts, corn, seeds, and popcorn has been challenged by recent studies which show no correlation with these foods and the development of diverticulitis (Strate et al. 2008). While the incidence of diverticulosis is low under the age of 30, the incidence increases with age and diverticula affect over 75% of patients over the age of 80. The true risk of developing diverticulitis given the presence of diverticulosis is unknown but is generally believed to range from 10%–25%. The spectrum of disease ranges from mild symptoms of left-sided discomfort to free perforation with fecal peritonitis. This chapter deals with the changing paradigms in the treatment of complicated and uncomplicated diverticulitis based on current guidelines and reviews of the literature.

Background/Historical Perspective

Diverticula were first reported by Littre in the 1700s and were initially considered pathologic curiosities which were unlikely to cause disease (Finney 1928). Diverticulitis was considered so rare that it was not even mentioned in British surgical textbooks in the early part of the twentieth century. In 1907, Dr. William Mayo reported five cases of diverticulitis to the American Surgical Association and demonstrated a modern understanding of the disease stating that the surgical treatment of diverticulitis of the colon depended on the condition present and that if significant obstruction or infection was present a "temporary artificial anus should be made." He recommended that it was better to perform a "primary resection of the affected part of the bowel, before abscess and fistula supervened" (Mayo et al. 1907).

The incidence of diverticulitis has increased markedly since Mayo's report and there are currently at least 200,000 admissions for diverticulitis annually in the USA (Salem et al. 2004). Data

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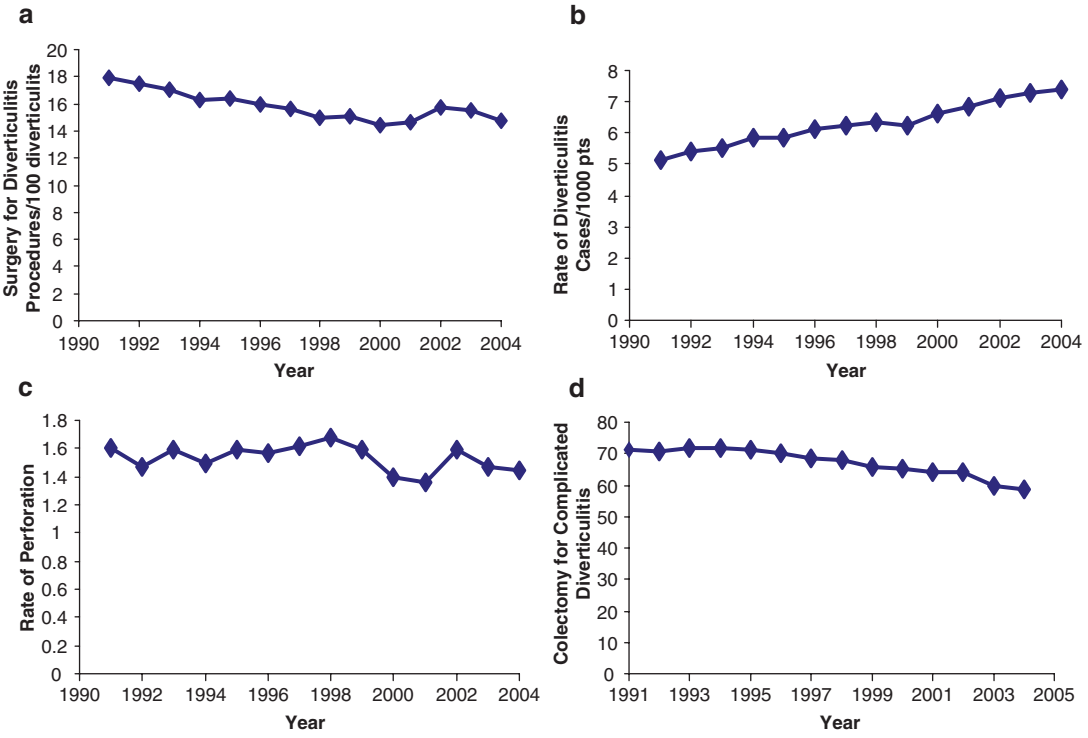

Figure 16.1. (**a**–**d**) Data from the National Inpatient Sample show that the incidence of diverticulitis is increasing while the incidence of free perforation remains the same, the number of colectomies performed for complicated disease has decreased and the number of colectomies per 100 patients diagnosed has decreased slightly (Ricciardi et al. 2009).

from the National Inpatient Sample, a 20% representative sample of hospitals from 37 states, suggest that the incidence of cases of diverticulitis has continued to increase over the past decade while the incidence of perforation has remained the same (Fig. 16.1a–d) (Ricciardi et al. 2009).

