Difficult Decisions in Surgery:
An Evidence-Based Approach

Neil Hyman
Konstantin Umanskiy *Editors*

Difficult Decisions in Colorectal Surgery

Springer

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Neil Hyman • Konstantin Umanskiy
Editors

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Editors
Neil Hyman
Medical Center
University of Chicago
Chicago, IL
USA

Konstantin Umanskiy
Medical Center
University of Chicago
Chicago, IL
USA

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I dedicate this book to my sons EJ and Seth, who have been a never-ending source of pride and joy from the moment they were born, and always the reason for everything.

Neil Hyman

I dedicate this book to my parents Yakov and Eugenia.

Konstantin Umanskiy

Preface

Colon and rectal surgery may very well be on the cusp of a golden age. Our specialty is thriving and our ACGME-approved training programs are extremely popular among the best and brightest general surgery residents. Breathtaking advances in minimally invasive surgery have occurred over the past quarter century including laparoscopic bowel resection, robotic surgery, endoscopic techniques such as endoscopic mucosal/submucosal resection, and transanal approaches such as transanal endoscopic microsurgery and transanal minimally invasive surgery. Innovation in these areas has made surgery safer for many of our patients, enabled sphincter preservation, and reduced the period of disability that many experience after treatment. However, in addition to the obvious benefits of these disruptive technologies, many long-standing questions persist and new ones have been raised.

1. What is the most appropriate use of this new and often more expensive technology? Does the evidence really support the notion that everything new is really better?
2. Considering the primacy of patient safety, how do we decide who should be credentialed to do what?
3. Should *any* surgeon be able to use any technique they wish, irrespective of cost, efficacy, and demonstrated competence?
4. Should these new technologies be evaluated first by a select group of high volume/experienced surgeons in a controlled and measured environment before more widespread adoption?
5. Do we really have adequate hypotheses and frameworks of understanding for the common diseases we treat?
6. Without them, can we really devise rational treatment approaches for these maladies?
7. As such, are almost all our treatments largely empiric and lacking in the basic scientific underpinnings that would move us beyond therapeutic "hail Mary's"?

The original version of this book was revised. An erratum to this chapter can be found at (DOI 10.1007/978-3-319-40223-9_51).

With this state of affairs, the practice of colon and rectal surgery has largely been driven by expert opinion and the practice of thought leaders – it is often the best we have. In this book, we have put together a select and highly respected group of leaders in our field and asked them both to critically review the evidence in a controversial area which they have typically contributed to and investigated during their career. We also asked them to supplement this with their clinical insights and personal experience. This is not a comprehensive textbook of colon and rectal surgery which attempts to review the basic anatomy and physiology of the vast spectrum of problems one may encounter in the small intestine, colon, rectum, and anus. Many excellent textbooks like this already exist. Rather, we have selected a broad array of difficult and often controversial problems that the surgeon who deals with colorectal disease often encounters. We asked our experts to imagine that they received a phone call from a busy surgeon in the surgeon's lounge who wanted to know how a particular challenging patient management issue should be handled. The goal was *not* to list every treatment that has ever been described or utilized.

1. What are my best options?
2. What is the best evidence for/against these options in the literature?
3. How do I decide?
4. What do you think and what do you do?

The reader will be able to see what the highest quality evidence available exists to guide our management decisions. However, it will be evident that there is always going to be considerable room for alternative opinions and approaches. A different acknowledged expert with considerable clinical experience and knowledge of the applicable evidence may see things differently and approach the same problem using a very different algorithm. Indeed, as much as we like to talk about evidence-based approaches, the "evidence" for much of what we do is often lacking and meager. We hope that the reader will find real help and a sense of perspective from this book. We particularly hope that we inspire our trainees and junior colleagues to uncover new paradigms of care, contribute high quality evidence to the literature, and advance the scientific underpinnings of our management decisions. Our patients deserve no less!

Chicago, IL, USA Neil Hyman

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We gratefully acknowledge the talents, expertise, and assistance of Ms. Abby Larson – without her, there would be no book. We also thank Dr. Mark Ferguson for his guidance and leadership and Kumar Athiappan of Springer for his diligence and responsiveness. We also thank our mentors, colleagues, fellows, residents, students, and patients who provide us the inspiration to learn and improve every day.

Contents

Part VIII Technique

Contributors

Maher A. Abbas Digestive Disease Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates

Nouf Y. Akeel, MD Department of Colon and Rectal Surgery, Digestive Disease Institute, The Cleveland Clinic Foundation, Cleveland, OH, USA

David J. Berler, MD Department of Surgery, Icahn School of Medicine at Mount Sinai, New York, USA

Richard T. Birkett, MD Lahey Hospital and Medical Center, Burlington, MA, USA

Joshua I.S. Bleier, MD, FACS, FASCRS Division of Colon and Rectal Surgery, Department of Surgery, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

Liliana Bordeianou, MD, MPH Colorectal Surgery Program, Department of Surgery, Massachusetts General Hospital (MGH), Boston, MA, USA

MGH Center for Pelvic Floor Disorders, Boston, MA, USA

W. Donald Buie, MD, MSc, FRCSC Department of Surgery, University of Calgary, Calgary, AB, Canada

Lisa Marie Cannon, MD Section of Colon and Rectal Surgery, Department of General Surgery, University of Chicago Medicine, Chicago, IL, USA

Peter A. Cataldo Colon and Rectal Surgery, University of Vermont College of Medicine, Burlington, VT, USA

C.E. Cauley Colorectal Surgery Program, Department of Surgery, Massachusetts General Hospital (MGH), Boston, MA, USA

Brad Champagne Lerner College of Medicine, Cleveland Clinic, Cleveland, OH, USA

Cleveland Clinic, Fairview Hospital, Cleveland, OH, USA

James Church, MBChB, FRACS Department of Colorectal Surgery, Sandford R. Weiss Center for Hereditary Colorectal Cancer, Cleveland Clinic Foundation, Cleveland, OH, USA

Tara M. Connelly, MB, BCh, PhD Department of Surgery, Waterford University Hospital, Waterford, Ireland

Meg Costedio Department of Colorectal Surgery, Digestive Disease Institute, Cleveland Clinic, Cleveland, OH, USA

Aneel Damle, MD, MBA Division of Colon and Rectal Surgery, University of Massachusetts Medical Center, Worcester, MA, USA

Conor P. Delaney, MD, MCh Digestive Disease Institute, Cleveland Clinic, Cleveland, OH, USA

Saleh Eftaiha, MD Division of Colon & Rectal Surgery, University of Illinois Chicago, Chicago, CL, USA

Jonathan Erlich University of Chicago Medicine, Section of Hospital Medicine, Chicago, IL, USA

David A. Etzioni, MD, MSHS Mayo Clinic College of Medicine, Rochester, MN, USA

James W. Fleshman Department of Surgery, Baylor University Medical Center, Dallas, TX, USA

Texas A&M Healthsciences, Dallas, TX, USA

Phillip Fleshner, MD Section of Colon and Rectal Surgery, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Wolfgang B. Gaertner Division of Colon & Rectal Surgery, Department of Surgery, University of Minnesota, Minneapolis, MN, USA

Julio Garcia-Aguilar, MD Colorectal Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Jose G. Guillem Colorectal Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Jason F. Hall, MD, MPH, FACS Lahey Hospital and Medical Center, Burlington, MA, USA

Brett Howe, MD Mount Sinai School of Medicine, Mount Sinai West Hospital, New York, NY, USA

Tracy Hull Department of Colon and Rectal Surgery, Digestive Disease Institute, The Cleveland Clinic Foundation, Cleveland, OH, USA

Roger D. Hurst, MD Department of Surgery, University of Chicago Pritzker School of Medicine, Chicago, IL, USA

Woon Kyung Jeong Colorectal Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Bobby Lynn Johnson III, MD Department of Surgery, University of Cincinnati, Cincinnati, OH, USA

Walker Julliard Department of Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Matthew F. Kalady, MD Department of Colorectal Surgery, Cleveland Clinic, Cleveland, OH, USA

Michael Keating, BA Case Western Reserve University School of Medicine, Cleveland, OH, USA

Scott R. Kelley, MD, FACS, FASCRS Division of Colon and Rectal Surgery, Mayo Clinic, Rochester, MN, USA

Gregory Kennedy Division of Gastrointestinal Surgery, Department of Surgery, University of Alabama at Birmingham, Birmingham, AL, USA

Walter A. Koltun, MD, FRCS, FASCRS Division of Colon and Rectal Surgery, Inflammatory Bowel Disease, The Pennsylvania State University, College of Medicine, Hershey, PA, USA

Geoffrey K. Ku, MD Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Miranda Kusters Department of Surgery, Catharina Hospital, Eindhoven, The Netherlands

David W. Larson, MD, MBA, FACS, FASCRS Division of Colon and Rectal Surgery, Mayo Clinic, Rochester, MN, USA

Elise H. Lawson, MD, MSHS Colon and Rectal Surgery, Farmington, CT, USA

Amy L. Lightner Mayo Clinic, Division of Colon and Rectal Surgery, Rochester, MN, USA

David A. Liska, MD Department of Colorectal Surgery, Cleveland Clinic, Cleveland, OH, USA

Walter Longo, MD, MBA Department of Surgery, Yale University School of Medicine, New Haven, CT, USA

Robert D. Madoff Division of Colon & Rectal Surgery, Department of Surgery, University of Minnesota, Minneapolis, MN, USA

Najjia Mahmoud Department of Surgery, University of Pennsylvania, Philadelphia, PA, USA

Justin Maykel, MD Division of Colon and Rectal Surgery, University of Massachusetts Medical Center, Worcester, MA, USA

Anders Mellgren, MD, PhD Division of Colon & Rectal Surgery, University of Illinois Chicago, Chicago, CL, USA

Nitin Mishra, MD Mayo Clinic College of Medicine, Rochester, MN, USA

Ido Mizrahi, MD Department of Colorectal Surgery, Cleveland Clinic Florida, Weston, FL, USA

Jesse Moore, MD, FACS, FASCRS University of Vermont Medical Center, University of Vermont College of Medicine, Burlington, VI, USA

W. Conan Mustain, MD Division of Colon and Rectal Surgery, University of Arkansas for Medical Sciences,, Little Rock, AR, USA

Bruce A. Orkin, MD, FACS, FASCRS Section of Colon and Rectal Surgery, Rush University School of Medicine, Chicago, IL, USA

Harry T. Papaconstantinou, MD Department of Surgery, Baylor Scott & White Healthcare, Texas A&M University College of Medicine, Baylor Scott & White Memorial Hospital, Temple, TX, USA

Ian M. Paquette, MD Division of Colon and Rectal Surgery, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Emily Carter Paulson Department of Surgery, University of Pennsylvania, Philadelphia, PA, USA

C. Peirce Department of Colorectal Surgery, Cleveland Clinic, Cleveland, OH, USA

Michael Pezold, MD, MS Department of Surgery, New York Presbyterian Hospital-Weill Cornell Medical, New York, NY, USA

Blase N. Polite, MD, MPP Section of Hematology/Oncology, University of Chicago Biological Science Division, Chicago, IL, USA

V. Prasad Poola, MD Southern Illinois University School of Medicine, Springfield, IL, USA

Lisa S. Poritz The Milton S. Hershey Medical Center, Pennsylvania State University College of Medicine, Hershey, PA, USA

Janice Rafferty, MD, FACS, FASCRS Division of Colon & Rectal Surgery, UC Health, Cincinnati, OH, USA

Jan Rakinic, MD, FACS, FASCRS Southern Illinois University School of Medicine, Springfield, IL, USA

Vikram Reddy, MD, PhD Department of Surgery, Yale University School of Medicine, New Haven, CT, USA

Feza H. Remzi Department of Colorectal Surgery, Digestive Disease Institute, Cleveland Clinic, Cleveland, OH, USA

Teresa C. Rice, MD University of Cincinnati Medical Center, Cincinnati, OH, USA

Patricia L. Roberts, MD Division of Surgery, Lahey Hospital and Medical Center, Burlington, MA, USA

Campbell S. Roxburgh Memorial Sloan Kettering Cancer Center, New York, NY, USA

David T. Rubin University of Chicago Inflammatory Bowel Disease Center, Chicago, IL, USA

Andrew J. Russ, MD, FACS, FASCRS University of Tennessee, Department of Surgery, Knoxville, TN, USA

Theodore J. Saclarides, MD Loyola University School of Medicine, Maywood, IL, USA

Nicole M. Saur, MD Division of Colon and Rectal Surgery, Department of Surgery, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

Anthony J. Senagore, MD, MBA Department of Surgery, UTMB- Galveston, Galveston, TX, USA

Shafik M. Sidani Department of Surgery, Virginia Hospital Center, Arlington, VA, USA

Clifford L. Simmang Chief Medical Officer and Vice President of Medical Affairs, Baylor Scott and White Medical Center at Grapevine, Grapevine, TX, USA

Marc A. Singer, MD, FACS, FASCRS Section of Colon and Rectal Surgery, Rush University School of Medicine, Chicago, IL, USA

Nathan R. Smallwood Division of Colon and Rectal Surgery, Baylor University Medical Center, Dallas, TX, USA

Eric A. Sparks, MD Department of Surgery, Baylor Scott & White Healthcare, Scott & White Memorial Hospital, Temple, TX, USA

Scott R. Steele, MD Department of Colon and Rectal Surgery, Case Western University, Cleveland, OH, USA

Randolph M. Steinhagen, MD Division of Colon and Rectal Surgery, Department of Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Scott A. Strong, MD, FACS, FASCRS Chief, Gastrointestinal and Oncologic Surgery, Surgical Director, Digestive Health Center, Northwestern Medicine James R. Professor of Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Larissa K. Temple Colorectal Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Konstantin Umanskiy Medical Center, University of Chicago, Chicago, IL, USA

Avery S. Walker, MD Department of Surgery, Brian Allgood Army Community Hospital, Yongsan, South Korea

Martin R. Weiser, MD Colorectal Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Mark L. Welton Department of Surgery, Stanford University School of Medicine, Stanford, CA, USA

Steven D. Wexner, MD, PhD (Hon) Department of Colorectal Surgery, Cleveland Clinic Florida, Weston, FL, USA

Richard L. Whelan, MD Mount Sinai School of Medicine, Mount Sinai West Hospital, New York, NY, USA

Sean Wrenn, MD University of Vermont Medical Center, University of Vermont College of Medicine, Burlington, VI, USA

Karen Zaghiyan, MD Colon and Rectal Surgery, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Chapter 1
Introduction

Konstantin Umanskiy

Where is the wisdom we have lost in knowledge? Where is the knowledge we have lost in information?

T.S. Eliot 1934

Tell Me a Story. The Importance of an Anecdote

At the center of medical decision-making is always the patient; their story, their feelings, their family support and their unique perception of the problem. At this intersection of medical art and science stands the surgeon who must combine the unique aspects of the ancient art of healing with modern medical science to provide the treatment most likely to create a good outcome. Instinctively we as surgeons tend to rely on impressions from our clinical practice, experiences during surgical training, or maybe what we have just heard at the morbidity and mortality conference this week. This anecdotal decision making, while typically thought of as rudimentary and not "evidence-based", is in fact one of the most basic forms of evidence based medicine(EBM). This method of medical practice has been known since antiquity where early EBM was based on ancient historical or anecdotal accounts. Teaching during this time was mainly authoritative and passed on with stories. By the seventeenth century, a renaissance era of medical practice had ushered the earliest form of modern EBM. During this period, written journals were kept and textbooks began to become more prominent.

Information Literacy. Learning the New Language

Fast forward to 1970–1990s, the era often called the transitional era of EBM. This time period was characterized by the rise of biomedical informatics, driven by the explosion of published information related to health care. At the same time came

K. Umanskiy
Medical Center, University of Chicago, Chicago, IL, USA
e-mail: kumanskiy@surgery.bsd.uchicago.edu

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the advent of the clinical trials and of clinical research, in general. An electronic version of Index Medicus which would ultimately become MEDLINE was expanding rapidly. An early version of what would become a World Wide Web was in advanced phases of development. The stage was set for an entirely new relationship between the world of medical practice, health care and the biomedical literature.

In 1991 the term 'evidence-based medicine' was declared to be both 'a new approach to teaching the practice of medicine' and 'a new paradigm of medical practice'. In 1992, the Journal of the American Medical Association proposed a radical change in the hierarchy of knowledge in which clinical evidence, particularly that stemming from randomized trials and meta-analyses, was placed above the pathophysiological understanding of disease process and 'clinical experience.'[1] This concept, while controversial, took the medical community by storm, fueled by reports such as the one published by Antman et al. [2] that demonstrated that thousands of patients with myocardial infarction had died unnecessarily as a result of failure to adequately summarize the trial evidence on the efficacy of thrombolytic therapy.

With the advent of public access to the Internet via the World Wide Web in 1995, the door had swung open to the proliferation of electronic biomedical resources. But with the rapid explosion of medical information, came the necessity of equipping the practitioners and teachers of medicine with resources to acquire 'information literacy'[3], a concept defined as an identification of the information needed and the process of performing a search, evaluating the quality of the evidence and, finally, integrating it with independent pre-existing information. This process that can be described as 'ask', 'acquire', 'appraise' and 'apply' became the instructional model for EBM [4].

Since the mid-1990's medical journals have featured a number of well-designed analyses and clinical practice guidelines put together by well-respected groups of experts. The number of publications with the keyword 'evidence-based medicine' has risen dramatically from 1984 to 2015 (Fig. 1.1). While the emphasis on evidence-based practice has been robust and quite persistent over the past two decades, the evidence provided often conflicts with other evidence, may be overtly misleading or even just plain wrong. One such conspicuous example was the recent excitement about avoidance of mechanical bowel prep in colon surgery [5], only to later realize that mechanical bowel prep with oral antibiotics as originally proposed by Nichols and Condon decades ago is demonstrably superior [6].

Without a doubt evidence-based medicine provides surgeons with a rational basis to support guidelines for treatment modalities and contributes to standardization of care, which in many instances results in improved quality of care and better patient outcomes. But with the guidelines may come an unwelcomed restrictiveness; many surgeons are reluctant to alter their practice and may have very legitimate concerns whether the generalized evidence really provides the best solution for the individual patient. The interpretation of data as presented in medical literature may require the reader to become 'information literate' to appraise the quality of the evidence and its true applicability to the individual surgeon's practice.

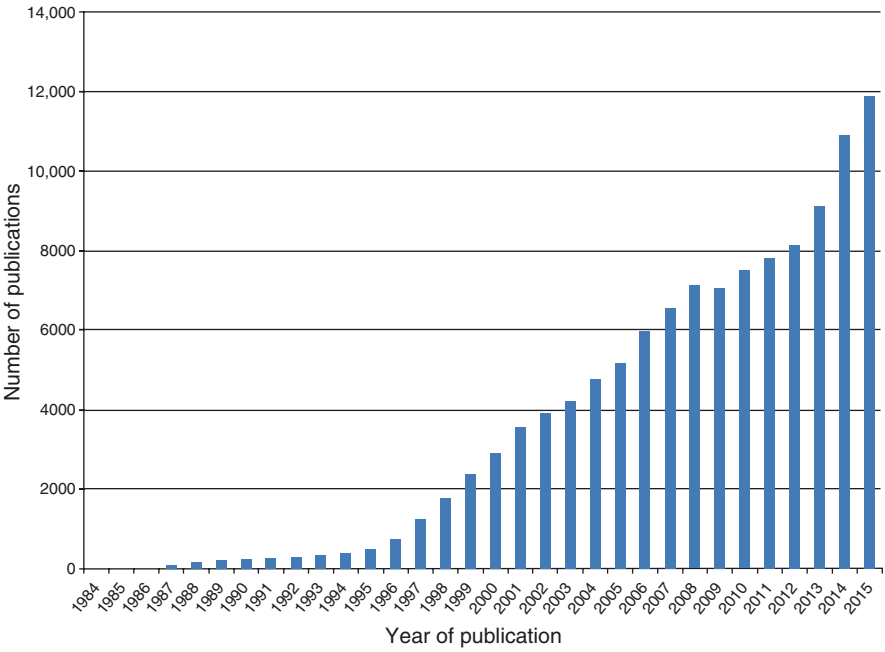

Fig. 1.1 PubMed entries with keywords 'evidence based medicine'

Introduction of new technology into colon and rectal surgical practice is resulting in a rapidly expanding technical armamentarium. Some surgeons self-described as "early adaptors" are quick to jump on the bandwagon to embrace new and often unproven technology, driven by a general desire to advance the field and push the envelope. An unbiased and thoughtful review of data and careful reflection on the ethical considerations based on the surgical dictum of "do no harm" should be liberally exercised.

Bringing It Together

Initially, EBM focused primarily on determining the best evidence and applying that evidence to the clinical situation at hand. This early approach lacked emphasis on traditional aspects of clinical decision-making such as physiologic rationale and individual clinical experience. Fortunately, with evolution of EBM came the realization that research-based evidence alone may not be an adequate guide to action. Instead, clinicians must combine their experience, the applicable scientific evidence and the patient's wishes and values before making a treatment recommendation. Figure 1.2 depicts a model for evidence-based decisions, which emphasizes "clinical expertise" as an overarching component in EBM decision-making. Clinical

Fig. 1.2 Current model of evidence-based clinical decision making (Adapted from: Haynes et al. [9])

expertise encompasses the patient's clinical state and surrounding circumstances, combining it with relevant research evidence, and the patient's preferences. Getting the diagnosis and prognosis right and knowing how to provide treatment demand more skill now than ever before because the options are many and patient expectations are high. Surgeons in the current clinical environment must be abreast of not only the scientific evidence; they must also acquire and hone skills needed to both interpret the evidence and apply it appropriately in clinical settings. Finally, and very importantly, the patients' goals, values and wishes remain the cornerstone to the best and informed decisions [7].

Why This Book?

How do we know that a parachute works? Well, one can say we don't know. Apparently there has never been a randomized, double blind, prospective, placebo-controlled trial assessing the efficacy of the parachute [8].

Sometimes common sense is all that is needed, and medicine in this regard is no exception. This book was conceived as an opportunity to hear the voice of a no-nonsense, wise mentor, who can build on the available evidence, put it in perspective and provide practical advice to tough clinical problems. While not all encompassing, this book has been designed to help surgeons with their decision-making on a very practical level based on the best available evidence. We asked many of the most 'information literate' experts in the field of colon and rectal surgery to comb through the evidence, evaluate and summarize it for our readers and provide their opinion and recommendation based on the years of experience caring for patients with com-

plex colon and rectal disorders. We are sincerely grateful to a wonderful group of colleagues and friends, recognized experts in the field of colon and rectal surgery, for their contributions to this book.

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Chapter 2
Evaluating Evidence

W. Donald Buie

Introduction

Evidence can be defined in the broadest sense as "… any empirical observation, whether systematically collected or not" [1]. Clinical evidence can include everything from the unsystematic observations of the individual clinician, physiologic experiments in animal models or the systematic observation of clinical events. Due to this wide variety of sources, it is of varying quality and applicability. How confident are we in the stated results? How accurate are the estimates of effect? Can the results be generalized to my patient? Evidence based decisions require not only the identification of all relevant evidence for a specified outcome but a systematic evaluation of the evidence such that *best* available evidence is used to support good clinical decisions.

Throughout this book, the quality of evidence and in turn the strength of the recommendations that follow is based primarily on GRADE (Grading of Recommendations Assessment, Development and Evaluation) [2]. GRADE is a transparent, structured, reproducible system for reviewing and evaluating medical evidence for any specified outcome. In its basic form, it can be used by a clinician to help identify the best treatment course for a specific clinical situation, and in its complete form by guideline developers to assess the literature on a broad topic to produce clinical practice guidelines (CPGs) on important patient specific outcomes [2]. This chapter will briefly outline the steps that are required to apply GRADE when evaluating evidence for specific clinical decisions. It will summarize the process of evaluating evidence by exploring stratification by study design, assessing random error and bias, identifying methodological limitations and assessing

W.D. Buie, MD, MSc, FRCSC
Department of Surgery, University of Calgary, Calgary, AB, Canada
e-mail: wdbuie@ucalgary.ca

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confidence in the measured effect. For a complete review of the GRADE system clinicians are encouraged to read a series of articles from the British Medical Journal [3–5] or a more recent series from the Journal of Clinical Epidemiology designed for guideline developers [2, 6–13]. The ideas and concepts in this chapter are summarized primarily from the latter series and the reader is encouraged to seek out these references for a more in depth discussion.

Initial Evaluation

Evaluation of evidence begins with a well-constructed clinical question including a specified population, a specific intervention, a comparator and specific outcomes, a process often abbreviated as PICO [14] (Fig. 2.1). A poorly designed question negatively affects the appropriateness of the collected evidence and in turn the evaluation of that evidence. With the ever increasing volume of evidence present in the medical literature and the constant turnover of best evidence, it is difficult for the clinician with limited time and resources to keep up to date. This has fuelled an explosion in structured reviews and CPGs that aim to summarize the literature in a structured and transparent fashion. Not all subjects are covered with a CPG and thus the clinician must be able to formulate an appropriate search and evaluate the literature independently.

Once a literature review is complete, each individual study must be vetted for its relevance to the topic. Does it address the outcomes of interest? Does it apply to the particular practice setting? Does it apply to the particular patient population? Not all studies will address all outcomes. However, the evidence for all important patient outcomes in a specific clinical situation must be evaluated. For example, in Stage IV rectal cancer when considering a palliative resection versus long-term chemotherapy, evidence for each management strategy must be evaluated for both quality and quantity of life. In addition the risk of a poor outcome *as viewed by the patient* due to either surgical or medical complications must be considered. For many questions a structured review or CPG exists that covers most of the outcomes of interest but a primary literature search may be required to supplement evidence for specific outcomes.

Stratifying Evidence

Once the evidence is collected, it is initially stratified by study methodology. Well designed structured reviews and meta-analysis based on well-designed RCTs are the highest order of evidence, followed by well designed RCTs themselves, lower quality RCT studies with methodological limitations and finally observational studies (cohort and case control). Within the GRADE system, expert opinion is not viewed as evidence in and of itself. In other words, while an expert is required to interpret evidence, expert opinion may or may not be based on best evidence.

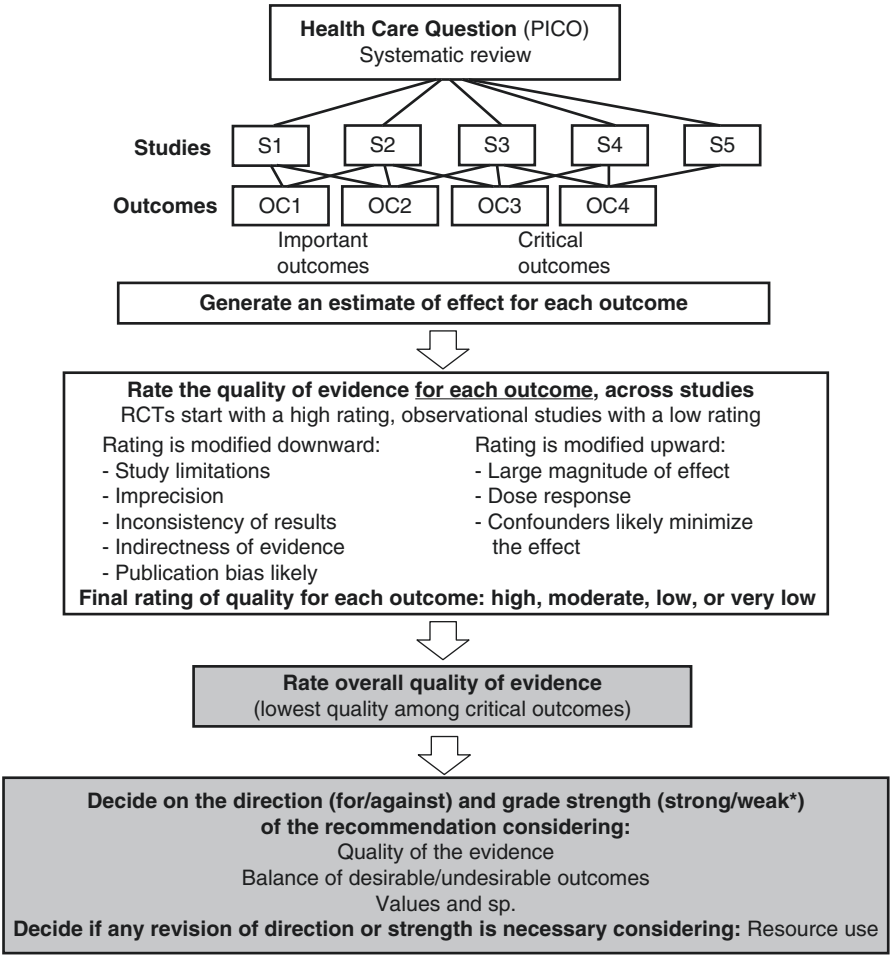

Fig. 2.1 The GRADE process for developing recommendations (Adapted from Guyatt et al. [2])

Random Error and Systematic Error (Bias)

All studies are subject to error, which may to a greater or lesser extent affect the results of a study and our confidence in the stated results. Error can be classified into two major categories: random error and systematic error or bias. Random error is the variation in outcomes due to chance alone. Studies are performed on sample populations from the population at large, thus the results of each study are estimates of the actual effect of an experimental intervention on the overall population. If a study is performed on 20 different sample populations replicating strict methodology each time, the final results of each trial will be closely approximated but will vary due to chance, much like a coin toss performed multiple times will not always add up to

exactly 50% heads and 50% tails. Random error is by definition variable and can occur in either direction, (you can toss 7 heads or 6 tails in a row), resulting in a positive or negative effect on the estimate of an outcome of interest. It can be minimized through the use of large sample sizes either in individual studies or by combining similar smaller studies in a meta-analysis. A well designed prospective study should have a sample size calculation for a specific outcome as part of its methodology.

Systematic error or bias results in a systematic or fixed effect on a study. This type of error is not affected by sample size as it is related to study methodology. Virtually no study is devoid of all bias. However, when evaluating a study one must try to determine whether the effect from systematic error or bias is large enough to significantly alter the observed effect of an experimental intervention.

Methodological Limitations (Bias)

There are four levels of evidence in the GRADE system; high quality, moderate quality, low quality and very low quality (Table 2.1) [7]. Evidence from RCTs starts out as high quality evidence but may be down graded to moderate or even low quality if bias or methodological issues are identified. Similarly, although evidence from observational trials is generally classified as low or very low quality, it may be upgraded under certain circumstances (Fig. 2.1).

Bias in randomized trials can occur in three parts of a study; differences observed at the start of a study, differences that arise as a study progresses and differences at the completion of a study [16] (Table 2.2). Blinding should be present at all levels of a trial starting with allocation and randomization, and including the patient, the care giver, the assessors and the data analysts. When absent, the results usually favor an overestimation of effect. Differences in treatment or exposure to confounding treatments in the experimental arm, incomplete follow up or loss to follow up and failure to adhere to the intention to treat principle in superiority trials are also associated with over estimation of effect. Loss to follow up takes on greater importance when the number of events in either the experimental or control group is small relative to the percentage lost to follow up or if the loss to follow up is imbalanced between the two groups.

Studies that investigate treatment with *observational* design are inherently subject to bias. While the investigator does not have any control over these biases, the clinician should look for statistical adjustments or the use of hard endpoints by the investigator. The clinician must evaluate whether the observed biases could potentially account for an observed treatment effect [16].

Although study design is important, GRADE applies to each specific outcome within a study. Bias may affect specific outcomes within the same study to a greater or lesser degree increasing or reducing our confidence in each observed outcome. For example lack of blinding of assessors may not affect the assessment of a post-operative outcome such as death but may be responsible for bias in the assessment of a wound infection.

Table 2.1 GRADE: levels of evidence and definitions

Category	Definition	Examples
High	We are very confident that the true effect lies close to that of the estimate of the effect	Randomized trials without serious limitations
		Well performed observational studies with very large effects
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Randomized trials with serious limitations
		Well-performed observational studies yielding large effects
Low	Our confidence in the effect estimated is limited: the true effect may be substantially different from the estimate of the effect	Randomized trials with very serious limitations
		Observational studies without special strengths or important limitations
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimated of effect	Randomized trials with very serious limitations and inconsistent results
		Observational studies with serious limitations
		Unsystematic clinical observations (case series or case reports)

Adapted from Balshem et al. [7]

Table 2.2 Study limitations in randomized trials

1. Lack of allocation concealment
Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (e.g., "pseudo" randomized trials with allocation by day of the week, birth date, chart number etc.)
2. Lack of blinding
Patient, care givers, those recording outcomes, those adjudicating outcomes or data analysts are aware of which arm patients are allocated
3. Incomplete accounting of patients and outcome events
Loss to follow-up and failure to adhere to the intention-to-treat principle in superiority trials; or in noninferiority trials, loss to follow-up and failure to conduct both analysis considering only those who adhered to treatment, and all patients for whom outcome data are available
4. Selective outcome reporting bias
Incomplete or absent reporting of some outcomes and not others on the basis of results
5. Other limitations
Stopping early for benefit
Use of unvalidated outcome measures (e.g. patient reported outcomes)
Carryover effects in crossover trial
Recruitment bias in cluster randomized trials

Adapted from Balshem et al. [7]

Confidence in Effect

Downgrading Evidence

A study may be well designed with minimal bias yet we may lack confidence in the degree to which the experimental effect is demonstrated. In other words, is the treatment really as good as the results suggest? In GRADE there are four additional qualities that must be evaluated for each specific outcome which when present will downgrade the evidence from a RCT either one or two categories depending on how serious the shortcomings are (Fig. 2.2)

Imprecision

Imprecision refers to the accuracy of the point estimation of effect. It is most easily identified by examining the 95 % confidence interval (CI) around the difference in effect; the larger the interval the less precise the estimate [10]. Examine the absolute and not the relative difference as the latter will inflate any observed effect. Use a theoretic test: if the true value was equal to the upper or lower 95 % CI and if this result would change the course of action, then consider the results imprecise and downgrade the evidence [10]. Be suspicious when the effect is large, yet both the sample size and the number of events are small even if the CIs are narrow; in other words, relatively few patients with relatively few incidents should call a large magnitude of effect into question.

Inconsistency

When the results of several well conducted RCT vary widely with respect to a specific outcome the evidence is inconsistent [11]. An attempt should be made to

A summary of GRADE's approach to rating quality of evidence

Study design	Initial quality of a body of evidence	Lower if	Higher if	Quality of a body of evidence
Randomized trials	High ⇒	Risk of Bias –1 Serious –2 Very serious Inconsistency –1 Serious –2 Very serious Indirectness –1 Serious –2 Very serious Imprecision –1 Serious –2 Very serious Publication bias –1 Likely –2 Very likely	Large effect +1 Large +2 Very large Dose response +1 Evidence of a gradient All plausible residual confounding +1 Would reduce a demonstrated effect +1 Would suggest a spurious effect if no effect was observed	High (four plus: ⊕⊕⊕⊕) Moderate (three plus: ⊕⊕⊕◯) Low (two plus: ⊕⊕◯◯) Very low (one plus: ⊕◯◯◯)
Observational studies	Low ⇒			

Fig. 2.2 A summary of GRADE's approach to rating quality of evidence (Adapted from Balshem et al. [7])

explain the variability between studies based on differences in populations, interventions, outcome measurement or other methodologic issues. Subgroup and sensitivity analysis may be necessary to illuminate these differences which may or may not downgrade the evidence based on the perceived effect on the outcome of interest.

Indirectness

There are two types of indirectness recognized within the GRADE system [12]. The first is when there is evidence comparing intervention A with intervention B and intervention B with C but no direct evidence from a comparison of A with C. In this case an inference can be made but the level of evidence for that outcome is marked down one level. This type of indirectness is more common in pharmacologic trials. Evidence may also be classified as indirect if there are differences between the best available evidence with respect to the populations under study, specific interventions, co-interventions or outcome measurements and the PICO (population, intervention, comparator and outcome) of the initial clinical question.

Publication Bias

Negative studies are less likely to be published resulting in publication bias [9]. These studies also suffer from lag time bias being published at a later date. Negative studies are often relegated to lower impact journals or as a thesis or abstract in an obscure publication such as proceedings of a meeting and in languages other than English. Omission of negative studies may lead to an overestimation of treatment effect.

Another form of publication bias is selective outcome reporting [9]. This should be suspected if some of the expected outcomes for a specific clinical problem are suspiciously absent. Selective outcome reporting may also occur when composite or derived outcomes are reported as significant and primary outcomes are either not significant or not discussed. It also causes an overestimation of the effects of an intervention.

Upgrading Evidence

Occasionally outcomes from descriptive or observational studies which are normally classified as low level evidence may be upgraded one level. GRADE has specified three situations whereby observational evidence may be upgraded usually from very low to low level evidence (Fig. 2.2).

Large Magnitude of Effect

Occasionally an observational study demonstrates a very large treatment effect [13]. GRADE defines a large effect as a relative risk (RR) of >2.0 and <5.0 based on consistent evidence from at least two studies with no significant confounders. A very large magnitude of effect is defined as a relative risk of >5.0 and <0.2. The effect should be based on direct evidence with no other perceived forms of bias. An example of this would be the original case series published on mesorectal excision where the reduction in local recurrence was far greater than either accepted levels in the literature following standard surgery at the time or the improvements obtained by adjuvant therapy [15].

Plausible Confounders

In this situation, a confounder effect would be expected to act in opposition to the observed effect [13]. For example, all plausible confounders would reduce the demonstrated effect or increase it if no effect was observed. Thus the presence of the confounder increases the likelihood that the observed effect is real and therefore the evidence may be upgraded.

Dose Response Gradient

When increased exposure to an intervention is associated with a larger treatment effect or greater harm, this may be considered a dose response gradient [13]. In this situation, the evidence may be upgraded as we have more confidence in the observed effect. This is not likely to occur in surgical studies as the treatment effect is usually an all or none phenomena.

Overall Quality Rating

Once the evidence for each outcome has been identified, stratified and evaluated for the presence of bias, an estimation of the confidence in the observed effect is determined based on the qualities in the previous section. This information is best summarized in an evidence profile table (EP) [2]. Next, a *quality rating* of the best available evidence is assigned for each separate outcome to one of the four categories (Table 2.1). This becomes the overall estimate of the confidence in the expressed treatment effect for a specific outcome [16]. Prior to a recommendation, an overall quality rating for all the evidence for all outcomes is determined. When there are

different levels of quality for each outcome, the GRADE system by convention bases the overall quality rating on the lowest quality of available evidence for the specified outcomes (Fig. 2.2).

The overall quality rating is the basis for the strength of any recommendations that follows (Fig. 2.1). Strength of recommendation is defined as "the extent to which we can be … confident that desirable consequences of an intervention outweigh undesirable consequences" [16]. GRADE classifies recommendations into two categories based on how strongly the evidence supports the recommendation. A strong recommendation indicates that a specific course of action would be appropriate for most patients in most situations. A weak recommendation on the other hand indicates that although the recommended course of action would be appropriate for most patients in this situation, for many patients it would not [17]. Occasionally evidence for a specific outcome is so inadequate that no evidence based recommendation can be made.

Conclusion

Clinical decisions must be based on best evidence. High quality structured reviews or CPGs with transparent evaluation of quality of the evidence using a system such as GRADE are invaluable. While the clinician may not have the time or training to perform a structured review, they must be able to evaluate studies for quality when information on a desired outcome is not part of a CPG.

While evidence is essential for good clinical decision-making, it cannot be applied in isolation. A clinician must consider the risks versus benefits and the burdens and costs of each management strategy. In addition, the goals, values and expectations of the patient as well as the experience of the clinician in similar situations must be considered. It is the responsibility of the clinician to assess and interpret the evidence as it applies to each individual patient's situation and guide the patient in the quest for optimal, safe, patient centered care.