Diagnosis and Initial Treatment of Uncomplicated Diverticulitis

Until recently, the recommendations for surgery for sigmoid diverticulitis have been fairly consistent. Elective resection was recommended after two well-established attacks of diverticulitis, generally treated on an inpatient basis, and resection was recommended after the first attack of complicated diverticulitis (Wong et al. 2000). Furthermore, surgery was strongly recommended after a single attack of diverticulitis in young patients, because the course of the disease was believed to be more virulent than in older patients. These guidelines were endorsed and published by a number of societies including the American Society of Colon and Rectal Surgeons, the Society for Surgery of the Alimentary Tract, the European Association for Endoscopic Surgery, and the American College of Gastroenterology (Kohler 1999; SSAT 1999; Stollman et al. 1999; Wong et al. 2000).

Recent data have questioned the conventional wisdom of these recommendations. A decision analysis suggested that surgery recommended after the fourth attack instead of the second attack of diverticulitis in patients over the age of 50 was associated with 0.5% few deaths and 0.7% fewer stomas (Salem et al. 2004). An additional decision analysis suggested that surgery be recommended after the third attack of diverticulitis (Janes et al. 2005). The latter review suggested that there were no data to support resection after the second attack of diverticulitis

(Janes et al. 2005) and a large review suggested that it was time to "rethink the rules" for surgery for complicated diverticulitis (Chapman et al. 2005).

In view of these conflicting findings, what is the optimal approach to patients who recover from an attack of uncomplicated diverticulitis? First of all, patients should be thoroughly assessed to ensure a diagnosis of diverticulitis. On occasion, patients have had the diagnosis of diverticulitis made and have been treated with courses of antibiotics without any imaging studies or objective findings of fever or leukocytosis during an episode of pain. The hallmarks of diverticulitis are left-sided abdominal pain, fever, and leukocytosis; absence of these findings should make the diagnosis suspect. Urinary tract symptoms may be present from the adjacent diverticular phlegmon or from a colovesical fistula. The widespread use of CT scanning for evaluation of acute abdominal pain has to an extent supplanted the use of physical examination and other imaging studies. The majority of patients presenting to an emergency room with abdominal pain will have an abdominal CT scan. Advantages of CT scanning include the ability to make an accurate diagnosis, the ability to potentially stage the severity of disease, early recognition of complicated diverticulitis, and the therapeutic ability of CT scan to drain an abscess. Disadvantages of CT scanning include radiation exposure and the cost of the scans.

While many clinicians are quick to make a diagnosis of diverticulitis in any patients with left-sided abdominal pain, fever, and leukocytosis, there may be considerable overlap in the signs and symptoms of patients with diverticulitis, inflammatory bowel disease, irritable bowel disease, and colorectal cancer. CT findings of acute diverticulitis include localized thickening of the colon wall, inflammation of the pericolic fat, abscess, extraluminal air (microperforation), and extraluminal contrast (Fig. 16.2). (Ambrosetti 1997) Colovesical fistulas may also be noted by air of contrast in the bladder. A recent report has suggested different perfusion characteristics of the colon in patients with diverticular disease compared to colon cancer (Goh et al. 2007). CT has also been used to classify patients into "mild" or "severe diverticulitis" with mild disease including localized thickening of the colonic wall and inflammation of the fat and severe being defined as any "mild findings" in addition to the present or abscess, extraluminal contrast or extraluminal air. Compared to patients with mild findings on CT scan, patients with severe diverticulitis are more likely to develop recurrent diverticulitis (39% vs. 14%) (Ambrosetti et al. 2002).

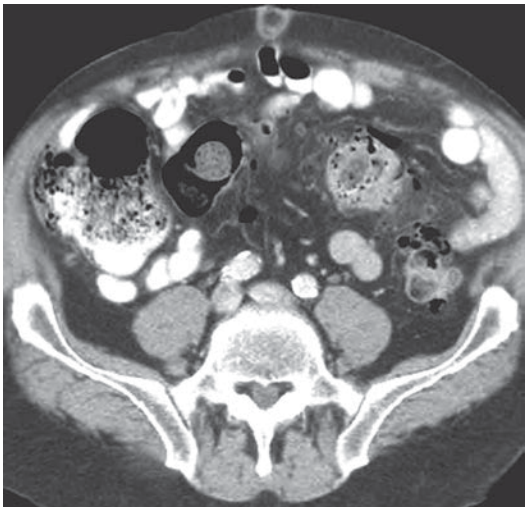

Figure 16.2. CT demonstrates acute diverticulitis with inflammation and fat stranding in addition to microperforation of the colon. Such patients are more likely to have recurrent diverticulitis.

Patients who are reliable, not toxic appearing and not immunosuppressed may be treated on an outpatient basis with oral antibiotics. Patients with signs of toxicity, high fevers, other co-morbidities, and the inability to tolerate oral fluids require hospitalization. A recent randomized controlled trial of oral vs. intravenous antibiotics for clinically diagnosed acute uncomplicated diverticulitis showed that oral antibiotics were not inferior to intravenous antibiotics in achieving clinical resolution. Moreover, a decrease in the C reactive protein was felt to be the best serological predictor of resolution in the groups (Ridgway et al. 2009).

Subsequent imaging of the colon, by either a combination of flexible sigmoidoscopy and air contrast barium enema or by colonoscopy excludes mucosal disease such as unsuspected colitis or colon cancer. Imaging studies of the colon are ideally performed after the inflammatory component of the disease has resolved (generally in 4–6 weeks after discharge from the hospital). While either imaging modality can be performed, the age of the patient and

previous screening examinations should be taken into consideration in recommending a particular modality. In a patient over 50 years who has not had any previous screening examinations, colonoscopy is considered. Barium enema has the advantage of providing a "road map of the colon" particularly if surgery is planned and may be helpful in diagnosing an unsuspected sinus or localized perforation. The density and distribution of diverticula may be easily noted.

The indications for elective sigmoid resection for uncomplicated diverticulitis are determined by the severity of the disease, the risk of subsequent attacks of diverticulitis, and complications of the disease in addition to the age and other co-morbidities of the patient.

Risk of Subsequent Attacks of Diverticulitis After Recovery from Uncomplicated Diverticulitis

Although diverticulosis develops in virtually all of the population in Western countries, only 10%–30% of patients are believed to develop symptoms of diverticular disease. Given the presence of diverticulosis, the risk of developing diverticulitis does not seem to be related to the size, number, or extent of diverticula in the colon. This often quoted frequency of disease is not population-based and is quoted from old data sources. Thus, the true risk of developing diverticulitis in large populations with diverticulosis is not known. After recovery from an attack of diverticulitis, approximately 30% of patients may develop another attack of diverticulitis, generally within few years. Once again, this frequently quoted figure is based on old data sources and is not population-based. A review of 521 patients with 99.6% follow-up, showed that of the 317 patients treated medically, only 78 (24.6%), had a subsequent attack, 12 (3.8%) had a third attack, and only 5 (1.6%) had a fourth attack (Parks 1969). In this series of patients, if surgery were performed after a second attack of diverticulitis, as has been conventionally recommended, 17 readmissions would have been prevented at a cost of 61 presumed unnecessary operations. Another cohort of 366 patients admitted over a 10-year period revealed a recurrence rate of 22% (Makela et al. 1998). In this group of patients, surgery performed after the second attack would have prevented 29 recurrent attacks by performing 57 operations of which 28 would not have been necessary. An additional study of 2,551 patients who were initially treated successfully medically for diverticulitis (with a mean follow-up of 9 years) resulted in only 13% of patients with recurrent attacks and only 7% of patients who required colectomy (Broderick-Villa et al. 2005). A conservative policy for managing acute sigmoid diverticulitis was found to be safe in the short and the long term in a prospectively followed cohort of 232 patients from 1990–2004 (Shaikh et al. 2007). Thus, several studies have suggested that the majority of patients who recover from an episode of diverticulitis have no further attacks. The risk of recurrent diverticulitis appears to be lower than the frequently quoted rate of 30% suggesting that a second attack of diverticulitis does not mandate sigmoid resection. The most recent practice parameters of the American Society of Colon and Rectal Surgeons suggest that the number of attacks of uncomplicated diverticulitis is "not necessarily the overriding factor in defining the appropriateness of surgery" (Rafferty et al. 2006).

Risk of Developing Complications After Recovery from an Attack of Uncomplicated Diverticulitis

The clinical course of diverticulitis appears to be determined by the first attack. Thus, patients who present with uncomplicated diverticulitis do not progress to have subsequent attacks of complicated diverticulitis (Chautems et al. 2002; Hagland 1979). Chautems and colleagues found that 25% of patients who recovered from uncomplicated diverticulitis had recurrent diverticulitis; none of these patients had subsequent attacks of complicated diverticulitis (Chautems 2002). A large population-based study of administrative data from 1987–2001 of 25,058 patients with acute diverticulitis suggested that after an initial episode of nonsurgical treatment of diverticulitis, only 5.5% of patients who subsequently required surgery needed emergency surgery with fecal diversion. The risk of requiring emergency colectomy and colostomy in young patients was slightly higher (7%) (Anaya and Flum 2005). Conversely, the first attack of

diverticulitis seemed to be the most severe attack; patients were more likely to present with perforation with no prior history of diverticulitis (Hart et al. 2000; Nylamo 1990; Lorimer 1997; Somaseker et al. 2002). Thus, the performance of elective colon resection after recovery from uncomplicated acute diverticulitis does not decrease the likelihood of emergency surgery with the need for fecal diversion or overall mortality.