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Part I
IBD

Chapter 3
IBD: Management of Symptomatic Anal Fistulas in Patients with Crohn's Disease

Lisa S. Poritz

Introduction

Approximately 30 % of patients with Crohn's disease (CD) will have or develop perianal fistulas (PF) during the course of their disease. Not only do symptomatic PF cause pain and drainage, they may also lead to sepsis, incontinence, restriction of activities, and decreased quality of life. Ultimately, some patients may end up with permanent fecal diversion either due to progression of disease or in some cases owing to complications from aggressive treatment.

The optimal treatment of these fistulas is controversial. The purpose of this chapter is to compare the results of medical and surgical treatment for symptomatic PF in CD patients. While there are numerous studies looking at the results of either medical or surgical treatment, little high quality comparative data exists and evidence based comparisons are challenging at best.

Not all fistulas in patients with CD are the same and both fistula characteristics and patient factors are integral in determining the best therapy. It is important to know whether there is active mucosal disease in the rectum, whether or not the patient is concurrently receiving medical therapy for luminal disease, the history of medication use and any adverse reactions, previous surgical treatment, and level of continence.

For the purposes of this chapter we will divide patients into three categories and assume that patients are not on medications for luminal CD. The literature and recommendations will be discussed as they pertain to the following patient scenarios:

L.S. Poritz
The Milton S. Hershey Medical Center, Pennsylvania State University College of Medicine, Hershey, PA, USA
e-mail: lporitz@outlook.com

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Scenario 1: The patient with a simple fistula and no macroscopic rectal disease
Scenario 2: The patient with either a simple or a complex fistula and macroscopic rectal disease
Scenario 3: The patient with a complex fistula and no macroscopic rectal disease

Search Strategy

A systematic review of the literature using PubMed was performed for the period: 1995–2015. Search terms included: CD, PF, fistula plug, ligation of internal fistula tract (LIFT) procedure, and mucosal advancement flap. Articles were limited to peer reviewed reports in English. Additional studies were identified from the references of the initial articles retrieved as appropriate.

The studies discussed will be primarily randomized controlled trials and large observational studies. In the case where neither exists for a given treatment modality, the best available data will be discussed. The quality of evidence and recommendations were made according to modified GRADE system (Tables 3.1 and 3.2).

Results

Patients who present with fistulizing perianal CD typically require examination under anesthesia (EUA), assessment of the rectal mucosa for disease activity, drainage of any abscesses and placement of setons as the initial step. The primary purpose of seton placement is control of anorectal sepsis; setons allow for continued drainage from the fistula tract and usually prevent abscess formation. Antibiotics are often prescribed simultaneously (primarily ciprofloxacin or metronidazole) until the perianal sepsis has resolved. Further therapy depends on the disease activity of the rectal mucosa and complexity of the fistula.

Scenario 1: The Patient with a Simple Fistula and No Macroscopic Rectal Disease

Patients with a simple superficial fistulas and no macroscopic rectal disease can often be treated by surgery alone without the need for medical therapy beyond initial antibiotics. If the fistula does not traverse any sphincter muscle, these patients

Table 3.1 PICO table

Patient population	Intervention	Comparator	Outcomes studied
Crohn's patients with symptomatic anal fistulas	Surgery	Medical Therapy	Remission rate
			Cure rate
			Adverse event

Table 3.2 Quality of evidence

Study	Patients	Treatment	Comparator	Response rate	Remission rate	Type of study	Quality of evidence
van Koperen et al. [2]	61	Fistulotomy/Seton/or advancement flap	None	NA	44–82 %	Retrospective	Low
Pearson et al. [6]	9 RCT	AZA or 6MP	Placebo	54 %: AZA or 6MP 21 %: placebo	NA	Meta-analysis	Moderate
Present et al. [7]	94	Infliximab	Placebo	IFX: 62 % Placebo: 26 %	IFX: 46 % Placebo: 13 %	RCT	Moderate
Sands et al. (ACCENT II) [8]	195	Infliximab	Placebo	IFX: 46 % Placebo: 23 %	NA	RCT	Moderate
Dewint et al. (ADAFI) [13]	76	ADA and Cipro	ADA and placebo	Cipro: 71 % Placebo: 47 %	Cipro: 65 % Placebo: 33 %	RCT	Moderate
Grimaud et al. [15]	77	Fibrin glue	Observation	NA	38 %: fibrin glue 16 %: observation	RCT	Moderate
Makowiec et al. [18]	32	Endorectal advancement flap	None	NA	50 % (initial primary healing 89 %)	Prospective	Low
Hyman [19]	14	Endorectal advancement flap	None	NA	50 % (initial rate 71 %)	Prospective	Low
Gingold et al. [20]	15	LIFT	None	NA	60 % at 2 months	Prospective	Low
Molendijk et al. [23]	232	Surgical therapy	Medical Therapy	Surgery: 97 % Medicine: 72.2 % Both: 93.2 %	Surgery: 91.7 % Medicine: 64.3 % Both: 86.6 %	Retrospective	Low
Gaertner et al. [24]	226	IFX and surgery	Surgery	NA	60 %: surgery 59 %: surgery and IFX	Retrospective	Low

RCT randomized controlled trial, *AZA* Azathioprine, *6MP* 6-mercaptopurine, *IFX* Infliximab, *LIFT* Ligation internal fistula tract, *ADA* Adalimumab

are good candidates for fistulotomy. For patients in whom the fistula traverses the sphincter muscle, fistulotomy may still be appropriate if the amount of muscle is small and the continence is not already compromised. Healing rates of up to 100 % have been reported [1–3]. The risk associated with primary fistulotomy is poor wound healing, recurrence and incontinence [2]. For patients in whom fistulotomy is not appropriate, a seton can be considered the primary treatment and left for long term drainage [4]. In some patients. the setons can be removed after the perianal sepsis resolves and the fistula tracts will close [1]. Indeed, a healing rate of up to 25 % has been found in the placebo groups in the medical trials discussed below. If the fistula recurs, the patients should be then be treated as if they have a complex fistula (scenario 3).

Scenario 2: The Patient with Either a Simple or a Complex Fistula and Macroscopic Rectal Disease

The presence of active disease in the rectum will significantly compromise the success rate of surgical intervention. After drainage of sepsis and placement of a seton(s), these patients should be evaluated for medical therapy to try and eradicate the inflammation in the rectum. In some cases, medical therapy may also cure the fistula. Placement of a draining seton prior to inititation of medical treatment has been shown to improve the results with anti-TNF therapy [5]. Below is a brief summary of the major classes of drugs used to treat perianal CD.

Antibiotics are useful to help control perianal sepsis and may also decrease pain, but there are no randomized clinical trials (RCT) that show that antibiotics alone can result in fistula closure. Uncontrolled studies show a benefit with the use of metronidazole or ciprofloxacin that is quickly lost on withdrawal of the drug.

As with antibiotics, there are no RCTs that support the use of azathioprine or its derivatives as single therapy for the treatment of PF in patients with CD. Pearson et al. performed a meta-analysis of RCTs using these drugs and in the subset of patients with perianal disease, found a 54 % response with the drugs versus 21 % with placebo [6]. However, these drugs are slow in onset and are rarely used as first line mono drug therapy for fistulizing perianal disease.

The first randomized placebo controlled trial using anti-TNF therapy in fistulizing CD was performed by Present et al. in 1999. They studied 94 patients and compared a 3 dose induction regimen with either 5 or 10 mg/kg of infliximab to placebo. They found a significantly higher number of patients treated with infliximab had a response and or achieved remission [7]. In this study there was no maintenance therapy and the duration of fistula closure was about 3 months. Subsequently, a maintenance study (ACCENT II) was performed taking patients who responded to induction with infliximab and randomizing them to maintenance every 8 weeks with infliximab or placebo. The infliximab maintenance group had a longer time until loss of response as compared to the placebo group [8].

Initial RCTs with adalimumab included a subgroup analysis for patients with fistulizing disease. In CLASSIC-1 and GAIN there was no benefit to adalimumab over placebo [9, 10]. However, in CHARM there was a significant benefit to the use of adalimumab [11].

Results in studies combining antibiotics and anti-TNF agents have been mixed. West et al. combined infliximab with either ciprofloxacin or placebo, and observed a nonsignificant trend toward a better response with concomitant antibiotics [12]. Dewint et al. performed a RCT adding either placebo or ciprofloxacin to adalimumab and found a significant increase in response and remission with combined therapy. However, the added benefit of the antibiotic was lost when it was discontinued [13].

The anti-TNF drugs have convincingly been shown to reduce fistula drainage and induce remission, but not without high cost and risks including infections, infusion reactions and malignancy. Even when fistula tracts are healed with biologic therapy, numerous studies have demonstrated residual tracts by ultrasound suggesting that the track may not be truly healed [14].

If the patient has a good response to medical therapy, drainage from the fistula will decrease and the setons will become more snug in the fistula tract. At that point they should be removed so as not to prevent complete healing. If the fistulas persist but the rectal mucosal disease resolves with medical treatment, then further surgical therapy may be considered. Simple fistulas can now be treated with fistulotomy as discussed above. For complex fistulas the most commonly utilized options include fibrin glue, fistula plug, endorectal advancement flap, and LIFT.

Fibrin glue has been used with inconsistent results in both patients with and without CD. Grimaud et al. performed a RCT comparing fibrin glue to observation and found a significantly higher response rate at 8 weeks (38 % vs. 16 %) [15].

A systematic review of the anal fistula plug was performed by O'Riordan et al. Of the 530 patients within the studies reviewed, 42 had CD. The rate of healing in this population was 54.8 % [16]. However, the authors felt that the population was too small and heterogeneous to be adequately evaluated.

Most studies looking at endorectal advancement flap for PF do not specify the disease etiology and segregating out the results for patients with CD can be difficult. A systematic review of all endorectal advancement flaps (CD and non CD) in 2010 identified only 91 CD patients treated by flap repair [17]. The weighted success rate was 64 % (range 33.3–92.9). Some of the best results were obtained by Makowiec et al. who had an initial 89 % success rate with a 33 % recurrence rate, however, half of the patients had a diverting stoma, and Hyman who had an initial 71 % healing rate with a 50 % long term healing rate [18, 19].

Gingold et al. performed a prospective evaluation of the LIFT procedure in 15 patients with CD related PF. They had a 60 % rate of healing of both the external opening and the surgical site at 2 months [20]. Newer surgical therapies such as injection of stem cells into the fistula tract may hold promise, but there is not enough data to warrant conclusions at this time.

For patients with severe complicated PF disease often coupled with incontinence, temporary fecal diversion is often a necessary adjunct to medical and sur-

gical therapy. However, most patients who undergo temporary diversion ultimately end up with permanent diversion. In a meta-analysis of 16 studies reporting temporary fecal diversion in patients with refractory perianal CD, Singh et al. found that only 16.6 % of patients were able to have their intestinal continuity restored long term. [21] Ultimately, some patients with PF and CD end up with a permanent stoma, with or without proctectomy. Mueller et al. reported their long term follow-up on 102 consecutive patients with complicated perianal CD. They had a 31 % permanent diversion rate; on multivariate analysis, the significant risk factors were complex PF, fecal incontinence, temporary diversion and rectal resection [22].

Scenario 3: The Patient with a Complex Fistula and No Macroscopic Rectal Disease

This group of patients is often the most difficult to evaluate because there are so many options. In the absence of rectal mucosal disease, medical therapy does not have to be instituted before surgical intervention and the choice between primary medical and surgical options is most pertinent. Unlike patients with a simple fistula, these patients should not be treated with fistulotomy as there is a significant risk of incontinence; however, the other surgical options discussed above are all usually applicable.

Medical therapy is a viable first option with success rates as discussed previously. However, treatment with anti-TNF agents require maintenance therapy for persistent remission. With longer exposure to these agents, the risk of untoward effects such as infusion reactions, opportunistic infections and cancer increase.

Choosing between medical therapy and surgical therapy in these patients can be difficult. In an attempt to compare medical and surgical therapy for PF in CD, Molendijk retrospectively evaluated 232 patients who had presented to their unit over a 20 year period [23]. They found that those patients who received medical therapy had a 72.2 % response rate and a 64.3 % rate of remission. Patients who had surgical therapy alone had a 97 % response rate with 91.7 % achieving remission. Patients who had combined therapy had a 93.2 % response and 86.6 % remission rate respectively Follow-up showed that in patients who achieved remission, the recurrence rate in the medical group was 15.6 %, surgery only 21.9 %, and combined group was 64.8 %. This is a retrospective study so the patients were not randomly assigned to the treatment groups and selection bias undoubtedly existed. Regardless, the efficacy of surgery in properly selected patients is clearly evident; however, a high recurrence rate is observed with all therapies.

Looking specifically at anti-TNF therapy, Gaertner et al. retrospectively examined 226 patients with CD and PF to evaluate the impact of infliximab on surgical results [24]. They reported a 60 % healing rate in surgical patients who received

infliximab versus 59 % in patients who had surgery alone. While this was also a retrospective study with potential selection bias, the success rate of surgery alone was equal to surgery plus anti-TNF therapy and similar to the success rate of medical therapy reported in other studies. Overall, anti-TNF therapy had a 46–65 % response/remission rate whereas surgery was associated with a 38–82 % remission rate. Based on this data it would be appropriate to treat patients with PF who do not have mucosal rectal disease with surgical intervention initially and then consider medical therapy if surgery fails to cure the fistula.

Recommendations Based on the Data

Scenario 1: The patient with a simple fistula and no macroscopic rectal disease: No specific recommendation can be made based on the low quality of the data

Scenario 2: The patient with either a simple or a complex fistula and macroscopic rectal disease: Examination under anesthesia, abscess drainage, seton placement followed by biologic therapy. If the fistula persists but the mucosal disease resolves, further surgical therapy should be considered (Strong recommendation).

Scenario 3: The patient with a complex fistula and no macroscopic rectal disease:

Surgical therapy (weak/conditional recommendation)
Medical therapy (weak/conditional recommendation)

A Personal View of the Data

I recommend patients undergo initial EUA with abscess drainage and assessment of rectal disease. The situation is then typically triaged into one of the categories discussed above. Patients without rectal disease are initially treated surgically without biologic therapy as this accomplishes 3 things: it avoids the adverse events associated with biologic therapy, it avoids committing the patient to long term medical therapy, and it "saves" biologic therapy for a later time when the patient may need it.

1. Simple fistulas without rectal disease:
   At the time of EUA, I consider fistulotomy if the patient is fully continent and the fistula does not involve a large amount of muscle or soft tissue. If these requirements are not met, I treat the patients as if they have complex fistulas without rectal disease.
2. Complex fistulas without rectal disease:
   At the time of EUA, these patients undergo seton placement and a course of antibiotics (usually Cipro or Flagyl) until the sepsis has resolved. After 1 month, if the sepsis is resolved, definitive surgical therapy is performed.

(a) Patients with imperfect continence or anal stenosis prohibiting advancement flap: These patients are often offered fibrin glue or fistula plug as the first line option. Although these modalities have lower cure rates, they also have little risk of incontinence and do not require the exposure necessary to perform an advancement flap. For patients who fail this therapy, I recommend a trial of biologic therapy (see #3)

(b) For patients with preserved continence and no rectal stricture, I offer (but do not recommend) fibrin glue or a fistula plug. Rather, I recommend advancement flap for these patients. If the fistula recurs after surgery, I recommend a trial of biologic therapy (see #3). If the patient cannot have biologic therapy (no response in the past, antibodies, severe adverse reaction) I would attempt a repeat advancement flap after several months if the fistula persists.

3. Simple and complex fistulas with rectal disease:
At the time of EUA, these patients also undergo seton placement and a course of antibiotics (usually Cipro or Flagyl) until the sepsis has resolved. Simultaneously, the patients are referred for biologic therapy. Once the patient is on biologic therapy, I reassess the perianal disease and if the fistula tracts are healing, which can often be determined by how easily the setons move in the tracts, I remove the setons. This can be during induction therapy or after maintenance therapy has started.

   (a) If the fistula closes, medical therapy is continued at direction of the gastroenterologist.

   (b) If the fistula remains symptomatic despite medical therapy, I repeat the EUA, reassess for any undrained abscesses, unidentified new fistula tracts and reassess the rectal disease activity.

      (i) If rectal disease persists, I would ask the gastroenterologist to reassess the patient and consider adding an agent, switching agents, or increasing dosage.

      (ii) If rectal disease has resolved, I then treat the patient as a complex fistula without rectal disease (Sect. 2) but maintain them on medical therapy throughout surgical treatment.

Additional comments:

1. Long term setons: When there are no good options for closing the fistulas, leaving setons in long term can control sepsis and substantially improve the quality of life for these patients.
2. Diversion:

   (a) Some patients present with multiple fistulas and abscesses. Fecal diversion may need to be one of the first steps in treatment to control the sepsis, pain, drainage, and often accompanying incontinence while medical therapy is being initiated.

   (b) Despite our best medical and surgical therapy, some patients will require proctectomy.

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Chapter 4
IBD: Management of a Painful Anal Fissure and Skin Tags in Patients with Crohn's Disease

Nicole M. Saur and Joshua I.S. Bleier

Introduction

Perianal manifestations of CD disease are usually chronic in nature, and often characterized by waxing and waning symptoms. The goals of treatment are typically achieved through multimodal management, which minimizes ablative surgical intervention and preserves the sphincter complex [1, 2]. While there is a spectrum of severity in the observed impact of perianal CD, even the minor issues of skin tags and fissuring can present the clinician with difficult decisions in management. In this chapter, we have attempted to provide some clarity to the decision process.

Question What is the best way to manage a painful fissure and skin tags in the setting of a patient with known Crohn's disease?

Fissures are identified in 19 % of patients with CD and although they were historically thought to be painless, 40–85 % of anal fissures in CD patients are associated with pain [1]. Additionally, persistent, unhealed fissures can lead to perianal abscess/fistulae in up to 20 % of patients with CD; this presents quality of life issues for the patient and a treatment dilemma for the surgeon [2]. Classically, the pathognomonic, 'elephant ear' or 'cock's comb' skin tags associated with CD are usually painless. However, skin tags that don't have the classic appearance are more likely to be associated with a chronic fissure, which is commonly characterized by pain. The long standing teaching has been to avoid removing these skin tags for fear of much more significant complications such as anal stenosis, sepsis or fecal inconti-

N.M. Saur, MD • J.I.S. Bleier, MD, FACS, FASCRS (✉)
Division of Colon and Rectal Surgery, Department of Surgery, University of Pennsylvania Perelman School of Medicine, 800 Walnut St. 20th Floor, Philadelphia, PA 19107, USA
e-mail: Joshua.Bleier@uphs.upenn.edu

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nence [3–5]. The primary thrust of this chapter will focus solely on the management of the painful anal fissure, rather than the incidental tag.

When chronic anal fissures in patients without CD fail to respond to conservative measures, limited lateral internal sphincterotomy (LIS) is performed with a high degree of success and limited morbidity. In the setting of active anorectal CD, however, even a minor anorectal procedure may carry an enhanced risk of morbidity, including wound complications, anorectal sepsis, fistulous disease and incontinence [1, 6]. Thus, a significant degree of caution must be applied when managing the refractory symptomatic fissure in the setting of CD.

Search Strategy

A MEDLINE search was conducted for the past 25 years (1990–2015) secondary to the paucity of the literature. Search terms included 'anal, fissure, Crohn's, and perianal, inflammatory bowel disease, skin tag'. Table 4.1 summarizes the population, intervention, comparator, and key outcomes (PICO) for the patient population.

Data Review/Recommendations

A review of the literature is summarized in Table 4.2 and the quality evaluated using the GRADE system. The studies in the literature are all retrospective small studies with little power and no standardization of outcomes. Only a single study compared botulinum toxin (Botox) to LIS after failure of medical management. D'Ugo et al compared Botox with or without fissurectomy to LIS. However, in patients with confirmed CD, Botox was performed instead of LIS and therefore there is no comparison between Botox and LIS in known CD patients [2]. Lozynskyy et al reported a 75 % healing rate with medical management in CD patients and reported they had not performed surgical treatment of a fissure associated with CD in the last 5 years of their study [7]. Fleshner et al reported a 50 % healing rate with medical fissure management. They then compared fissure healing rates when patients underwent anorectal procedures versus bowel resection for proximal disease. They showed an

Table 4.1 PICO table for painful fissure associated with Crohn's disease

Patient population	Intervention	Comparator	Key outcomes
Patients with Crohn's disease and painful anal fissure	Lateral internal sphincterotomy (LIS)	Conservative medical management (including Botox injection in internal anal sphincter)	Morbidity, pain resolution/ healing, need for additional intervention

Table 4.2 Literature reported outcomes and quality of evidence

Study	Patients (n)	Interventions (n)	Outcome classification	Healing (%) medical management	Healing (%) surgical management	Morbidity (%) surgical treatment	Quality of evidence (GRADE)
D'Ugo (2013) [2]	41, CD (22 with definitive diagnosis)	Medical management (27), surgical treatment (Botox/ fissurectomy vs LIS; 14)	Healing rate, complication rate	65.8	78.5 % (recurrences)	57.1	Very low quality
Lozynskyy (2009) [7]	60 CD	Medical management (45), surgical treatment (Maslyak's method; 15)	Healing rate	75	NR	NR	Very low quality
Fleshner (1995) [8]	56 CD (49 symptomatic)	Medical management (35), surgical treatment (LIS, fissurectomy, bowel resection; 15 (8 anorectal))	Healing rate	50	67	NR	Low quality

88 % healing rate with anorectal procedures (LIS, fissurectomy) versus 43 % with proximal bowel resection for active ileal or colonic CD [8].

Several additional retrospective studies have been performed but very little outcome data exists. For example, Wolkomir et al evaluated 25 CD patients undergoing 27 procedures for anal fissure. However, they did not directly report on the healing or complication rates in their study. They did describe a mean follow up of greater than 7 years and noted that 22 patients had a healed wound by 2 months; however, 11 patients subsequently developed anorectal pathology of whom three developed recurrent fissure [9]. Similarly, Sangwan et al studied 21 patients with anal fissure of whom six underwent LIS and one underwent fissurectomy. However, again, no outcome data was reported in this study [10].

Although it is stated in many review articles that LIS should be reserved for patients without active anorectal CD [1, 6, 11], active CD simply has not been assessed as a study variable in any recent literature. This may be because it is assumed to be unsafe to proceed with LIS in the setting of active CD. However, this assumption may not be valid, especially in the era of biologic treatment for CD, and should be validated in future studies.

In summary, there is a paucity of literature evaluating medical versus surgical management of painful Crohn's fissures. Additionally, the literature to date consists of low to very low quality retrospective studies with incomplete outcome data. To further clarify the treatment algorithm in the presence of CD, new, well-designed studies are needed, especially those comparing Botox to LIS in patients who have failed conservative medical management.

Personal View of the Data

Our approach to painful anal fissures in CD revolves around treating the underlying CD first in the setting of active anorectal CD. Multidisciplinary management is standard and medical management (eg biologics) is the first line treatment for perianal disease associated with CD. Conservative management to treat anal fissures is employed including optimization of bowel habits and a trial of topical nitroglycerin paste or calcium channel blocker cream. In the presence of a CD fissure failing medical management, Botox (20–50 units) can be injected on either side of the fissure into the internal sphincter muscle or in the intersphincteric groove for temporary paralysis. If Botox injection does not result in healing of the fissure, continued medical management should be undertaken with fecal diversion only as a last resort to palliate symptoms. LIS is not performed in the presence of active anorectal CD.

In patients without active anorectal disease, the algorithm is essentially the same as for patients without a diagnosis of CD. Medical management is attempted as a first line and followed by Botox injection or LIS in the event of an unhealed fissure (Fig. 4.1). Even in the apparent absence of active anorectal CD, the presence of an atypical fissure, or a fissure located anywhere other than the anterior- or posterior-midline, should raise suspicion for CD involvement.

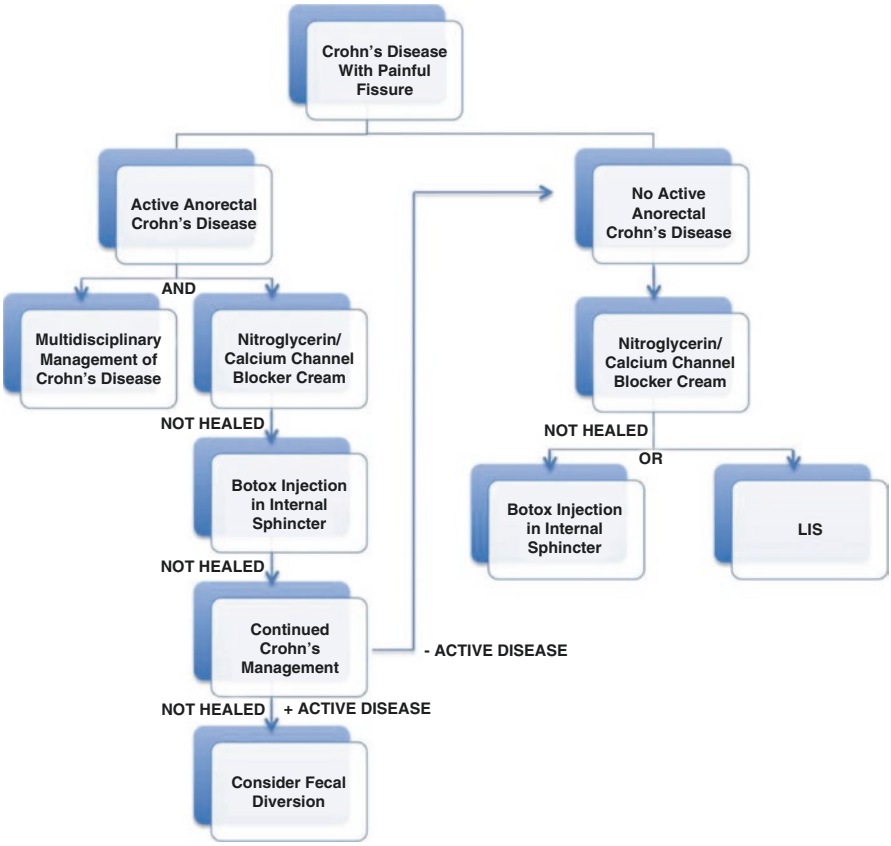

Fig. 4.1 Algorithm for management of fissure associated with Crohn's disease

In patients with Crohn's disease and asymptomatic anal fissure, medical management should be initiated. Surgical intervention is reserved only for patients with a persistent or recurrent fissure *without* evidence of active anorectal Crohn's Disease (evidence quality very low, weak recommendation).

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Chapter 5
IBD: Elective Surgical Management in Patients with Ulcerative Colitis-How Many Stages?

Roger D. Hurst

Introduction

For the last three decades, restorative proctocolectomy with J-pouch ileoanal anastomosis has been the primary treatment for ulcerative colitis patients who require surgery. While most patients requiring surgery for ulcerative colitis are young and are at baseline in good health, many are at least temporarily debilitated from either severity of disease, infection, malnutrition, obesity, or from side effects of immunosuppressant medications. These factors can greatly increase the risk for poor surgical outcomes both in the short and long term. Even when conditions are optimized, the ileoanal anastomosis is known to be a high risk anastomosis with frequent leaks and pelvic sepsis. Leak rates for the procedure are reported to be between 5 and 14 % [1]. This high risk for anastomotic dehiscence was recognized early in the development of the procedure and strategies have been implemented in the hopes of diminishing the risks and consequences of poor anastomotic healing. For these reasons performing the operation in multiple stages was the initial standard approach. However, the absolute need for staging has been questioned and many have advocated for a strategy of omitting the approach of multiple stages in selected cases and some have advocated for omitting staging in almost all cases [2–4]. This chapter will review the current available evidence to support the need for staging of the operations for the treatment of ulcerative colitis.

The ileoanal pouch procedure can be performed in either a single stage, two-step, or three-step approach [5, 6]. The decision points for the staging center around two separate issues (Tables 5.1 and 5.2).

R.D. Hurst, MD
Department of Surgery, University of Chicago Pritzker School of Medicine,
5841 S. Maryland Ave, Chicago, IL 60637, USA
e-mail: rhurst@surgery.bsd.uchicago.edu

N. Hyman, K. Umanskiy (eds.), *Difficult Decisions in Colorectal Surgery*,
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Table 5.1 Omission of diverting stoma

Pt population	Intervention	Comparator	Outcomes studied
Ulcerative colitis patient Undergoing ileo-anal procedure	Omission of diverting Stoma	Diversion of fecal stream	Anastomotic leaks, pelvic sepsis, long-term function, cost, length of hospital stay

Table 5.2 Total colectomy as initial operation

Pt population	Intervention	Comparator	Outcomes studied
Ulcerative colitis patient Undergoing initial surgery	Total abdominal Colectomy as initial operation	Ileo-anal anastomosis as initial operation	Anastomotic leaks, pelvic sepsis, long-term function, cost, length of hospital stay

1. When constructing the ileal pouch-anal reservoir and performing the ileoanal anastomosis, should the fecal stream be diverted from the pouch and the anastomosis with a loop ileostomy to allow for healing?
2. In patients who are temporarily debilitated, should a total abdominal colectomy with end ileostomy and de-functionalized Hartmann's pouch be performed to allow for physiologic recovery prior to undertaking the more risky reservoir construction and ileoanal anastomosis?

This chapter will review each of these controversies.

Search Strategy

A medline Ovid database search was performed on publications from 1985 through October 2015 comparing ileal pouch-anal anastomosis with or without diverting loop ileostomy. MeSH search headings utilized: restorative proctocolectomy, ileo-anal, ileo-anal anastomosis, ileal pouch, ileal reservoir, ileostomy, loop ileostomy and infliximab. References found from these articles were also searched and reviewed. Additionally "Find Citing Articles" function was utilized to further enhance the extent of the search.

Results

Diverting Loop Ileostomy

Multiple reports have been published regarding the value of diverting loop ileostomy when performing pouch construction and creating the ileoanal anastomosis. No definitive conclusive study exists as each of these studies is flawed by either a lack of adequate numbers, poor study design, or significant bias. Many studies are retrospective reports comparing only highly selected cases. Case control studies do

exist, but again in most instances these studies involve highly selected patients or insufficient numbers. Further complicating matters, the results of these studies have been conflicting. Some studies suggest an increased risk for anastomotic leaks and pelvic sepsis when the diverting stoma is omitted [7–12] while other studies suggest that the presence of the stoma does not affect the rate of anastomotic complications [13–29]. The studies supporting and opposing the use of a temporary diverting stoma are listed in Tables 5.3 and 5.4.

Table 5.3 Studies supporting the use of diverting stomas

Author	Date	Study type	Patients with stoma	Patients without stoma	Quality of evidence
Cohen et al. [7]	1992	Retrospective, selected	87	71	Low
Tjandra et al. [8]	1993	Matched controls	50	50	Moderate
Williamson et al. [9]	1997	Selected	50	50	Low
Kienle et al. [10]	2003	Prospective cohort, Selected	27	32	Low
Weston-Petrus [11]	2008	Meta-analysis			Moderate
Mennigen et al. [12]	2011	Selected, retrospective	89	33	Low

Table 5.4 Studies supporting omission of diverting stoma

Author	Date	Study type	Patients with stoma	Patients without stoma	Quality of evidence
Everett et al. [13]	1990	Selected	35	29	Low
Matikainen et al. [14]	1990	Consecutive	21	25	Low
Galandiuk et al. [15]	1991	Retrospective matched controls, selected	37	37	Low
Grobler et al. [16]	1992	Randomized control study, selected	23	22	Low
Sagar et al. [17]	1992	Consecutive, selected	28	30	Very Low
Gorfine et al. [18]	1995	Retrospective, selected	69	74	Low
Gullberg et al. [19]	1995	Consecutive	7	13	Low
Hainsworth et al. [20]	1998	Selected	30	72	Low
Antos et al.	1999	Selected	20	23	Low
Dolgin et al. [22]	1999	Consecutive, prospective nonrandomized	14	16	Low
Mowschenson et al. [23]	2000	Retrospective, selectided	28	102	Low
Heuschen et al. [24]	2001	Matched controls, selected	144	57	Moderate
Lepisto et al. [25]	2002	Retrospective	154	332	Moderate
Ikeuchi et al. [26]	2005	Retrospective, selected	92	150	Low
Remzi et al. [27]	2006	Retrospective, selected	1725	277	Low
Joyce [28]	2010	Retrospective	715	120	Low
Gray et al. [29]	2012	Selected	28	22	Low

A common design strategy employed in many of these reports is to allow the operative surgeon to make a judgment regarding the need for the loop ileostomy (those with "selected" study designs as designated in Tables 5.3 and 5.4). The surgeon therefore decides who is at high risk and then places these patients in the diverted group and patients judged to be a low risk are placed in the un-diverted group. While this strategy may well be a reasonable approach in the management for patients undergoing surgery for ulcerative colitis, when applied to a clinical study, this method of patient selection creates bias such that interpretation of the results can be difficult. So when such studies show no difference between the two groups, it would be difficult to conclude that there is no benefit to the loop ileostomy.

The absence of a difference between the two groups may result from the loop ileostomy effectively taking high risk patients and decreasing their risk to that of the lower risk group. It should also be noted that there are several studies with results that would indicate that even in patients selected in this manner, those without a loop ileostomy have an inferior outcome [7, 9, 12].

So one can really only claim that patients judged to be at low risk for anastomotic complications will do as well as a high risk cohort when the loop ileostomy is omitted.

There is only one randomized controlled trial looking at the value of diverting loop ileostomy in restorative proctocolectomy [16]. But this study was markedly underpowered with only 23 patients in the loop ileostomy group and 22 patients in the un-diverted group. In each group there is only one incidence of anastomotic leak; even with this study the patients that were randomized had been preselected by the operating surgeon as having had a low risk for anastomotic leak.

Perhaps the best the available study to suggest that loop ileostomy may not be necessary is a matched-pair controlled study conducted by Heuschen et al. [24] In this study 57 patients in the study group (no diversion) were compared to 114 matched controls. Heuschen et al. found no significant differences in early complications including pouch related septic complications. Conversely, Tjandra, et al., also reported a study with matched controls with 50 patients in each group and found a 14 % risk for anastomotic leak and pelvic sepsis in patients who had not been diverted compared to 4 % in the controls [8].

In 2008, Weston-Petrides published a meta-analysis for the data available from 1978 through 2005 from all comparative studies looking at restorative proctocolectomy with or without covering ileostomy [11]. This analysis indicated that restorative proctocolectomy without a diverting loop ileostomy resulted in similar long-term functional results but was associated with an increased risk for anastomotic leak and pelvic sepsis. The conclusion of the authors was that the loop ileostomy should only be omitted in carefully selected patients.

The goal of avoiding an anastomotic leak is worthwhile as poor anastomotic healing has major consequences both in the short and long term. Pelvic sepsis after ileal pouch-anal anastomosis has significant effects on long-term outcomes. For instance, patients who experience pelvic sepsis are five times more likely to require excision of their pouches when compared to those patients who avoided anastomotic

leakage and pelvic sepsis [1, 30, 31]. Those patients who have pelvic sepsis but are able to retain their pouches are more likely to have anal incontinence [1].

While many of the studies looking at the value of fecal diversion focus on the risk for anastomotic leak, there are other considerations that come into play when deciding which operative strategy is best for the patient. Studies looking at the total length of stay and total costs have favored the approach of performing the ileoanal anastomosis without a loop ileostomy. While performing the operation in a single step tends to lead to a longer initial hospitalization, when the length of hospital stay for the reversal of the loop ileostomy is taken into account, the total hospitalization is shorter with the one step approach [9, 12, 14, 16–18, 20, 21, 26, 28]. Additionally total costs have been shown to be lower in those patients undergoing the procedure without a diverting loop ileostomy [28].

When considering a staged approach the morbidity associated with the loop ileostomy itself must also be considered [32]. Some have suggested that the overall morbidity associated with loop ileostomy is substantial [33], but others have noted that severe complications are not frequent [34]. Additionally a large study published in 2005 involving 1504 patients from the Cleveland Clinic demonstrated that closure of the ileostomy can be accomplished with an overall complication rate of 11.4 % and a risk of intra-abdominal sepsis of only 1 % [35].

Initial Colectomy Prior to IPAA

The value of an initial total abdominal colectomy prior to ileal pouch-anal anastomosis in patients with intra-abdominal sepsis or severe co-morbid disease has not been subject to comparative studies, as the risks to these sick patients would be difficult to justify. However, reports of patients who have undergone either a two or three step approach have identified certain parameters under which a three stage approach would be prefered [36–38]. Traditionally these have included urgent surgery, sepsis, fulminate disease, anemia, hypoalbuminemia, steroids, and uncertain diagnosis [3, 5, 38, 39].

A more recent and significant controversy surrounds the risks for perioperative complications for patients who are being treated with anti-TNF agents. In 2005 the anti-TNF antibody, infliximab, was approved for use in patients with ulcerative colitis [40]. Shortly after the widespread use of infliximab for the treatment of ulcerative colitis, the Mayo Clinic and the Cleveland clinic both reported a substantial increase in postoperative related infectious complications in ulcerative colitis patients treated with infliximab [41, 42]. This finding is not entirely consistent across all reports and is somewhat surprising, given that infliximab had been used for many years in the treatment of Crohn's disease and no significant increase in perioperative complications had been seen in these patients [43–49]. This may be explained by the fact that the ileal pouch-anal anastomosis is normally a high risk anastomosis even under ideal conditions. It may well be that infliximab generates a relatively small effect on healing in general, but that this effect is magnified in this very delicate anastomosis.

In response to the findings suggesting that anti-TNF therapy increases risk for anastomotic leaks, many surgeons have changed their approach to the surgical management by utilizing a three-step approach in patients treated with anti-TNF agents [50, 51]. In a study from the Cleveland clinic Gu et al. looked at patients undergoing surgery for ulcerative colitis without an initial total abdominal colectomy [50]. They found that those patients on anti-TNF therapy had a significantly greater risk for pelvic sepsis (32 % versus 16 %; p = 0.012) when the procedure is not staged with an initial total abdominal colectomy. However, they reported no difference in outcomes between the patients who had been treated with anti-TNF therapy as compared to those who had never been treated with anti-TNF agents when patients initially undergo a staged colectomy. These findings not only indicate that the use of anti-TNF therapy increases the risk for septic complications, they also indicate that utilizing an initial total abdominal colectomy can mitigate the negative effects of the anti-TNF agents.

Recommendations Based on the Data

1. A diverting loop ileostomy may be omitted in highly selected patients undergoing ileal pouch-anal anastomosis. (Weak Recommendation based upon low-quality of evidence)

From the current available data it is difficult to give strong recommendations as to appropriateness of omitting a diverting loop ileostomy with restorative proctocolectomy. Even investigators intimately involved in the subject have had difficulties with this. For instance in 1992 Sagar, et al. initially reported a comparison of one stage versus two-stage ileoanal procedures and found no significant difference in the risk for anastomotic leaks or other complications and concluded that omission of the loop ileostomy may be a reasonable option in selected patients [17]. The same group later reported in 1997 that with further experience, they found that patients undergoing a one stage restorative proctocolectomy had significantly higher risk for severe septic complications and cautioned against the routine use of a one stage proctocolectomy [9]. Similarly, Tjandra et al. initially reported 1994 a matched control study and found that in equally favorable cases restorative proctocolectomy without diversion was not as safe as with diversion [8]. The same institution later reported a retrospective study indicating no difference in septic complications [27]. The senior author on both of these studies subsequently co-authored a meta-analysis indicating that restorative proctocolectomy without a diverting ileostomy was associated with an increased risk for anastomotic leak [11].

Even with these difficulties, there is general consensus among experts that the diverting loop ileostomy can be omitted in highly selected patients. And this has been the recommendation from expert panels from both Europe and North America [52, 53]. Patient selected for omission of loop ileostomy are best not to have any of the risk factors listed in Table 5.5. Despite the recommendations from these expert

Table 5.5 Factors that may increase risk for poor anastomotic healing

1. Severe or fulminate colitis
2. Sepsis
3. Malnutrition
4. Hypoalbuminemia
5. Obesity
6. Technical difficulties
7. Steroid use
8. Use of immunosuppressants
9. Technical concerns
10. Tension on anastomosis
11. Fecal contamination
12. Anemia
13. Anti-TNF therapy

panels that omission of the loop ileostomy is reasonable in selected patients, many practicing surgeons appear to adopt a very conservative approach to this issue. A recent survey of colorectal surgeons in North America indicated that 73 % would perform a diverting loop ileostomy even in low risk patients [54].