Severity of Disease

The severity of disease is determined at initial presentation. Patients who present with uncomplicated diverticulitis generally do not progress to development of complicated diverticulitis. In a cohort of patients initially treated medically for uncomplicated diverticulitis, 25% recurred; none had complicated disease (Chautems 2002; Haglund et al. 1979). Patients who present with free perforation or require emergency surgery generally do so on the first attack of diverticulitis. Hart noted that 78% of patients with perforated diverticulitis had no prior attacks of diverticulitis (Hart 2000). Somesaker reported 104 patients who required emergency surgery and only three had a prior history of diverticulitis (Somesaker 2002).

The widespread use of CT scanning as the initial imaging modality in patients with suspected diverticulitis has allowed (in addition to history and physical examination) for assessment and grading of the severity of disease. CT findings in diverticulitis include the presence of diverticula, pericolic inflammation, colonic wall thickening, and the presence of abscesses or fistula. The findings which correlate with severe disease include the presence of abscess, extraluminal air, and extraluminal contrast (Poletti et al. 2004) while findings associated with mild disease include localized sigmoid wall thickening and inflammation of the pericolic fat. Severe findings on CT scan predict poor outcome and the likelihood of recurrent disease and the need for surgical intervention (Chautems 2002). In a study of 312 patients who underwent CT scanning for evaluation of acute left-colonic diverticulitis, the finding of abscess and pockets of extraintestinal gas 5 mm in diameter or larger correlated with unfavorable outcome of nonoperative treatment (Poletti et al. 2004).

Young Patients and Diverticulitis

From a historical standpoint, diverticulitis in younger patients (under the age of 50) has been described as more virulent, more likely to be associated with complications and more likely to require resection (Schauer et al. 1992; Ouriel and Schwartz 1983). Young patients have been variably defined as under 50 years in some series, and under 45 or 40 years in other series. Despite the definition of what age defines a "young patient," all series of younger patients with diverticulitis have a striking male predominance in contrast to older series which have a slight female predominance (Acosta et al. 1992). Earlier series of young patients in the pre-CT scan era have had a high number of patients undergoing resection, presumably since the patients were frequently diagnosed preoperatively with appendicitis. These patients then underwent laparotomy and subsequent resection when diverticulitis and not appendicitis was encountered. Currently, there is no consensus on whether younger patients are at greater risk for complications or recurrent diverticulitis. Because of a longer life span, younger patients are at greater risk for a higher cumulative recurrence. In one series which stratified patients on the basis of severity of disease noted on CT scan, patients under the age of 50 were more likely to have severe disease than older patients (Ambrosett 2005). Another series suggested that younger patients with diverticulitis had an identical clinical course compared to older patients (Vignati et al. 1995). Furthermore, some series have suggested that young patients comprise a higher percentage of patients with diverticulitis than previously noted. Young patients with diverticulitis have comprised 18%–34% of patients in more recent series (Biondo 2002; Broderick-Villa 2005; Guzzo and Hyman 2004; Schweitzer et al. 2002), compared with 1.3%–8.2% (Eusebio 1973; Parks 1969) of patients in older series.

Complicated Diverticulitis

Complicated diverticulitis generally refers to diverticulitis associated with perforation, fistula, or obstruction. In an effort to be able to compare different groups of patients with perforation/

abscess, the Hinchey classification has been used and is divided into categories of stage 1 through IV (Hinchey et al. 1978). Stage I is diverticulitis associated with pericolic abscess, stage II is a more distant abscess such as a pelvic or retroperitoneal abscess, stage III is purulent peritonitis, and stage IV is fecal peritonitis. Modifications of the Hinchey classification have been made by (Warsavary et al. 1999) and utilized by others (Kaiser et al. 2005) but the original Hinchey classifications remain the most common classification system used. The original and modified Hinchey classifications are outlined in Table 16.1. Other scoring systems such as the Mannheim peritonitis index and the colorectal (Cr)-POSSUM (the colorectal physiologic and operative severity score for the enumeration of mortality and morbidity) may be better tools to assess operative risk in the future (Senagore et al. 2004; Billing et al. 1994).

Diverticular Abscess

Diverticular abscess occurs in approximately 15% of patients with acute diverticulitis. Abscesses include pericolic abscesses, pelvic or retroperitoneal abscesses. The findings of diverticular abscess may be more common in the past decade with the increased use of CT scanning; prior to this time, patients were often treated empirically with antibiotics and small abscesses may not have been detected. Furthermore, early CT scanning may also lead to increased detection of small fluid collections associated with diverticulitis which may not necessarily be abscesses.