2. Ulcerative colitis patients with sepsis, severe comorbid factors, or who have been treated with anti-TNF therapy should undergo an initial total abdominal colectomy prior to ileal pouch-anal anastomosis. (Weak recommendation based upon low-quality of evidence)

There is little controversy that the sickest of patients should undergo a three stage approach. At the same time, there is insufficient evidence to accurately delineate the circumstances in which the three stage approach is the best option. Early evidence suggests that the use of anti-TNF therapy poses a risk for increase in anastomotic leaks and pelvic sepsis and that these risks can be diminished by utilizing a three-stage approach [50]. Further study, however, is required to confirm the advantage of this approach.

A Personal View of the Data

Unfortunately the data on the value of staging the surgeries for the ileoanal procedure are conflicting. Thus, it is truly a difficult decision as to whether to omit the diverting loop ileostomy. Likewise it is also a difficult decision as to when to perform an initial total abdominal colectomy prior to the ileoanal procedure. Ultimately it is up to the discretion of the experienced surgeon working in concert with the patient's wishes to determine the best approach for each individual case.

In the past as many as one third of this author's patients underwent an ileoanal procedure in a single step. With the advent of anti-TNF therapy, this however has changed and now most patients in my practice undergo surgery with a staged

approach. The reports of poor anastomotic healing with anti-TNF therapy are concerning. This combined with my personal, albeit anecdotal, experience with anastomotic problems in patients receiving anti-TNF therapy has made staging in my practice much more common. Additionally, the decision to stage the operations has become somewhat more attractive with the advent of laparoscopic surgery. The decrease morbidity and enhanced recovery after laparoscopic total abdominal colectomy makes the decision for staging easier to accept as it is much better tolerated than an open procedure [55].

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Chapter 6
Which Ulcerative Colitis Patients Should Not Have Ileal Pouch-Anal Anastomosis

Scott A. Strong

Approximately 10–15 % of patients diagnosed with ulcerative colitis will ultimately require operative management of their disease [1, 2], and proctocolectomy with ileal pouch-anal anastomosis (IPAA) has evolved into the most commonly performed procedure [3, 4]. However, not all patients are best managed by a proctocolectomy and ileal pouch-anal anastomosis, and some are better served by undergoing another operation such as proctocolectomy with end ileostomy. The most appropriate choice of operation is largely predicated upon multiple patient-dependent variables that may impact long-term outcome best measured as health-related quality of life.

PICO table

Patients	Intervention	Comparator	Outcome
Patients with ulcerative colitis requiring operation	Proctocolectomy with ileal pouch-anal anastomosis	Proctocolectomy with end ileostomy	Health-related quality of life (HRQOL)

Search Strategy

A comprehensive literature search of Cochrane Database of Collected Research, EMBASE, MEDLINE, and PubMed was performed to identify all of the English-language publications related to ulcerative colitis, colectomy, and ileal pouch-anal

S.A. Strong, MD, FACS, FASCRS
Chief, Gastrointestinal and Oncologic Surgery, Surgical Director, Digestive Health Center, Northwestern Medicine James R. Professor of Surgery,
Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: sstrong2@nm.org

N. Hyman, K. Umanskiy (eds.), *Difficult Decisions in Colorectal Surgery*,
Difficult Decisions in Surgery: An Evidence-Based Approach,
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anastomosis and quality of life (QOL) outcomes from 1985 to 2015. Key search terms included the following: “colectomy,” “colitis,” “ileal pouch-anal anastomosis,” “inflammatory bowel disease,” “proctocolectomy,” and “ulcerative colitis.” Studies were excluded if they did not directly contrast proctocolectomy with ileal pouch-anal anastomosis to proctocolectomy with ileostomy, failed to measure any component of health-related quality of life, included patients with Crohn’s disease or familial adenomatous polyposis, included only patients with ulcerative colitis plus specific conditions (e.g., primary sclerosing cholangitis), or included pediatric patients. Only the most recent study was included if similar studies from the same institution were encountered. The references of the included studies were reviewed to identify additional studies that were incorporated as appropriate.

Results

Over the past three decades, only a few studies have reported health-related quality of life outcomes in patients with ulcerative colitis undergoing proctocolectomy and ileal pouch-anal anastomosis or ileostomy. Some of the initial studies were plagued by poor methodology using quality of life metrics that had not been validated. However, reports published in past 15 years have tended to use validated global, generic, or disease-specific instruments to measure health-related quality of life [5–12].

Studies that employed global instruments to contrast health-related quality of life between patients who underwent proctocolectomy and ileal pouch-anal anastomosis or ileostomy reported conflicting results. Emblem and associates [5] used a non-validated questionnaire that showed patients managed by an ileostomy were markedly more likely to experience social restrictions. While McLeod et al. [6] found no differences in several global measures, Kuruvilla and colleagues [11] reported the Cleveland Global QOL was significantly better for patients with an ileal pouch-anal anastomosis, particularly related to current energy level and current quality of health.

Of the studies using a generic measure, no difference in scores was found between the two patient groups regardless whether the non-validated “lifestyle satisfaction score,” [7] validated EuroQol Group’s EQ-5D-3 L questionnaire [11], or validated Short Form (SF)-36 Health Survey [9, 10] was used. However, O’Bichere and associates [8] used a questionnaire developed in-house to specifically measure seven selected items, and they found patients with an ileostomy were significantly less bothered by altered bowel emptying and diet.

A disease-specific instrument, the Inflammatory Bowel Disease Questionnaire (IBDQ), was employed in three studies [9, 10, 12] and an abbreviated version, the short (S) IBDQ, was used in another report [11]. No differences in scores were found between the two groups in any of the studies [9–12], but van der Kalk et al. [12] did report ileal pouch-anal anastomosis patients had higher quality-adjusted life years compared to ileostomy patients.

Health-related quality of life is obviously a different outcome measure than morbidity. But, it is interesting that the morbidity rate of ileostomy patients was higher in three of the four studies that reported this outcome parameter [5, 6, 10, 12].

Study	Patients (N) IPAA *vs* Ileostomy	QOL measure	Results IPAA *vs* Ileostomy	Quality of evidence
Emblem [5]	19 *vs* 35	Social restriction	0 % *vs* 67 % (P < 0.05)	Low
McLeod [6]	37 *vs* 28	Direct questioning of objections Sickness-Impact Profile Time trade-off	Comparable Comparable Comparable	Moderate
Liddell [7]	25 *vs* 10	Lifestyle satisfaction	Comparable	Low
O'Birchere [8]	30 *vs* 30	SF-36 Altered bowel emptying Body image Clothes Diet Noise Odor Sexual relationship	Comparable 8 *vs* 5 (P = 0.01) Comparable Comparable 5.5 *vs* 2 (P = 0.02) Comparable Comparable Comparable	Moderate
Nordin [9]	56 *vs* 42	IBDQ SF-36	Comparable Comparable	Moderate
Camilleri-Brennan [10]	19 *vs* 19	IBDQ SF-36	Comparable Comparable	High
Kuruvilla [11]	35 *vs* 24	EQ-5D-3 L Cleveland QOL FIQL SIBDQ	Comparable 0.9 *vs* 0.8 (P = 0.03) Comparable Comparable	Moderate
van der Valk [12]	81 *vs* 48	IBDQ Quality-adjusted life years	Comparable 0.9 *vs* 0.84 (P < 0.01)	High

Recommendations

Patients requiring an operation for ulcerative colitis can undergo proctocolectomy and ileostomy rather than proctocolectomy and ileal pouch-anal anastomosis without compromising their health-related quality of life. (Evidence: moderate; Recommendation: strong)

Patients needing surgery for ulcerative colitis are typically offered a proctocolectomy and ileal pouch-anal anastomosis in one, two, or three stages with the two-stage approach most often employed in elective scenarios. However, this restorative procedure is occasionally contraindicated because of disease-related complications, unachievable for technical reasons, or ill-advised due to excessive risk for operative morbidity or impaired quality of life. In these selected settings, proctocolectomy and ileostomy may be offered, and the patient can be reassured that her/his health-related quality of life will be comparable to that associated with a sphincter-sparing procedure.

Personal View

Patients with colorectal adenocarcinoma complicating their ulcerative colitis need to undergo a sound oncologic operation. If the tumor encroaches upon the sphincter mechanism, excision of the levators and anal canal is usually required, and a sphincter-sparing procedure such as an ileal pouch-anal anastomosis is contraindicated. Colorectal cancers that have metastasized to distant sites are commonly managed with chemotherapy unless bleeding or obstruction mandates resection or diversion. Regardless, a restorative proctocolectomy and ileal pouch-anal anastomosis would be generally contraindicated because it would potentially delay the more important systemic therapy.

Management of adenocarcinomas of the mid or lower rectum penetrating the muscularis propria or involving one or more mesorectal lymph nodes without distant metastases usually entails a combination of chemotherapy, radiotherapy, and resection. If the tumor is situated above the anorectal ring, a sphincter-sparing operation can be performed. However, patients receiving pre-operative external beam radiotherapy are at increased risk for ileal pouch failure secondary to pouch dysfunction [13] despite no significant increase in operative morbidity [14]. Pouch failure also occurs more frequently in patients receiving post-operative radiotherapy [15]. Accordingly, an ileal pouch-anal anastomosis should be likely avoided in many patients with ulcerative colitis and rectal cancer when management requires external beam radiotherapy.

Successful restoration of bowel continuity after proctocolectomy warrants construction of a tension-free ileal pouch-anal anastomosis. Patients with visceral obesity may have a shortened mesentery that physically precludes reach of the ileal pouch to the anal canal. In those where reach can be achieved, the risk for pouch-related complications (e.g., anastomotic separation, anastomotic/pouch stricture, pouch fistula) is generally increased [16–18].

Proctocolectomy and diverted ileal pouch-anal anastomosis is an operation associated with a relative high risk for operative morbidity. Specifically, stricture, pelvic sepsis, and fistula occur in 10.7 %, 7.5 %, and 4.5 % of patients, respectively [19], and hemorrhage complicates 3.6 % of the operations [20]. Patients with cardiac disease, pulmonary disorder, or renal impairment can expect an even greater likelihood

of experiencing a post-operative complication. These co-morbidities in isolation or combination can introduce prohibitive risk that serves as a relative contraindication to proctocolectomy and ileal pouch-anal anastomosis.

Patients with primary sclerosis cholangitis complicating their ulcerative colitis represent a special group of patients because some are at greater risk for compromised outcomes following proctocolectomy with ileal pouch-anal anastomosis. An ileal pouch operation in a cirrhotic with primary sclerosis cholangitis is associated with a high incidence of early post-operative complications such as bleeding (44 %), worsening liver function (31 %), and pelvic abscess (19 %) [21]. Pelvic sepsis is a particular concern in this population because of its link with patient death [21].

Regardless of the degree of liver dysfunction, patients with primary sclerosis cholangitis and ulcerative colitis are at significantly greater risk for acute pouchitis and tend to have worse ileal pouch function compared to those without primary sclerosis cholangitis [22]. Moreover, patients with large duct primary sclerosis cholangitis experience even worse pouch function and a significantly compromised quality of life [22].

Liver transplantation prior to proctocolectomy and ileal pouch-anal anastomosis can ameliorate some problems, and these patients can expect an acceptable risk for operative morbidity and reasonable pouch function [23].

Another cohort of patients who may experience impaired ileal pouch function and diminished quality of life are those with low (<40 mmHg) pre- and post-operative anal sphincter resting pressures. These reduced pressures are associated with an increased incidence of pad usage, seepage, and incontinence as well as reduced quality of life and satisfaction with surgery that do not improve over time [24]. Similarly, patients with pre-operative fecal incontinence unrelated to urgency are not good candidates for an ileal pouch-anal anastomosis because of the same reasons. However, a patient with pre-operative continence despite an anterior sphincter defect does not usually experience a similar outcome [25].

Selected patients with absent proctitis, adequate rectal compliance, and reasonable sphincter strength are potential candidates for colectomy and ileoproctostomy [26]. In these cases, the benefits of less operative morbidity, preserved female fecundity, and reasonable function must be weighed against the risk of neoplasia and recurrent disease. The likelihood of the patient requiring a proctectomy is 16–26 % at 10 years and 31–54 % at 20 years [4].

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Chapter 7
Management of Pouch-Vaginal Fistulas

Ido Mizrahi and Steven D. Wexner

Introduction

Since the initial description of restorative proctocolectomy in 1978 by Parks and Nicholls [1], the stapled ileal-pouch anal anastomosis (IPAA) has evolved into the mainstay surgical treatment for most patients who require surgery for ulcerative colitis (UC) and many others with familial adenomatous polyposis (FAP) [2–5]. Pouch vaginal fistula (PVF) is a specific complication after IPAA, first reported by Wong et al. in 1985 [6]. Though not a common problem, with reported incidence rates ranging from 2.9 to 16.7 % [7–19], PVF is a source of considerable morbidity for the patient and a technical challenge for the surgeon. PVF typically presents in the first year after surgery; however, a late presentation might occur even after 10 years from surgery. The optimal management of PVF is not yet determined due to the relative paucity of published data. Most authors agree that the management depends on four basic etiologic/clinical factors: surgery related, sepsis related, disease related, and the location of the fistula.

Surgical technique in any operation is important for successful clinical results, especially in complex procedures such as IPAA. In fact, increased experience has been shown to decrease complications after IPAA [20, 21]. Tissue ischemia at the anastomosis must strictly be avoided and therefore a tension-free anastomosis with good blood supply should be obtained. It is crucial not to damage the rectovaginal septum or "button hole" the vagina when dissecting the rectum, and to avoid incorporation of the posterior vaginal wall when firing the stapler. If identified at the time of surgery, the anastomosis can be disconnected, the vagina repaired, and a hand-sewn anastomosis re-constructed.

I. Mizrahi, MD • S.D. Wexner, MD, PhD (Hon) (✉)
Department of Colorectal Surgery, Cleveland Clinic Florida, Weston, FL, USA
e-mail: wexners@ccf.org

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Despite this specific mechanism of injury associated with the double stapled technique, large scale studies have shown no difference in the incidence of PVF after stapled and hand-sewn anastomosis [18, 22–25]. Further, it is important to note that a stapled anastomosis is likely to be more cephalad. Therefore pouch advancement to the dentate line is more likely to be a good remedial option when PVF complicates a stapled anastomosis. Conversely, following an index hand-sewn anastomosis, pouch advancement may not be a viable option. As for pouch type, Wexner et al. found no difference in the incidence of PVF for different pouch types [15].

Pelvic sepsis remains a major determinant in the development of PVF, as highlighted by the high rate of this complication in patients with PVF. Groom et al. [14] found that 65 % of patients with PVF had pelvic sepsis compared with 16 % without PVF. Wexner et al. [15] reported pelvic sepsis in 35 % of their PVF patients. Lee et al. [23] found a significantly greater incidence of pelvic sepsis in patients with a PVF than in those without (26.3 % vs. 6.3 %; $p = 0.003$). Pelvic sepsis can either be ascending – originating from a disrupted anastomosis, or descending – resulting from an intraoperative contamination or a pelvic hematoma [15, 23]. These mechanisms further emphasize the importance of meticulous technique with attention to hemostasis, contamination, and a tension-free anastomosis with adequate blood supply. Furthermore, pelvic sepsis might be caused by cryptoglandular perianal disease, which is more common in patients with colitis and may lead to an anovaginal fistula [8]. Typically, PVF of cryptoglandular origin is associated with an internal opening of the fistula below the IPAA. A series from St Mark's Hospital reported 2 out of 17 PVFs arising below the IPAA and most likely independent of the original pouch procedure [14].

Careful review of appropriate histopathologic materials by an expert gastrointestinal pathologist may be crucial to future management options. This step is especially true for the small percentage of patients, approximately 2–3 %, who undergo IPAA for UC only to find the long-term diagnosis is Crohn's disease (CD). Lee et al. [23] found a high correlation between PVF and CD, with 12 of the 23 women (52 %) with a preoperative diagnosis of UC eventually diagnosed with CD. Other studies have shown similar results. The average time to development of a PVF is typically longer in patients with CD. Importantly, these patients suffer from a significantly higher rate of pouch failure and ultimately excision. Patients who undergo IPAA for indeterminate colitis also have a high rate of pouch complications including PVF and pouch failure [26]. However, patients whose indication for surgery is familial adenomatous polypos present with a significantly low rate of PVF when compared to IBD patients [27, 28], implying inflammation plays a role in the pathogenesis of PVF.

Patients with PVF may be asymptomatic or present with minor symptoms. They may also present with severe symptoms such as vaginal discharge of fecal material or gas, recurrent vaginitis, and vulvar irritation. Some cases of asymptomatic PVF are found on routine pouchography prior to ileotomy closure. Once PVF is

suspected, further investigation is needed to confirm the diagnosis and establish its nature. As noted above, the surgeon should request the pathology slides for expert pathology review. If not clinically evident, a perineogram and a water soluble contrast pouchogram may help to diagnose the presence and the level of the fistula tract. Imaging with computed tomography (CT) scanning, ideally with contrast enema, may also help to identify fistulous tracts, although magnetic resonance imaging (MRI) (T1 weighted with fat suppression and IV gadolinium) is preferable. In expert hands, endoanal ultrasound is also helpful in detecting sphincter deformity, especially in women with a history of vaginal delivery. However, the reliability of endoanal ultrasound is poor for fistula detection because the fistulous tracts in PVF are short and wide.

Although clinical examination in the office will often confirm the diagnosis, careful examination under anesthesia (EUA) may be preferable. EUA allows access to the fistula and excludes associated sepsis while overcoming the potential limitations of patient discomfort. It also allows identification of the level of the internal opening, its relation to the anastomosis (usually the staple line), the direction of the tract, and the location of the external orifice in relation to the vaginal wall, vaginal fourchette, labia, or perineum. While most tracts are short and straight, they can be complex and branched, and a low PVF can mask the presence of a higher fistula from the pouch-body to the mid-body of the vagina. If necessary, introduction of dye, such as methylene blue, into the pouch with white swabs in the vagina to identify staining is useful. Alternatively, for low fistulae, hydrogen peroxide gently instilled into the anus may demonstrate bubbles as they emerge from the vaginal opening. Lastly, patients should typically undergo anal manometry to assess the sphincter pressures, and a pudendal nerve terminal motor latency study to assess for neural impairment, especially in women after childbirth.

Search Strategy (See Table 7.1)

A literature search was carried out to identify articles on PVF. The search was done on the electronic databases PubMed, Embase, and Medline, from 1980 to December 2015. The main search terms used were ‘pouch-vaginal fistula’, ‘ileoanal pouch-vaginal fistula’ or ‘anal pouch-vaginal fistula’.

Table 7.1 Search Strategy

P (patients)	I (intervention)	C (comparator)	O (outcomes)
Patients who underwent restorative proctocolectomy with ileal pouch anal anastomosis and developed pouch-vaginal fistula	See Table 1	Not applicable	Fistula healing Pouch retention

Results

Many procedures have been proposed for the treatment of PVF, most of them adopted from rectovaginal fistula repairs [29, 30]. The procedures can basically be divided into those performed via a perineal approach or via an abdominal approach. Of note, there are no randomized controlled trials and only one systematic review on the management of PVF. All studies provide level IV evidence. Significant heterogeneity, a small number of patients, and differing reporting practices preclude meta-analysis of the data. Pooled results for the different types of PVF repair are presented in Table 7.2.