Table 16.1. Although the Hinchey classification is the most commonly used system to stage perforated diverticulitis, modifications of the initial classification system have been made

Hinchey Classification (Hinchey 1978)	
Stage 1	Pericolic or mesenteric abscess
Stage II	Pelvic or retroperitoneal abscess
Stage III	Purulent peritonitis
Stage IV	Feculent peritonitis
Modified Hinchey Classification (Wasvary 1999)	
Stage 0	Mild clinical diverticulitis
Stage Ia	Confined pericolic inflammation-phlegmon
Stage Ib	Confined pericolic abscess (within sigmoid mesocolon)
Stage II	Pelvic, distant intra-abdominal or intra-peritoneal abscess
Stage III	Generalized purulent peritonitis
Stage IV	Fecal peritonitis
Fistula	Colovesical/vaginal/enteric/colocutaneous
Obstruction	Large and or small bowel obstruction

In patients with diverticulitis who are found to have a pericolic or pelvic abscess (i.e., Hinchey stage I or II disease), the goal is to treat the inflammatory process and ideally, to operate on an elective basis when the risk of infectious complications is less therefore optimizing the likelihood of performing a single-stage procedure and primary anastomosis and not a two-stage procedure with Hartmann resection. The management of diverticular abscess changed in 1986 with the report of Saini et al. (1986) who reported percutaneous drainage of diverticular abscess followed by single-stage resection in seven of eight patients.

The debate centers around which patients can be treated with antibiotics alone and which patients require percutaneous drainage and which patients require emergency surgery. Small abscesses (generally less than 2–3 cm) may resolve with antibiotics alone. Larger abscesses or abscesses in patient who remain with signs of sepsis require intervention with either percutaneous drainage or laparotomy depending on their clinical condition. While larger abscesses are more likely to require surgical intervention (Siewert et al. 2006), one series suggested that the size of an abscess did not determine the outcome and patients who were managed medically had an identical outcome as those who underwent drainage (Macias et al. 2004). The findings of an abscess in association with sigmoid diverticulitis was previously defined as complicated diverticulitis; it is debatable as to whether a small abscess which resolves with antibiotics is clinically significant and warrants a recommendation for surgical intervention. Brandt and colleagues evaluated 66 patients with diverticular abscess who underwent percutaneous drainage vs. antibiotics alone. The groups were note randomized and patients underwent treatment with antibiotics alone if the abscess could not be percutaneously drained. Antibiotics alone had a success rate of 81% (Brandt et al. 2006).

The location of an abscess may predict the need for resection. In a series of 76 patients with either mesocolic or pelvic abscess, 515 of patients with pericolic abscess required resection while 71% of patients with pelvic abscess required resection (Ambrosetti et al. 2005). Thus, a small pericolic abscess which resolves quickly with antibiotics and bowel rest does not necessarily mandate resection. However, patients with the finding of an abscess do have more severe disease and are more likely to have treatment failure and recurrence (Kaiser 2005).

After successful percutaneous drainage of a diverticular abscess, there is no established time frame to then proceed with definitive surgery. While percutaneous drainage is generally not considered definitive treatment and sigmoid resection is subsequently recommended, there are reports of patients who have not had subsequent attacks of diverticulitis. Broderick-Villa and associates followed 2,366 patients with diverticulitis; 13% of patients had recurrent diverticulitis and there was no difference in a subset of 35 patients treated with percutaneous drainage (Broderick-Villa 2005). Macias followed 28 patients who presented with abscess on CT scan and of those patients who underwent percutaneous drainage, 70% never had a recurrence (Macias et al. 2004).

Perforated Diverticulitis

Approximately 1% of patients with diverticulitis develop free perforation which may include purulent or fecal peritonitis. These categories are defined as Hinchey stage III or IV. The mainstay of treatment for perforated diverticulitis over the past several decades has been the Hartmann procedure which resects the disease and eliminates the septic focus. A disadvantage to the procedure is the requirement for a second major surgical procedure to reverse the colostomy and the attendant morbidity of the procedure. Data from large administrative databases suggest that at least one-third of patients may never undergo reversal (Maggard et al. 2004) and up to 70% of patients over 77 years may not undergo reversal (Salem et al. 2005).

There has been renewed interest in performing resection and primary anastomosis in selected patients with Hinchey III and IV diverticulitis. A number of systematic reviews and meta-analyses have suggested that primary anastomosis is superior to Hartmann resection for patients with perforated diverticular disease; however there is considerable selection bias (Abbas 2007; Salem and Flum 2004). The Hartmann resection still has an established role in the treatment of the septic patient with perforated diverticulitis.

Based on a small series of successful laparoscopic lavage for treatment of patients with perforated diverticulitis and purulent peritonitis, a prospective multi-institutional study of 100 patients has recently been reported (Myers et al. 2008). Patients with perforated diverticulitis and generalized peritonitis underwent laparoscopic lavage as definitive treatment. The median age was 62.5 years with a follow-up of 36 months. Eight patients were converted to an open procedure and underwent resection. However, 92 patients were successfully treated with laparoscopic lavage with a 4% morbidity and a 3% mortality. Two patients later required intervention for a pelvic abscess and two patients presented with diverticulitis in the study period. These data certainly challenge our conventional dogma with respect to complicated diverticulitis suggesting that cohort of patients may be definitively treated without resection.

Diverticular Fistulas

Colovesical fistulas are the most common fistulas. Patients often present with prominent urinary symptoms including polymicrobial urinary tract infections, pneumaturia, and fecaluria. CT scanning reveals air and/or contrast in the bladder (Fig. 16.3). If performed, cystoscopy shows inflammation generally at the dome of the

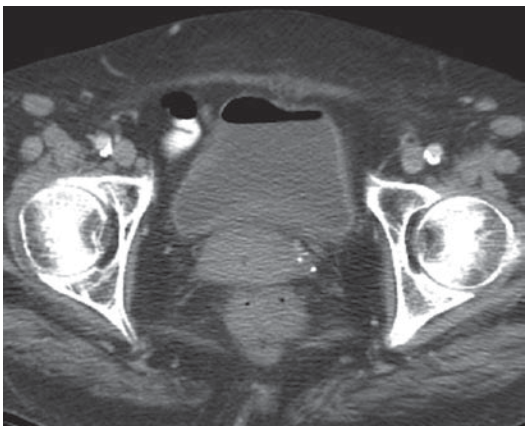

Figure 16.3. A colovesical fistula is noted with air in the bladder.

bladder and on occasion, vegetable material in the urine. The surgical principles include resecting the sigmoid colon and pinching the fistula off at the dome of the bladder. On occasion, even intraoperatively, the precise site of the fistula may be difficult to determine. Omentum is used to interpose between the anastomosis and the bladder. Ureteral stents are generally not needed.

Colovaginal fistulas occur almost exclusively in women who have undergone prior hysterectomy (Fig. 16.4). Signs and symptoms include vaginal discharge and passage of air. Often, women have seen a gynecologist initially. A single-stage sigmoid resection can generally be performed, pinching off the site of the fistula and interposing omentum.

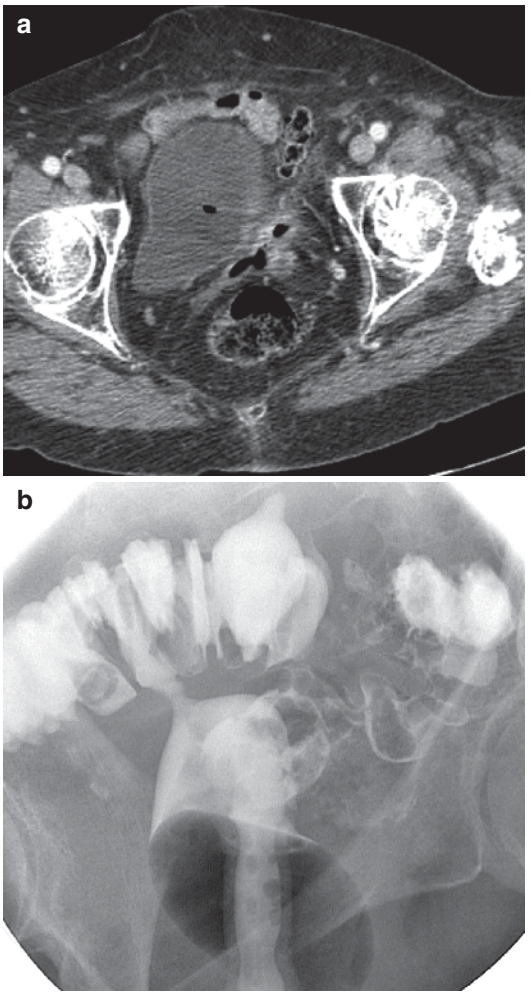

Figure 16.4. (**a**–**b**) A colovaginal fistula is noted on CT with air in the vaginal cuff, inflammation, and fat stranding (**a**). The fistula is also demonstrated on vaginogram (**b**).

Other fistulas include colocutaneous fistulas which rarely occur de novo and generally are seen in patients who have had prior colectomy or percutaneous drainage (Fazio et al. 1987). Risk factors for the development of a colocutaneous fistula include unsuspected Crohn's disease and anastomosis to the distal sigmoid and not the proximal rectum.

Obstruction

Following repeated attacks of diverticulitis, a sigmoid stricture or complete large bowel obstruction may develop. The differential diagnosis of patients presenting with large bowel obstruction includes not only diverticular disease, but also colon cancer or ischemic stricture.