Perineal Approach

Seton Drain A draining seton is mainly used for establishing drainage of an associated abscess and for defining the fistula tract. Keighley et al. [12] reported a success rate of 25 % in patients with the use of a seton as definitive treatment. However, Wexner et al. (0/2) [15], Mallick et al. (0/3) [10] and Shah et al. (0/5) [18] all reported 100 % failure rates. Tsujinaka et al. [31] showed complete healing in one patient with an asymptomatic fistula. Arguments against its use are that the seton may damage any residual anal sphincter, which is already thinned out in many women, and that it may encourage further leakage. To date, there is no evidence to

Table 7.2 Pooled results for the different types of PVF repair

Type of repair	Success rate
Perineal approach	
Seton [10, 12, 15, 18, 31]	5/15 (33 %)
Fistulectomy [12, 14, 15]	3/22 (14 %)
Biological Collagen plug [33] Fibrin glue [31, 42]	0/11 (0 %) 2/6 (33 %)
Transanal ileal advancement flap [9, 10, 14, 15, 18, 23, 31, 34]	81/173 (47 %)
Transvaginal [10, 12–15, 18, 35, 36]	48/79 (60 %)
Gracilis muscle interposition [15, 31, 37–39]	6/10 (60 %)
Trans-anal pouch advancement [19, 41]	2/4 (50 %)
Abdominoperineal approach	
(a) Abdominoperineal approach [10, 15, 16, 18, 19, 31, 42–44]	Overall success rates 50–75 %
Pouch advancement	8/16 (50 %)
Redo pouch	20/39 (51 %)
(b) Pouch excision 60/401 (15 %)	100 %

(a) Some studies not indicating different success rates for pouch advancement vs. redo pouch

(b) Number represents the percentage of patients eventually requiring pouch excision

support seton use except for initial control of sepsis before definitive repair. However, there are no studies to show whether use of a seton before definitive repair of PVF improves outcomes. One exception might be a fistula below the IPAA involving little or no sphincter muscle, where a draining seton followed by fistulotomy may be successful.

Fistulectomy Coring out of the fistula tract with repair of the internal opening at the pouch level has been described with disappointing results [12, 14, 15]. There is currently no evidence to support its use in the management of PVF.

Biological Therapy

The use of a collagen button plug to treat PVF was first reported by Gonsalves et al., with healing observed in 4/7 (57 %) of ileal pouch-vaginal fistulas at 16 weeks [32]. The technique involves securing the button portion of the collagen plug on the pouch side of the fistula with four dissolvable sutures. The button of the plug detaches within 4 weeks with the collagen matrix left in situ. Disappointingly, these results were not maintained long-term with 0/11 PVF successfully healed at 2 years [33]. Early success probably related to the persistence of the collagen plug within the tract, but failure of local tissue in-growth coupled with the relatively short length of PVF led to long-term failure. Given these results, the use of biological tissue plugs cannot be recommended for the management of PVF. Tsujinaka et al. [31] reported the instillation of fibrin glue in the fistula tract with complete healing in 1 patient with a minimally symptomatic fistula and failure in 2/3 symptomatic patients who eventually required pouch advancement and a redo pouch.

Transanal Ileal Advancement Flap

An ileal pouch advancement is essentially a variation of the mucosal advancement flap used for a high perianal fistula. A flap of mucosa and submucosa is mobilized from the ileal pouch, the internal opening is excised, and the flap is advanced and sutured beyond the internal fistula opening. Mallick et al. [10] reported healing rates of 42 % (20/48) when advancement flap was performed as a primary procedure and 66 % (4/6) when performed secondarily after a different procedure. Similar results have been reported by others. Tsujinaka et al. [31] showed healing rates of 60 % (6/10), while Shah et al. [18] and Ozuner et al. [34] reported success rates of 44 % (17/39) and 45 % (15/24), respectively. Lee et al. [23] had a slightly higher success rate of 50 % (10/20), with the rate increasing to 83 % (10/12) when excluding patients with CD. Wexner et al. [15] reported successful fistula healing in 8/16 patients with this approach in a survey of North American colorectal units, whereas Groom et al. [14] reported only one success in 10 attempts. Advantages of the ileal pouch advancement flap include the relative simplicity of the procedure and that the flap has more distal mobility [9]. The disadvantages of this approach include the

suboptimal exposure, the risk of damage to the sphincters in patients with borderline incontinence, and the fact that the flap lies on the high pressure side of the PVF. Circumferential advancement of the pouch is both technically easier and ensures more mobilization than does anterior or anterolateral flap advancement.

Transvaginal Repair

Sagar et al. [35] reported the results of transvaginal repair for PVF in 11 patients, each of whom had previously undergone an attempt to close the fistula with a collagen button plug. Nine (81 %) were successful at a median follow-up of 14 (6–56) months and the remaining two patients described symptomatic improvement. Burke et al. [36] published the St. Mark's Hospital experience with transvaginal repair for PVF in 14 patients. They reported total success in 11/14 patients (78 %), although 8 required multiple attempts to achieve long-term success. The largest series of transvaginal repair of PVF reported by Mallick et al. [10] from the Cleveland Clinic described a 55 % healing rate (15/27) when repair was performed as a primary procedure and 40 % (2/5) when performed secondarily after a different procedure. O'Kelly et al. [13] reported successful repair in 5/7 patients (71 %) with this approach, and once again some patients in this series required more than one attempt before complete healing was achieved. Others have reported success rates of 0 % (0/1) [18, 31], 27 % (3/11) [15], and 100 % (1/1) [12, 14]. The repair can also be augmented by placement of a collagen patch between the pouch and the vagina.

Advantages of the transvaginal approach include better exposure than the transanal approach, decreased risk of damage to the anal sphincters, and decreased tension. The procedure can be repeated if necessary and yields satisfactory results with relatively less morbidity. Possible complications include dyspareunia, although none of the patients reported dyspareunia in the series from St. Mark's [36], and hematoma because of the vascularity of the vagina. However, this risk can be minimized with meticulous technique, drainage, and use of a vaginal pack [13, 18]

Gracilis Muscle Interposition Flap

There are five small published series reporting on the utility of the gracilis muscle interposition flap specifically for the treatment of PVF. Gorenstein et al. [37] reported successful repair in two women with PVF. Previous attempts at local repair had failed in both patients and a simultaneous diverting loop ileostomy was constructed. Anterior sphincteroplasty was performed in one patient for associated incontinence. Wexner et al. [15] reported results of a multicenter study including treatment of PVF in 26 patients, 4 of whom underwent gracilis interposition flap with a 50 % success rate. In a later publication, Wexner et al. [38] published results of gracilis flap in 53 patients, two of whom for the indication of PVF. One patient had complete healing and the patient who did not heal was

eventually diagnosed with CD and opted to have a permanent ileostomy. Zmora et al. [39] published their experience with the gracilis interposition flap in 9 patients. Only one patient had a PVF and the fistula ultimately completely healed. Another report by Tsujinaka et al. [31] described one patient with a failed gracilis interposition. In general, interposition flaps are particularly useful after previous failed repairs as well as when abdominal procedures are contraindicated. The expected perioperative morbidity is 33–50 % and includes perineal wound infection, urethral stricture, fever, urinary retention, and perineal bleeding [38, 40]. Perhaps because of the technical challenge, the procedure seems to have been underused. This procedure should be preceded by fecal diversion. At present, the low reported numbers and the relative complexity of the procedure prevent it from being strongly recommended as a first-line treatment. Another form of flap used for treating rectovaginal fistulas is the martius flap; however results with treating PVF have not been published.

Transanal Pouch Advancement

The technique of transanal disconnection of the ileal pouch from the IPAA, advancement of the pouch, and re-suture at the dentate line can be employed in patients with PVF, especially in slimmer patients with demonstrable mobility of the pouch above the level of the anastomosis. As noted above, advantage of this procedure is that it allows healthy, full thickness tissue to be delivered to the perineum. This operation should be offered after stoma creation. Both Fazio et al. [41] and Heriot et al. [19] showed that this procedure was successful in 1/2 of their patients.

Abdominoperineal Approach

"High" PVF that arises from the mid-body of the ileal pouch requires a transabdominal approach. This approach may also be selected after failed local repairs and in patients with ongoing pelvic sepsis due to abscess cavities with granulation tissue that cannot be completely removed using a local approach. The pouch needs to be carefully mobilized down to the level of the pelvic floor with attention given to the anterior wall of the pouch and the posterior wall of the vagina. There are basically three surgical options: pouch advancement, pouch redo with a new handsewn IPAA, and pouch excision. The reported overall success rates for treating a PVF via the abdominoperineal approach are approximately 50–75 %[10, 15, 16, 18, 19, 31, 42–44]. Despite these relatively high success rates, it should be noted that transabdominal revision of the pouch is technically demanding, carries a significant risk of loss of the pouch [10, 16, 18], and an unsuccessful attempt may result in significant loss of small bowel with the risk of short gut syndrome. The patient needs to be fully counseled about these risks and preferably referred to a center of excellence in this field.

Diversion

A diverting ileostomy is commonly used in patients with PVF, mainly to control patient symptoms and pelvic sepsis and to divert fecal material from the repair. Some authors have reported healing with the ileostomy only [15, 31]; however, most authors combine construction of the diverting ileostomy either before or at the time of repair [10, 18, 23]. Lee et al. [23] found higher success rates (60 % vs. 45 %) when a diverting ileostomy was performed before a transanal pouch advancement. However, there is little evidence that a diverting ileostomy improves the chance of PVF healing. A permanent diversion, with or without pouch excision, is opted when all other attempts have failed.

Recommendations

As noted above, all studies provide low quality data, providing weak recommendations.

1. Patients presenting with pelvic sepsis should undergo EUA and seton drainage.
2. A diverting ileostomy should be considered for all patients before or at the time of repair.
3. Local repair should be attempted first for low PVF.
4. An abdominoperineal approach should be reserved for “high” PVF and failed attempts at local repair.

A suggested algorithm based on results and recommendations is presented in Fig. 7.1.

Personal View of the Data

The management of pouch complications such as PVF presents a major challenge to the surgeon. Therefore, these patients should ideally be referred to large volume experienced centers for a more optimal outcome. The surgeon should diligently study the patients’ prior relevant history including pathology and operative reports, as well as physiologic and imaging tests in order to tailor the correct procedure for each patient. Patient counseling includes explaining that successful treatment often requires several operations over a long time period in order to achieve healing. Patients with CD should also be aware of the higher rate of pouch failure they may encounter. Local repair via the perineal approach should be considered when dealing with a low PVF, and that the transanal ileal advancement flap, gracilis interposition, and pouch advancement are all viable options with equivalent success rates. The abdominoperineal approach should be left for high fistulas and those failing previous local attempts. Although not supported by high quality data, a laparoscopic

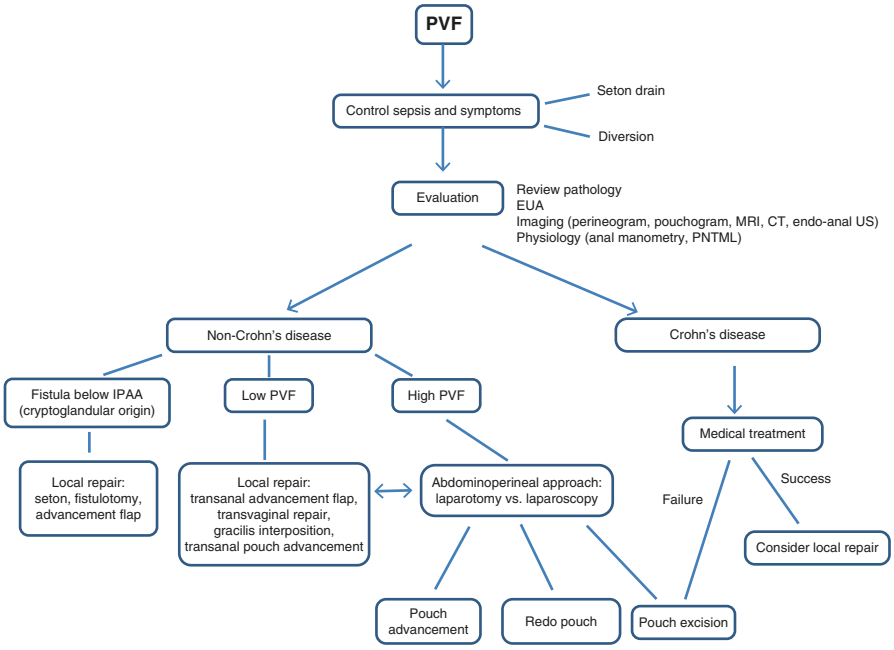

Fig. 7.1 Suggested treatment algorithm

diverting loop ileostomy before or at the time of repair offers the patient symptom relief, better sepsis control, and perhaps an increased chance of healing. It seems that no single procedure is appropriate for all cases of PVF; therefore the surgeon should be familiar with the existing armamentarium of treatment options and be continually updated on their success rates.

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Chapter 8
Crohn's Colitis and Ileal Pouch Anal Anastomosis

C. Peirce and Feza H. Remzi

Introduction

Traditionally, the ileal pouch anal anastomosis (IPAA) operation has not been offered to patients with Crohn's disease (CD). Patients with Crohn's colitis are often excluded from undergoing IPAA related to a number of key concerns: the risk of developing recurrent disease in the pouch necessitating pouch excision with possible ensuing short bowel syndrome, coupled with the risks of significant pouch dysfunction and the need for long-term medical therapy. However, surgical dogma is being challenged in more recent times with authors now reporting encouraging outcomes following IPAA in patients with either a preoperative or postoperative diagnosis of Crohn's colitis.

Patients with Crohn's colitis for whom an end ileostomy is not an acceptable option at that time have three potential reconstructive options to restore bowel continuity: ileorectal anastomosis, ileal pouch rectal anastomosis (IPRA) or ileal pouch anal anastomosis (IPAA), also known as restorative proctocolectomy. The first two restorative operations require either complete rectal sparing or sparing of the distal rectum whereas the latter is the only option to restore intestinal continuity in patients requiring proctectomy as a result of Crohn's proctitis. This chapter focuses specifically on these patients i.e., patients with documented CD of the colon and rectum requiring either a proctocolectomy or completion proctectomy after initial subtotal colectomy for disease management.

C. Peirce
Department of Colorectal Surgery, Cleveland Clinic, Cleveland, OH, USA

F.H. Remzi (✉)
Department of Colorectal Surgery, Digestive Disease Institute, Cleveland Clinic,
9500 Euclid Avenue – A30, Cleveland, OH, USA
e-mail: remzif@ccf.org

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Methods

A search of all English language PubMed articles from 1990 to 2015 was performed using the following terms: Crohn's disease, Crohn's colitis, ileal pouch anal anastomosis, restorative proctectomy, restorative proctocolectomy, completion proctectomy, proctocolectomy and ileostomy. These terms were in keeping with the PICO table below on which this chapter is based. All relevant articles were reviewed and appropriate references interrogated.

Patient Population	Intervention	Comparator	Outcomes studied
Crohn's colitis	Ileal pouch anal anastomosis (IPAA)	Proctocolectomy/completion proctectomy with end ileostomy	Pouch morbidity; pouch excision; quality of life

Results

There is a clear division in the literature regarding the outcomes of IPAA in CD in terms of the time of diagnosis of the primary disease. Studies divide the timing of the CD diagnosis as preoperative (resulting in an 'intentional' IPAA formation), perioperative (IPAA formation with 'incidental' or 'accidental' CD diagnosis on analysis of the surgical specimen) or at a later date following IPAA creation (so called 'delayed' diagnosis). A comparison of the data for these three distinct groups has been reported in prior studies. However, the ensuing recommendations and debate are based solely on those studies pertaining to patients with a documented diagnosis or high clinical suspicion of CD prior to undergoing IPAA, the aforementioned 'intentional' IPAA cohort.

The first published paper of 'intentional' IPAA formation in CD (patients in whom there was a high clinical suspicion based on the findings described below) was from Hyman and colleagues from the Cleveland Clinic in 1991 [1]. They reported on 25 patients with a postoperative pathologic diagnosis of CD out of 362 consecutive patients undergoing IPAA for a preoperative diagnosis of ulcerative colitis (UC). Of these 25 patients, 9 had preoperative features suggestive of CD: 5 with perianal disease (fistula, fissure or stricture), 2 with abnormal distribution of colonic disease, 1 with a cecal stricture and possible terminal ileal disease and 1 with a rectovaginal fistula. Although none of these 9 patients had a definitive preoperative diagnosis of CD, the above pathology would frequently be cited as a reason not to perform IPAA in cases with indeterminate pathology. At a mean follow-up of 34.8 months, only 1 of the 9 patients had a functioning pouch. Of the remainder, 1 died, 1 remained diverted and 6 had their pouch excised at a mean of 17.6 months postoperatively. The authors concluded that patients who manifest clinically as CD and have confirmatory pathology do very poorly following IPAA with short disease-free intervals and a high pouch failure rate.

Following this, Panis and colleagues published their initial results [2]. From 1985 onwards, they considered IPAA in selected CD patients in whom a proctectomy was required for either proctitis or rectal stenosis. Strict inclusion criteria were employed to ensure the disease was confined solely to the colorectum: all patients underwent an examination under anesthesia prior to IPAA to exclude anoperineal disease and also had a small bowel contrast study to exclude concurrent enteric disease. Eighteen patients were recruited over an initial 7-year period. These 18 patients were combined with a further 13 patients with a pre-IPAA diagnosis of indeterminate colitis (IC) which was subsequently shown to be CD in the postoperative specimen. This group then totaled 31 patients and reported outcomes were for the group as a whole (i.e., n = 31) and were not subdivided into the specific diagnostic timeframes of pre-operative (n = 18) or post-operative (n = 13) CD diagnosis. The results were encouraging: 6 patients had a CD-related complication with 2 of these ultimately requiring pouch excision and the remaining 4 patients reporting acceptable pouch function. Overall, 90 % of the cohort had a functional pouch at 5-year follow up. When compared with a corresponding ulcerative colitis (UC) cohort (n = 71) over the same time period, there was no demonstrable difference in terms of stool frequency, continence, gas/stool discrimination, leak or need for protective pads and sexual activity.

The same group subsequently reported on their experience with 41 patients, 26 of whom had a preoperative CD diagnosis [3]. Once again, the results in terms of CD-related complications are reported for the whole group and not reported in subgroup analysis for the intentional IPAA patients and incidentally diagnosed CD patients following IPAA. Twenty patients were followed for 10 years or more with a CD-related complication rate of 35 % and an impressive pouch excision rate of only 10 %.

The Cleveland Clinic adopted the intentional IPAA in CD patients in the late 1990's and subsequently reported its initial experience [4]. The analysis included 20 patients who underwent an intentional IPAA out of the study cohort of 204 patients (additional 97 patients with incidental diagnosis and 87 patients with delayed diagnosis). These 20 patients had a median time of 6.6 years from CD diagnosis to IPAA with a median follow up of 5 years and were more likely to be female. The 10- year pouch retention rate in the 20 patient strong intentional group was 85 % and thus closely mirrored the long-term follow up reported by Regimbeau and colleagues of 90 % pouch retention at 10 years as described above. For those patients with retained IPAA, 72 % reported near-perfect or perfect continence, 68 % reported rare or no fecal urgency and the median number of daily bowel movements was 7 (range 2 – 20). Interestingly, these patients also reported their quality of life and quality of health as 9/10 and 9/10 respectively and happiness with the IPAA procedure as 10/10.

The Mount Sinai Medical Center, New York, reported their experience with 13 patients who received an IPAA, 4 of whom were definitively diagnosed preoperatively with CD [5]. None of these patients had perianal disease and all had disease solely limited to the colon. Two of these 4 patients (50 %) subsequently developed perianal disease, 2 (50 %) developed postoperative complications and 1 patient

(25 %) required a pouch excision. Of note, the outcomes for all 13 CD patients were compared with a matched cohort of patients undergoing IPAA for chronic UC; the CD patients had fewer bowel movements per 24 h, a lower incidence of incontinence and a lower incidence of pouchitis.

The most recent series on the intentional use of IPAA in CD patients reported on 17 patients [6]. Seven of 17 patients (41 %) developed recurrent CD following IPAA and this compared with a corresponding postoperative incidence of 11 % in a UC cohort undergoing IPAA during the same time period. The pouch excision rate over an average follow up of 60 months in the 17 preoperatively diagnosed CD patients was an impressive 6 %. This study is also notable in that 9 of the 17 patients had a preoperative diagnosis of CD outside of the colorectum: 5 patients had previously undergone small bowel resections with no evidence of active small bowel disease and 4 patients had perianal disease (3 perianal fistulae, 1 anal stenosis), where the fistulae were managed by insertion of draining setons with subsequent evaluation demonstrating no evidence of active perianal sepsis.

The most current study on this topic is a United States multi-institutional study examining the cost-effectiveness of two surgical options in patients with Crohn's colitis [7]. They compared what is referred to as 'colectomy with permanent ileostomy' with IPAA. It should be noted that some of the evidence for the former group involves patients described in a prior study who underwent either total abdominal colectomy with end ileostomy or panproctocolectomy with end ileostomy [8] and the reader cannot determine whether it was only the panproctocolectomy patients who were included in the cost analysis by Taleban and colleagues. Additionally, Taleban and colleagues assumed that patients undergoing J-pouch formation would have 'complete mucosectomy', yet this is clearly not the operative approach employed by all. Nonetheless, colectomy with permanent end ileostomy was shown to be more cost-effective unless the associated surgical cost exceeded $20,167 at which point IPAA was the more effective option. They also reported that IPAA was the more effective strategy with an incremental cost-effectiveness ratio of $70,715 per QALY gained.

Author	Year	Number of patients	Postoperative morbidity	Pouch excision	Quality of evidence
Hyman	1991	9	8/9 (89 %)	6/9 (67 %)	Low
Panis	1996	31 (18 intentional; 13 incidental)	11/31 early (35 %) 6/31 CD related (19 %)	2/31 (6 %)	Low
Regimbeau	2001	41 (26 intentional; 15 incidental)	10/41 early (24 %) 11/41 CD related (27 %)	3/41 (7 %)	Low
Melton	2008	20	Not reported	2/20 (10 %)	Low
Grucela	2011	4	2/4 (50 %)	1/4 (25 %)	Low
Le	2013	17	4/17 early (24 %) 7/17 CD related (41 %)	1/17 (6 %)	Low

Recommendations Based on the Data

Since the introduction of IPAA as part of our surgical armamentarium, there have only been 67 patients reported with a preoperative diagnosis of CD and thus an intentional IPAA. This number can be increased to 76 when the 9 patients with a high preoperative suspicion of CD reported in the initial study from the Cleveland Clinic are included. Based on this, the evidence for intentional IPAA in Crohn's colitis is low and the recommendation for IPAA formation in patients with Crohn's colitis is weak.

A Personal View of the Data

The top priority is providing a personalized and tailored plan of care for each patient. We believe that some of the most critical and complex parts of working with a patient with Crohn's disease occur outside of the operating room. Not only is it imperative that detailed medical and surgical histories are obtained, but it is also essential to develop a relationship with the patient at the first encounter and to gain an understanding of the patient's goals in terms of the potential for surgery and possible outcomes. The patient and their family/caregivers should be approached on a personal level, understanding their own goals and work for open, honest dialogue whilst forming a specific individual surgical strategy. Having done this, together the patient and colorectal surgeon embark on a lifelong relationship. In our experience, this specific group of patients are very well informed on the potential surgical options and present to us with the intention of undergoing IPAA.

The formation of an IPAA for Crohn's colitis is considered provided there are no gross manifestations of small bowel disease (unless it is backwash ileitis) or perianal CD; a single, limited perianal fistula can be acceptable but a rectovaginal fistula is not. CT enterography is the preoperative imaging modality of choice to examine the small bowel and a thorough bedside perianal examination is performed and if there are questionable findings, patients proceed to a formal examination under anesthesia. Risk factors, especially a personal history of smoking and a family history of CD, are always sought as these patients are at increased risk for subsequent development of CD of the ileal pouch. Patients referred from other institutions may undergo repeat colonoscopy with biopsies and all previous outside pathology slides are reviewed again by a dedicated inflammatory bowel disease histopathology team. All patients have their nutritional status optimized preoperatively. Preoperative counseling regarding the potential for complications is extensive, with particular emphasis on the risk for significant small bowel loss if there is a requirement for pouch excision and that a re-do pouch may not be an option. Similarly, patients are advised that even if preoperative imaging is reassuring, there is always the potential that small bowel CD may be discovered perioperatively.

The technical approach to IPAA relies on careful and meticulous handling of the bowel and dissection in natural, anatomic tissue planes. When presented with a new patient with isolated Crohn's colitis, a 3-stage procedure is recommended and patients should ideally be steroid and biologic free prior to the second stage (i.e., pouch formation). We do not recommend a one-stage procedure and will perform a 2-stage procedure in select cases. Regardless of the operative approach (open or laparoscopic), the small bowel must be examined in its entirety from the ligament of Treitz to the ileocecal valve and if there is a suspicious area, this should be interrogated and may require an enterotomy to ensure there is no luminal evidence of disease. We strongly favor the total mesorectal excision technique when performing proctectomy. Residual distal tissue may lead to pouch emptying issues, which may significantly affect pouch function and quality of life. The J-configuration is the pouch subtype of choice and the double-stapled pouch-anal anastomosis technique is favored. In highly motivated patients who wish to avoid a permanent ostomy in whom there is limited perianal disease as previously referred to, a mucosectomy and hand-sewn anastomosis can be utilized when necessary. We have previously reported on the learning curve for IPAA formation which is estimated to be 23 cases when performing the stapling technique [9]. All new IPAAs are defunctioned after their creation for a minimum of 3 months and interrogated with a radiological contrast enema prior to ileostomy closure.

In the unfortunate case when a Crohn's patient with an IPAA develops anoperineal sepsis or anastomotic issues, the algorithm is to begin by checking one's own 'footsteps': it is critical to distinguish symptoms due to sequelae of Crohn's disease from a technical complication (which are more likely to develop within 3 months of surgery). These have very different solutions and management approaches to say the least.

IPAA surgery in patients with Crohn's disease is technically and emotionally challenging, but is also rewarding in that it offers a life-changing avenue for the patient and surgeon alike.

Patients with Crohn's colitis and no evidence of small bowel or perianal disease are candidates for IPAA following thorough preoperative counseling and discussion regarding potential postoperative outcomes (evidence low; weak recommendation).

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Chapter 9
Steroid Management in Patients Undergoing Surgery for IBD

Karen Zaghiyan and Phillip Fleshner

Introduction

Often faced with the challenge of operating on steroid-treated patients with inflammatory bowel disease (IBD), colorectal surgeons must be well versed in the perioperative steroid management of this patient cohort. Historically, standard practice has entailed stress-dose or high-dose perioperative steroids in these patients undergoing surgery to prevent perioperative adrenal insufficiency (AI), cardiovascular collapse and death. Stress-dose steroids typically consist of hydrocortisone 100 mg intravenous (IV) given preoperatively and continued every 8 h postoperatively with a taper down to the preoperative dose over 2–3 days [1]. However, this practice is anecdotal and largely based on case reports from the 1950 s [2, 3] demonstrating cardiovascular collapse and death in 2 patients whose steroids were abruptly discontinued before surgery.

Furthermore, perioperative high-dose steroids are not without consequence and have been associated with impaired wound healing, hyperglycemia, hypertension, fluid and electrolyte imbalance, immunosuppression and psychological effects [4]. It has been suggested that the typical recommendation for supplementation with 200–300 mg of hydrocortisone per day is supraphysiologic and a much smaller (maximum of 150 mg/day) dose is necessary to overcome surgical stress [5]. While suppression of the hypothalamic-pituitary-adrenal (HPA) axis is known to occur with chronic corticosteroid supplementation [4], the amount and duration of steroid exposure necessary to suppress an appropriate response to surgical stress is unknown, nor is the

K. Zaghiyan, MD • P. Fleshner, MD (✉)
Section of Colon and Rectal Surgery, Cedars-Sinai Medical Center,
8737 Beverly Blvd. Suite 101, Los Angeles, CA, USA
e-mail: kzaghiyan@yahoo.com; pfleshner@aol.com

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Table 9.1 PICO questions

P (patients)	I (intervention)	C (comparator)	O (outcomes)
Steroid-treated patients with or without IBD undergoing colorectal or non-colorectal surgery	Low-dose perioperative steroids	High-dose or stress-dose perioperative steroids	Perioperative hemodynamic instability, adrenal insufficiency, morbidity, mortality, infectious complications
Patients with or without IBD, previously treated with steroids within 1 year undergoing colorectal or non-colorectal surgery	No corticosteroids	High-dose or stress-dose perioperative steroids	Perioperative hemodynamic instability, adrenal insufficiency, morbidity, mortality, infectious complications

duration of time necessary to overcome this HPA axis dysfunction [6]; some reports suggest this may take up to a year [7]. Thus, stress-dose steroids have even been advocated for patients previously treated with corticosteroids within the past year.

Over the past 6 decades, several studies in IBD and non-IBD patients have challenged the treatment algorithms for the use of perioperative stress-dose steroids. Yet, there remains great variability in perioperative steroid dosing for IBD patients undergoing colorectal surgery [8]. In this chapter, the literature pertaining to perioperative steroid dosing is reviewed and followed by our recommendations for steroid management in patients with IBD undergoing colorectal surgery.

Search Strategy

Relevant PICO (Population, Intervention, Comparator, Outcome) questions were generated (Table 9.1). A Medline and PubMed search was conducted for publications in the English language between January 1952 and November 2015 using the following search terms: (‘inflammatory bowel disease’ or ‘IBD’ or ‘ulcerative colitis’ or ‘Crohn’s’ or ‘organ transplant’ or ‘transplant’ or ‘rheumatoid arthritis’ or ‘steroid-treated’) and (‘corticosteroid’ or ‘steroid’) and (‘colorectal’ or ‘colorectal surgery’ or ‘surgery’ or ‘surgical’ or ‘operation’ or ‘operative’ or ‘perioperative’) and (‘stress-dose’ or ‘high-dose’ or ‘low-dose’ or ‘dosing’ or ‘coverage’ or ‘previous steroid’) and (‘adrenal insufficiency’ or ‘hemodynamic’ or ‘outcome’ or ‘complication’ or ‘morbidity’ or ‘mortality’). We also searched the reference section of each relevant article to identify additional articles pertaining to this topic. Retrospective and prospective, observational and randomized studies were included. Given the paucity of studies investigating IBD patients undergoing colorectal surgery, the search was expanded to include organ transplant recipients and other non-IBD steroid treated patients undergoing non-colorectal surgery.

Results

Over the years, several studies have been performed to assess the clinical utility and optimal dose of perioperative corticosteroids in steroid-treated patients undergoing surgery (Table 9.2). Initial studies challenging the concept of stress-dose steroids were performed in an era where there were serious concerns about operative wound healing. In these studies, patients underwent surgery without any perioperative steroids, and clinical parameters and HPA function were evaluated. In 1962, Solem and Lund reported 30 patients whose steroids had been stopped more than 4 weeks before surgery undergoing various surgical procedures (IBD undergoing major colorectal surgery, n = 4) without perioperative steroid cover and showed no impending hemodynamic collapse with this management [9]. Two studies investigated patients on steroids at the time of surgery who were operated on without perioperative steroids, measured HPA axis testing and clinical parameters. Hypotension attributed to AI occurred in 4 out of 125 patients combined [10, 11].

In a follow up study, Kehlet and Binder showed that preoperative ACTH stimulation testing correlated with perioperative HPA function in 48 steroid treated patients undergoing surgery (colorectal, n = 7) without perioperative steroids, but no patients had perioperative hemodynamic instability or required stress-dose steroids [12]. In 1981, Knudsen performed a retrospective study evaluating 250 steroid-treated IBD patients undergoing major colorectal surgery [13]. In 50 patients, perioperative steroid cover was provided whereas the remaining 200 patients underwent surgery without perioperative steroids. The study included 3 groups of patients: (1) patients on steroids at the time of surgery (n = 48); (2) patients whose steroids were stopped 1 week to 2 months before surgery (n = 76); and (3) patients off steroids greater than 2 months before surgery (n = 126). Intraoperative hypotension occurred in 29 patients (11.6 %) but was less common in the cohort off steroids more than 2 months before surgery (5.6 %). In 9 patients, intraoperative rescue hydrocortisone was given, although none of these patients had proven biochemical evidence of adrenocortical insufficiency. Of 8 patients developing postoperative hypotension, 2 patients on steroids at the time of surgery who underwent surgery without steroid cover were thought to have AI (1 biochemically proven). These early studies suggested the need for perioperative steroids in patients on steroids at the time of surgery. However the optimal perioperative steroid dose necessary to prevent AI and the utility of stress-dose steroids remained unclear at that time.

Subsequent studies evaluated various perioperative steroid dosing regimens consisting of low-dose steroids or maintaining patients on their preoperative steroid dose without a stress-dose. In 1981, the utility of a single preoperative stress-dose (hydrocortisone 100 mg) versus no stress-dose followed by reinstitution of the patient's preoperative steroid dose after surgery was prospectively studied in 61 steroid-treated patients with rheumatoid arthritis undergoing 107 major or minor orthopedic operations [14]. The authors found no significant difference in the need for perioperative rescue steroids in patients treated with stress-dose steroids (24 %) or not (17 %). In a small study of 14 steroid-treated patients (IBD, n = 7) compared

Table 9.2 Studies evaluating perioperative steroid dosing

First author (year)	Patients studied	Intervention	Study design	N	Outcome	Quality of evidence
Solem (1962) [9]	Patients previously treated with steroids/various surgeries (n = 4 IBD/CRS).	No periop steroids	R	30	No unexplained death attributed to AI	Very low
Jasani (1968) [10]	RA/anterior synovectomy	No periop steroids	PO	21 steroid treated vs. 20 controls	1 patient with abnormal preop ACTH had hypotension responsive to steroids.	Very low
Kehlet (1973) [11]	Steroid-treated patients undergoing various major/minor operations	No periop steroids	PO	104	3 patients with hypotension and low cortisol thought to be AI	Low
Knudsen (1981) [13]	IBD/CRS	200 with no periop steroids, 50 received steroids	R	250	11 cases of hypotension treated with steroids/ possible AI	Very low
Lloyd (1981) [14]	RA/Orthopedic surgery	Stress-dose vs. usual daily dose.	PO	61	No difference in periop steroid supplementation between the 2 groups	Very low
Symreng (1981) [15]	Various patients (n = 7 IBD, n = 16, CRS)	If impaired ACTH stim test > HC 25 mg IV preop then 100 mg IV/24 h. If normal ACTH stim test: no periop steroids. Return to usual daily dose postop.	PO	14 steroid-treated patients and 8 steroid-naïve controls	No hemodynamic instability	Very low

First author (year)	Patients studied	Intervention	Study design	N	Outcome	Quality of evidence
Bromberg (1991) [16]	Renal transplant patients admitted w/significant physiologic stress	Usual daily dose	PO	40	No unexplained hemodynamic instability	Very low
Bromberg (1995) [17]	Renal transplant patients/various surgeries	Usual daily dose	PO	52	No clinical or laboratory evidence of adrenocortical insufficiency	Very low
Friedman (1995) [18]	Renal-transplant or RA/major orthopedic surgery	Usual daily dose	PO	28	All patients with endogenous adrenal function. No unexplained hemodynamic instability.	Very low
Glowniak (1997) [20]	Various (colorectal n=2) with positive ACTH stim test	Stress-dose vs. placebo. Return to usual daily dose postop.	RCT	18	No episodes of AI. One in each group with hypotension.	Very low
Thomason (1999) [21]	Organ transplant/gingival surgery	Stress-dose vs. placebo. Return to usual daily dose postop.	RCT	20	No hemodynamic instability	Very low
Mathis (2004) [19]	Organ transplant/lymphocele drainage	Stress-dose vs. no steroid. Return to usual daily dose postop.	R	58	No hypotension, arthralgia, ileus, mental status changes. Blood glucose higher with stress-dose	Very low
Zaghiyan (2011) [24]	IBD/CRS previously on steroids within 1 year	No periop steroids	R	49	No difference in hemodynamic instability	Low
Zaghiyan (2012) [22]	IBD/CRS	HDS vs. LDS	RO	32	No unexplained hemodynamic instability	Very low

(continued)

Table 9.2 (continued)

First author (year)	Patients studied	Intervention	Study design	N	Outcome	Quality of evidence
Zaghiyan (2012) [23]	IBD/CRS	HDS vs. LDS	R	97	No difference in hemodynamic instability	Moderate
Aytac (2013) [25]	IBD/CRS	Stress-dose vs. usual daily dose	R	235	More tachycardia with stress-dose otherwise no difference in hemodynamic instability	Moderate
Zaghiyan (2014) [26]	IBD/CRS	HDS vs. LDS	RCT	92	Non-inferiority of LDS vs. HDS with respect to postural hypotension; no difference in hemodynamic instability. More infections with HDS.	High

IBD inflammatory bowel disease, *CRS* colorectal surgery, *RA* rheumatoid arthritis, *ACTH* adrenocorticotropic hormone, *HDS* high-dose steroids, *LDS* low-dose steroids, *R* retrospective, *PO* prospective observational, *RO* retrospective observational, *RCT* randomized controlled trial

We recommend that steroid-treated patients undergoing major colorectal surgery be managed with low-dose perioperative steroids in the perioperative period (*evidence quality high; strong recommendation*)

with 8 steroid-naïve controls undergoing various operations (major colorectal surgery, n = 16), Symreng and colleagues showed that steroid-treated patients with abnormal preoperative ACTH-stimulation testing (n = 6) can be managed with low-dose steroids (hydrocortisone 25 mg IV at the induction of anesthesia followed by 100 mg IV over the next 24 h) followed by reinstitution of the preoperative dose, whereas patients with a normal ACTH stimulation testing can be managed without steroids on the day of the operation [15]. This steroid regimen resulted in perioperative plasma cortisol levels similar to steroid-naïve patients and no patients had signs of hemodynamic collapse.

In the 1990s, Bromberg and colleagues performed 2 prospective cohort studies evaluating renal transplant recipients admitted with significant physiologic stress (n = 40) or for various operations (n = 52) who were managed with only their usual steroid dose [16, 17]. Whereas almost all patients had normal urinary cortisol levels and no signs of unexplained clinical hemodynamic insufficiency, ACTH-stimulation testing appeared to overestimate adrenal dysfunction in a majority of patients. In 1995, Friedman and colleagues prospectively evaluated 28 renal-transplant or rheumatoid arthritis patients on an average prednisone dose of 10 mg/day undergoing major orthopedic surgery [18]. All patients had endogenous adrenal function and no episodes of AI occurred. In 2004, another retrospective study of 58 pancreas and kidney transplant recipients undergoing lymphocele drainage showed no difference in hypotension, arthralgia, mental status changes, ileus or wound healing in patients treated with stress-dose steroids or not, but patients treated with stress-dose steroids had more hyperglycemia [19].

Two underpowered randomized-controlled studies were performed in the 1990s. The first was a randomized, double-blind study of 18 steroid-treated patients with positive ACTH stimulation test undergoing various surgical procedures (2 colorectal) managed with either stress-dose steroids or placebo plus the patient's baseline steroid dose [20]. Two episodes of hypotension occurred, one in each group, both related to bleeding or hypovolemia. The authors concluded that patients with secondary AI do not experience hypotension or tachycardia when given only their preoperative steroid dose for surgical procedures. The second study was a randomized, double-blind, crossover study of 20 organ transplant recipients on prednisone (5 – 10 mg) undergoing gingival surgery, randomized to hydrocortisone 100 mg IV or placebo preoperatively during their first surgery and the opposite for the second surgery [21]. Despite several cases of abnormal ACTH stimulation testing, no patients developed perioperative hypotension or tachycardia.

With these studies, the concept of maintaining steroid-treated patients on their preoperative steroid dose in the perioperative period emerged. Despite this, colorectal surgeons managing IBD patients on high doses of preoperative steroids undergoing major colorectal surgery remained reluctant to apply this practice [1, 8]. Recently, our group performed several studies comparing low-dose steroids (LDS) versus high-dose steroids (HDS) in steroid-treated IBD patients undergoing major colorectal surgery. Our LDS protocol entailed one-third IV hydrocortisone equivalent to the daily preoperative steroid dose (IVED) given at the time of surgical incision, then one-third IVED every 8 h postoperatively, followed by a taper. For

patients off steroids at the time of surgery, no perioperative steroids were given. HDS entailed hydrocortisone 100 mg IV given preoperatively, then every 8 h after surgery followed by a taper to oral prednisone over 3 days. On hospital discharge, steroids were either discontinued or tapered.