Initial management consists of bowel rest, intravenous hydration, and nasogastric tube. If the obstruction does resolve, the options for treatment for complete obstruction include placement of a colonic stent or surgery with resection, on table lavage and primary anastomosis (Lee et al. 1997) with or without diversion or Hartmann resection. While the use of colonic stenting is well-established for patients with malignant obstruction, stenting seems to be less successful for obstruction from benign etiologies. In a series of 104 procedures from one center, eight patients had obstruction from benign etiology. After colonic stenting, many required reinterventions and only three patients achieved a benefit from stenting (Meisner et al. 2004). As Cochrane reviews have shown that mechanical bowel preparation is not necessary (Guenaga et al. 2005), there is probably little role for on-table lavage. The consideration to perform primary anastomosis with proximal fecal diversion or Hartmann resection is best determined by a variety of intraoperative factors including patient co-morbidities, intraoperative stability of the patient, and the edema of the proximally dilated bowel.

Immunocompromised Patients

Immunocompromised patients include patients on systemic steroids, patients with diabetes mellitus, renal failure, transplant patients who are immunosuppressed, cirrhosis, underlying

malignancy, and patients being treated with chemotherapy or radiation therapy. There has been a suggestion of an increased risk of diverticular disease in patients with polycystic kidney disease but the evidence is largely anecdotal.

Patients who are immunosuppressed are more likely to present with free perforation, presumably because of the inability to mount an inflammatory response and wall off the infection and are therefore more likely to require emergency surgery with resultant increased postoperative morbidity and mortality (Nagourney et al. 1985; Tyau et al. 1991; Lederman et al. 1998; Perkins et al. 1984).

Technical Aspects of Surgery for Diverticular Disease

The goals of surgery for diverticulitis are to resect the sigmoid colon, restore intestinal continuity, and minimize the change of anastomotic complications and recurrent diverticulitis. Two studies have examined the level of anastomosis and the risk of recurrent diverticulitis and have concluded that an anastomosis to the proximal rectum as opposed to the distal sigmoid is associated with a lower incidence of recurrent diverticulitis (Benn et al. 1986; Thaler et al. 2003). In addition, the risk of anastomotic complications, particularly the development of a colocutaneous fistula, appears to be increased with anastomosis to the distal sigmoid colon (Fazio1987). The proximal extent of resection is less well-defined, although it should be in soft pliable bowel in an area relatively free of diverticula. While diverticula should not be incorporated into the anastomosis itself, there is no need to resect proximal diverticula. Splenic flexure mobilization is not required but is occasionally necessary to achieve a tension-free anastomosis. Alternatively, the rectum can be mobilized to add length or to facilitate easy insertion of the EEA stapler.

Although the rectum is not primarily involved with diverticulitis, inflammation of the proximal rectum may be encountered from the diverticular phlegmon or from an associated pelvic abscess or diverticular perforation. In such cases, the surgical judgment may dictate primary anastomosis with proximal fecal diversion or anastomosis to the mid-rectum.

In cases of fistulas to the bladder or the vagina, the fistula may be simply "pinched off" and a resection of bladder and/or vagina is not necessary. In these cases, it may be helpful to identify the ureter proximally and trace its course down instead of attempting to identify it in the midst of the inflammation. Ureteral stents are not routinely used but may be helpful in those cases with hydronephrosis or extensive retroperitoneal inflammation. Ureteral stents do not decrease the rate of injury but improve the ability to identify the ureters intraoperatively and easily identify any potential injury (Leff et al. 1982). Once the fistula is pinched off, omentum can be used to interpose between the bladder and/or vagina and the colon.

Determination of 1 or 2 Stage Procedures

Although the goal of surgery for diverticular disease is to perform a single-stage resection with primary anastomosis, a substantial number of patients present emergently or require urgent intervention. The emergency surgical management of diverticular disease has undergone substantial evolution in the past several decades. In the early mid-twentieth century, a three-stage procedure was advocated. Initially, sepsis was controlled by drainage and a defunctioning, generally transverse loop, colostomy. The diseased segment was subsequently excised at the next stage and the final stage consisted or colostomy takedown was performed. With this approach, the mortality rate approached 25%, the septic focus was left in situ at the initial procedure, and a number of patients failed to progress through all three stages and had remained with a permanent colostomy (Krukowski and Matheson 1984). Hartmann's procedure subsequently became the procedure of choice as it appeared to reduce the operative mortality by half and had less morbidly and length of hospitalization than the three-stage procedure (Krukowksi and Matheson 1984). In the 1980s and 1990s, the Hartmann procedure was considered to be the standard of care for emergency surgical management of left colon emergencies (Goyal and Schein 2001). While there is certainly some selection bias in this series, the Hartmann's procedure which resects the diseased segment of bowel, eliminates the septic focus, and allows for restoration of bowel continuity on an elective basis remains one of the most common procedures in patients

undergoing emergency laparotomy for Hinchey stage III and IV perforated diverticulitis.

Generally, the patient is approached through a midline laparotomy both to confirm the diagnosis, and assess the degree of contamination and inflammation. Preoperative stoma site marking is helpful. The diseased bowel is mobilized and a proximal to distal approach is generally easiest and safest. The bowel can be transected proximally and dissection carried down to the sacral promontory. The ureter should be identified. All diseased and thickened bowel should be resected and the resection margin should ideally be the proximal rectum. Alternatively, distal sigmoid, if not inflamed, can be left in place for later resection at the intended Hartmann reversal. The proximal rectum is transected with a stapler or oversewn depending on individual preference. The stoma is brought out on the left side; splenic flexure mobilization may be necessary to achieve adequate length particularly if there is significant foreshortening of the mesentery from the diverticular phlegmon.

There are a number of drawbacks to the Hartmann procedure. Up to 35% of patients may never undergo colostomy reversal (Seetharam et al. 2003; Maggard et al. 2004). In a systematic review of 1,051 patients in 54 studies, the mortality associated with the Hartmann's procedure was 18.8%, the wound infection rate was 24.2%, and stoma complications occurred in 10.3% (Salem et al. 2005, 2004). In view of these considerations, there has been renewed interest in examining the role of primary resection and anastomosis without diversion for nonelective surgery for diverticular disease. A review noted a mortality of 9.6% vs. 15.1% for patients undergoing primary anastomosis vs. Hartmann's resection for perforated diverticulitis (Constantinidas et al. 2006). The patients were matched for ASA (American Society of Anesthesiologists) grade. However, the retrospective nature of the data and the degree of selection bias limits the ability to make clinically sound conclusions about which patients can safely undergo primary resection and anastomosis in the nonelective setting. In addition, use of Hinchey staging only to stratify severity of diverticulitis may omit several other important clinical parameters. The Cleveland Clinic Diverticular Disease Propensity Score has been used to identify factors based on patient presentation and intra-abdominal contamination which can provide a risk estimate for nonrestorative resection in patients undergoing surgery for diverticular disease. Factors predicting a Hartmann's resection vs. resection with primary anastomosis included BMI >30, Mannheim peritonitis index >10, and Hinchey stage >11 (Aydin et al. 2006).

Selection of patients who may safely undergo resection and primary anastomosis in the acute setting requires considerable judgment and must take into consideration patient-related and disease-related factors. Primary anastomosis is not advisable in patients with hemodynamic instability, diffuse fecal or purulent peritonitis, immunocompromised patients, or those with severe anemia or malnutrition and those with ischemia or edema of the bowel at the proposed site of anastomosis (Rothenberger and Gasrcia-Aquilar 1998).

Laparoscopic Surgery

While diverticular disease was initially felt to be a relative contraindication to laparoscopic surgery, the feasibility and advantages of laparoscopic sigmoid resection for diverticular disease have been well-established and include shorter hospital stay, quicker return of gastrointestinal function and better cosmetic results. The inflammatory reaction may make the dissection more difficult and ultimately lead to conversion to open laparotomy. The largest series of laparoscopic resections for diverticular disease includes 1,545 patients from 52 institutions over a 7-year period. The morbidity was 17%, the mortality was 0.4%, and the overall conversion rate was 6.1% (Schneidach et al. 2004).

Hand-assisted laparoscopic techniques use a device which allows the operating surgeon to insert a hand generally through a Pfannenstiel or a low midline incision. Thus, the surgeon is able to maintain pneumoperitoneum but also have the tactile sensation of open surgery. Preservation of tactile sensation is an advantage in patients with an inflammatory phlegmon associated with diverticular disease. Two series looking at patients with straight laparoscopic vs. hand-assisted laparoscopic sigmoid colectomy have shown a lower conversion rate with a hand-assisted approach (Lee et al. 2006; Chang et al. 2005).

While laparoscopic surgery was initially applied for uncomplicated diverticulitis, with increased expertise and progression through the learning curve, laparoscopic techniques may be used successfully in selected cases of patients

Table 16.2. Outcome of laparoscopic sigmoid resection for diverticulitis

Author	Year	Number of patients	Morbidity (%)	Mortality (%)	Conversion rate (%)
Bouillot et al.	2002	179	14.9	0	13.9
Schneidach et al.	2004	1545	17	0.4	6.1
Chang et al.	2005	85 (straight lap)	23	0	0
			31		13
		66 (hand-assisted)			
Hassan et al.	2007	125	25	0	26
Garrett et al.	2008	200	18.5	0	8

with complicated disease including abscess and fistula (Bartus et al. 2005; Zapletal et al. 2007).

Outcome of laparoscopic sigmoid resection is detailed in Table 16.2

Conclusion

The past decade has seen a reassessment of our guidelines for management and treatment of sigmoid diverticulitis. The prior routine recommendation for resection after two episodes of uncomplicated diverticulitis has been reexamined and the notion that further episodes will lead to complicated diverticulitis and high mortality has been refuted. The ability to stratify patients by CT findings combined with clinical assessment has led to a better understanding of the natural history of diverticulitis. Advances in surgical techniques including laparoscopy, diagnostic modalities, and medical therapy have changed management and outcome of diverticulitis.

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