In 2012, we performed a pilot study evaluating 32 steroid-treated IBD patients (10 patients on steroids up until surgery and 22 patients treated with steroids in the past year) managed with LDS [22]. Hypotension occurred in 16 % of patients, but all cases resolved with no intervention, fluid bolus, or blood transfusion and no patients were treated with vasopressors or high-dose corticosteroids for AI. We then compared LDS (n = 54) versus HDS (n = 43) in IBD patients on steroids (n = 48) or previously treated with steroids (n = 49) undergoing major colorectal surgery [23, 24]. For patients previously treated with steroids, median duration since last steroid dose was 4 months (range: 0.1 – 12 months) and median maximum steroid dose in the past year was equivalent to prednisone 25 mg/day (range: 5 – 60 mg/day). Aside from a higher incidence of tachycardia in patients previously treated with steroids managed with HDS [24], we found no significant difference in hemodynamic instability between the 2 patient groups and no patients required rescue high-dose steroids for AI.

Another study performed by Aytac and colleagues in 2013, retrospectively analyzed 48 IBD patients on steroids and 187 patients off steroids at the time of proctocolectomy [25]. Eighty-nine patients were treated with stress-dose steroids and 146 without. There was more sinus tachycardia in patients managed with stress-dose steroids. While there were no episodes of adrenal crisis, one patient in the stress-dose group was readmitted with hypotension, fatigue and bloating and diagnosed with AI. In 2014, our group performed a prospective, randomized non-inferiority study evaluating 92 steroid-treated IBD patients undergoing major colorectal surgery randomized to HDS or LDS [26]. LDS were found to be non-inferior to HDS with respect to our primary outcome, absence of postural hypotension on postoperative day 1, which occurred in 95 % of patients randomized to HDS versus 96 % of patients assigned to LDS, p = 0.007. This study included 41 patients previously treated with steroids (median duration since last steroid dose of 4 months; interquartile range: 2 – 6 months), of which 25 were randomized to LDS (no perioperative steroids given). There was no difference in hemodynamic instability between the 2 patient groups and no patients were treated with rescue HDS for AI. There was, however, an insignificant trend toward more infectious complications in HDS (16 %) versus LDS-treated patients (4 %); p = 0.11.

Recommendations Based on Data

Based on various retrospective and observational studies and few randomized prospective studies, stress-dose steroids appear to be unnecessary in IBD patients undergoing major colorectal surgery. Several studies in both IBD and non-IBD patients have suggested that patients can be maintained on their usual preoperative

steroid dose in the perioperative period. For patients previously treated with steroids within the past year, perioperative steroids can be avoided altogether [9, 13, 24, 26]. While preoperative ACTH stimulation and perioperative plasma cortisol levels may be evaluated, these tests tends to overestimate adrenal insufficiency and a majority of patients do not experience hemodynamic instability even when perioperative steroids are held altogether [11, 12, 15–17, 20]. Thus a low-dose perioperative steroid protocol consisting of the intravenous equivalent to the patient's preoperative dose appears to not only be sufficient, but may avoid infectious complications associated with high-dose steroids. Based on the available data, we recommend that steroid-treated IBD patients undergoing major colorectal surgery be managed with low-dose perioperative steroids in the perioperative period (*evidence quality high; strong recommendation*).

Personal View of Data

In our view, high-dose perioperative steroids are unnecessary and may increase perioperative risk. In our practice we maintain patients on their preoperative steroid dose in the perioperative period. Our perioperative protocol entails one-third IVED given at the time of surgical incision, then one-third IVED every 8 h postoperatively, followed by a taper. For patients off steroids at the time of surgery, no perioperative steroids are given. Patients are monitored closely in the perioperative period and any unexplained hemodynamic instability is followed by ACTH stimulation test. If patients are unresponsive to conservative measures and ACTH stimulation testing is positive, then high-dose steroids are given. In our experience, however, no patients have required additional high-dose steroids for AI with this protocol.

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Chapter 10
IBD: Management of Dysplasia in Patients with Ulcerative Colitis

Tara M. Connelly and Walter A. Koltun

Introduction

The risk of colorectal cancer (CRC) in the ulcerative colitis (UC) population is real and is the cause of death for up to 15 % of inflammatory bowel disease (IBD) patients [1, 2]. Controversy surrounds the use of prophylactic colectomy when dysplasia is detected. The relatively high risk of progression to CRC must be weighed against the risks associated with total proctocolectomy (TPC) ± ileal pouch anal anastomosis (IPAA), which, in contrast, are relatively low, particularly when performed in an elective setting and by an experienced surgeon. In addition to substantially reducing the CRC risk, TPC results in the elimination of future UC flares and the necessity for medical treatment whilst eliminating the need for frequent CRC surveillance. As more powerful techniques for lesion detection become widespread, the detection of dysplasia will likely increase, increasing the relevance of the question 'What is the most appropriate management of patients with ulcerative colitis and dysplasia?'

T.M. Connelly, MB, BCh, PhD
Department of Surgery, Waterford University Hospital, Waterford, Ireland

W.A. Koltun, MD, FRCS, FASCRS (✉)
Division of Colon and Rectal Surgery, Inflammatory Bowel Disease, The Pennsylvania State University, College of Medicine, 500 University Drive, Hershey, PA 17033-0850, USA
e-mail: wkoltun@hmc.psu.edu

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Search Strategy

The PubMed database was searched using the following terms 'dysplasia, carcinoma, neoplasia, DALM, ALM, dysplasia associated mass or lesion, adenoma like lesion or mass and ulcerative colitis or inflammatory bowel disease or IBD.' The search was limited to full length English language manuscripts published between Jan 1, 1980 and Oct 1, 2015. All references in each manuscript identified from the PubMed search were then individually reviewed and examined for relevance and potential inclusion.

Results

Patients, interventions, comparator and outcomes are highlighted in Table 10.1. The most salient studies reviewed are shown in Table 10.2.

Incidences of Dysplasia and Colorectal Cancer (CRC)

Studies on UC dysplasia typically provide incidence rates obtained from the use of conventional endoscopy. Any grade of dysplasia is found in up to 2 % of UC patients at 5 years and 33 % at 15 years [4, 18]. Ten and 15 year rates of high grade dysplasia (HGD) of 7 % and 12 % respectively have been reported. Similar to CRC, incidence is highest in patients with pancolitis [15].

Median time from UC diagnosis to CRC diagnosis varies from 4 to 23 years [4, 19]. Compared to the general population, the relative risk of CRC in UC patients is as high as 16-fold [20]. Meta-analysis inclusive of 116 studies has demonstrated an overall prevalence of CRC in UC patients of 3.7 %, increasing to 5.4 % in the presence of pancolitis [21]. IBD-CRC patients are approximately 7 years younger than sporadic CRC and share the same cancer specific mortality rates on a stage for stage basis [22]. The mean age at CRC diagnosis ranges from 43 to 60 years and the mean interval between diagnosis of UC and CRC is approximately 16 years [17, 23, 24], which is consistent with the majority of UC diagnoses being made in individuals in their 20s to early 30s [21].

Table 10.1 PICO

Patient population	Intervention	Comparator	Outcomes studied
UC patients with dysplasia	Surgery	Expectant management	Cancer risk

Table 10.2 Studies examined

Study	Ulcerative colitis patients	Typical risk of cancer for immediate surgery when dysplasia is detected	Relative risk of cancer for surveillance	Quality of evidence
Choi et al. (2015) [3]	Patients with extensive[a] UC and LGD (median follow up = 48 months) 21 = immediate colectomy 151 = surveillance	33 and 14 % of colectomy specimens demonstrated CRC and HGD respectively	13 and 8.6 % developed HGD or CRC respectively CRC found in 5 of 11 specimens of patients who developed HGD and underwent colectomy Only 30 % of patients who developed CRC had a prior HGD lesion	High-mod
Jess et al. (2006) [4]	29 of 692 IBD registry patients with neoplasia[a] (CD patients included)	NA	0 of 5 with fLGD who underwent surveillance progressed to HGD or CRC (median of 17.8 years) 2 of 18 with ALMs developed LGD or DALM (median 9.3 years) PSC and dysplasia proximal to the splenic flexure were associated with risk for progression	Mod-low
Zisman et al. (2012) [5]	42 with pancolitis ≥8 years' with LGD (mean follow up = 3.9 years)	NA	A higher grade in the colectomy specimen was found in 27 % who underwent resection 6 and 2 progressed to HGD and CRC respectively 17 % had persistent LGD, 64 % had indefinite dysplasia or no dysplasia at the end of the study	High-mod
Ullman et al. (2003) [6]	46 with fLGD (median follow up = 15 months) 11 = immediate colectomy 21 = surveillance	Colectomy specimens showed: LGD n = 7, no dysplasia n = 1, HGD n = 1 and CRC n = 2	19 had LGD and 2 had HGD at the study's end 14 of the 46 progressed to advanced neoplasia (median time to progression = 25 months) 57 % of colectomy specimens showed more advanced neoplasia than biopsy specimens 6 DALM patients were managed with polypectomy followed by surveillance. No CRC developed	High-mod

(continued)

Table 10.2 (continued)

Study	Ulcerative colitis patients	Typical risk of cancer for immediate surgery when dysplasia is detected	Relative risk of cancer for surveillance	Quality of evidence
Blackstone et al. (1981) [7]	27 with fLGD in random biopsies 12 with DALMS 9 = immediate colectomy 22 = surveillance	6 colectomy specimens had CRC (including all polypoid lesions). None had a preoperative CRC diagnosis	Of the 2 DALMs that underwent surveillance, 1 developed CRC Of 20 fLGD undergoing surveillance, 6 underwent colectomy. 1 CRC was found. The degree of dysplasia was less severe or absent on follow up in 12	Low
Woolrich et al. (1992) [8]	22 with neoplasia (mean disease duration = 13.5 years)	NA	The first repeat set of biopsies showed dysplasia in six and a CRC in one patient Of the 13 patients with negative first repeat biopsies, who did not undergo colectomy to avoid surveillance: 23 % had CRC in the colectomy specimen (including 1 resection for UC symptoms)	Mod
Befrits et al. (2002) [9]	60 with flGD and UC > years (mean follow up = 10 years)	NA	LGD was only present at index colonoscopy in 16. 73 % had LGD in subsequent colonoscopies. None progressed to HGD in fLGD, except in 2 cases with DALM Five of the 11 with DALMs underwent colectomy. Six underwent endoscopic removal of lesions. None developed HGD or CRC (mean follow-up of 6 years).	Mod
Ullman et al. (2002) [10]	18 with fLGD (median follow up = 32 months)	NA	50 % developed advanced neoplasia (only 1 CRC) Of the patients who underwent colectomy: 2 for DALMs (1 = DALM in colectomy specimen, 1 = no dysplasia) 1 for HGD and 3 for LGD (all had the same results in the colectomy specimen) 5 for refractory disease (1 = DALM, 1 = LGD in the colectomy specimen) The cumulative incidences of progression = 13 % at 1 year, 26 % at 2 years, and 33 % at 5 years All three DALMs that were found on subsequent colonoscopies eventually developed HGD	Mod-Low

Lim et al. (2003) [11]	29 with extensive UC >8 years and LGD and 97 UC without dysplasia	NA	After 10 years, 10 % of LGD patients underwent colectomy for CRC vs 4 % without LGD No difference in colectomy or death rates between the two groups was seen Agreement of LGD diagnosis between pathologists was poor	Low
Rutter et al. (2006) [12]	46 with LGD, 19 with HGD, 28 DALMs and 32 ALMs with extensive disease for >8 years (mean follow up = 8.5 years)	CRC was found in 20 and 45 % LGD and HGD colectomies respectively 30 % of LGD DALM and 33 % HGD DALM patients had CRC in their resection specimen	Of the 36 LGD surveillance patients: 16 = no further dysplasia, 8 = further LGD, 9 = HGD, 3 = CRC Of the 8 HGD surveillance patients: 1 = developed CRC, 6 = developed HGD, 1 = subsequent LGD 21 % with LGD DALMs developed CRC, 28 % with HGD DALMs developed CRC, none who had endoscopic resection developed CRC, 6.3 % of 32 ALM patients developed CRC 13 of the 30 CRCs did not have a preoperative diagnosis of CRC	Mod
Pekow et al. (2010) [13]	28 with LGD (Mean follow up = 50 months)	NA	1 fLGD progressed to HGD and 1 polypoid LGD progressed to CRC For fLGD, polypoid LGD and PSC the incident rate of advanced neoplasia was 4.3, 1.5 and 10.5 cases per 100 person-years at risk	Mod
Goldstone et al. (2011) [14]	121 with extensive UC > 7 years and LGD (median follow up = 37 months)	NA	7.9 % with raised and 25 % with flat dysplasia progressed to advanced neoplasia The interval for progression was significantly shorter among patients with distal vs. proximal LGD	Mod

(continued)

Table 10.2 (continued)

Study	Ulcerative colitis patients	Typical risk of cancer for immediate surgery when dysplasia is detected	Relative risk of cancer for surveillance	Quality of evidence
Stolwijk et al. (2013) [15]	293 with UC >8 years	NA	Dysplasia of any grade was detected in 24.6 % (LGD n = 55) 33 % who had subsequent colonoscopies progressed to HGD and/or CRC. LGD preceded HGD/CRC in 44 % 5.1 % were diagnosed with CRC with a minimal interval from symptom onset to CRC of 10.2 years The cumulative incidence of any dysplasia, HGD and CRC after 10 years was 23.5 %, 6.6 and 4.0 %. After 15 years it was 33.3, 12.1, and 6.8 % In the colectomy specimens, 82 % confirmed the biopsy result, 13 % showed a higher degree of dysplasia	Mod
Provenzale et al. (1995) [16]	A computer generated population of 10,000 30 year old UC patients with pancolitis >10 years	Prophylactic colectomy increased life expectancy by 2–10 months vs surveillance and by 1.1–1.4 years vs. with no surveillance.	Yearly colonoscopic surveillance for LGD increased life expectancy by up to 1.2 years vs no surveillance. If colectomy for LGD is not undertaken, surveillance every 3 years for the first 20 years, every 2 years for the next 8 years, and yearly thereafter and colectomy for HGD or CRC provides the greatest life expectancy.	Poor
Wanders et al. (2014) [17]	Meta-analysis of 10 studies, 376 patients with polypoid dysplasia (combined 1704 years' follow-up)	NA	The pooled CRC and HGD rates were 6.7 and 9 per thousand years of patient follow-up Increased study duration did not correlate with an increase in advanced neoplasia rates	High

UC ulcerative colitis, *LGD* low grade dysplasia, *CRC* colorectal cancer, *HGD* high grade dysplasia, *CD* Crohn's disease, *fLGD* flat low grade dysplasia, *DALM* dysplasia associated mass or lesion, *ALM* adenoma-like mass or lesion

[a]Extensive UC = UC proximal to the splenic flexure

Disease Defined Risk Factors: Disease Duration, Age of Onset, Disease Extent, PSC

CRC incidence dramatically increases 8–10 years after the onset of UC symptoms. Cumulative probabilities of developing CRC are up to 4 % by 10 years and 8 % by 20 years [15, 21, 25]. Rates after 30 years are less uniformly reported and vary from 2.6 to 34 % [20, 25, 26]. Primary sclerosing cholangitis (PSC) has consistently been shown to increase the risk of CRC through a yet undetermined pathophysiological mechanism. Studies on a potential correlation between young age at UC diagnosis and/or childhood onset and CRC are conflicting with the majority showing no correlation [25]. Dysplasia is typically but not universally found in areas of current or burnt out colitis [27, 28], leading to an increased risk in more extensive disease distribution [20, 25]. An earlier CRC onset has also been suggested in pan vs left sided colitis [29].

Patient Defined Risk Factors: Family History of CRC, Medication Usage, Smoking, Patient Awareness

Family history is a known risk factor for both sporadic carcinoma and IBD associated CRC. CRC risk is at least doubled in UC patients with relatives with CRC and is ninefold greater if the relative is under the age of 50 at CRC diagnosis [23, 30]. Conversely, a family history of IBD does not increase UC-CRC risk [20]. Studies on medication usage in UC and CRC are limited to the older anti-inflammatory drugs, with data on the newer biologics and anti-integrins lacking. Several previous studies including a meta-analysis of 9 studies and 1932 patients, have suggested a protective effect with regular 5-aminosalicylic acid (5-ASA) use [21, 23, 24, 31]. Although a paradoxical effect of smoking and decreased UC incidence and disease severity is well known, the effect of smoking on UC-CRC risk is understudied. Eaden's small case control study demonstrated no association [23].

CRC risk may be underappreciated by UC patients themselves and probably negatively impacts care. The majority of 199 survey respondents with UC for an average of 8 years recognized that CRC risk was increased, however approximately 75 % stated that they were "unlikely" or "very unlikely" to develop CRC within the next 10 years [32].

Classification of UC Dysplasia

Dysplasia in UC has typically been regarded as flat in most cases. When it is raised and found within areas of inflammation, it has been termed a dysplasia associated lesion or mass (DALM) and classically has been viewed as colonoscopically

unresectable. These definitions and concepts are now in question with the development of newer more advanced techniques of endoscopic polyp removal. A polypoid lesion found in an area free of inflammation is termed an adenoma-like mass or lesion (ALM) and is akin to an adenomatous polyp in a non-UC patient.

Grading of dysplasia ranges from mild or low grade (LGD) to more severe or high grade dysplasia (HGD). LGD is histologically similar to inflammation with tall columnar epithelial cells with mild nuclear stratification. HGD is similar to carcinoma in situ [7]. Salient features of HGD include prominent heterochromatin and more irregular nuclear stratification within the epithelial layer. These subtle differences lead to poor interobserver agreement between grading pathologists especially for LGD. When LGD slides are reviewed by a second set of pathologists, agreement with the original LGD diagnosis ranges from 7 to 43 % and varies depending on the number of pathologists reviewing [4, 11, 33, 34]. Dixon et al demonstrated a similarly poor consensus of agreement on HGD, as low as 33 % [35]. Correlation was not improved when specialist gastrointestinal pathologists grated the specimens, compared to general histopathologists [36].

1. A second pathologist's opinion for LGD is often necessary (Strong recommendation based on moderate-high quality evidence).

Inadequate tissue sampling during colonoscopy may lead to missed lesions. Mathematical modelling to determine the number of random biopsies required to detect dysplasia with 90 % confidence calculated that 45 biopsies would be required. When the number of biopsies decreases to 10, 26 % confidence was predicted [37, 38]. New enhanced methods of lesion detection including chromoendoscopy which began in the early 2000s, have dramatically increased the sensitivity of surveillance colonoscopy particularly for difficult to detect, flat dysplastic lesions [39–42].

Dysplasia Management

Neoplastic Progression

Unlike sporadic CRC which follows a usual sequence of normal mucosa → adenoma → carcinoma, UC associated CRC does not necessarily follow the expected progression of LGD → HGD → CRC. This makes surgical recommendations problematic, especially in the individual patient. As demonstrated in several studies in Table 10.2, carcinoma is often detected in colectomy specimens in which only LGD or even no dysplasia was detected in prior colonoscopies. In Stolwijk's study of over 290 UC patients undergoing surveillance, LGD preceded HGD or CRC in only 44 % of cases [15]. None of the 5 of 46 flat LGD (fLGD) patients that progressed to CRC had an interval finding of HGD in Ullman's study [43]. In Rutter's

surveillance program of 600 patients with extensive colitis, CRC was found in 20 % of specimens that were resected for only LGD [12]. Choi and Zisman report similar rates of unexpected CRC in resections performed for LGD [3, 5].

A focus of UC dysplasia, especially HGD has been suggested to be a marker for synchronous lesions, including CRC [44–46]. An early study of 590 UC TPC specimens demonstrated that patients with a focus of HGD or LGD were 36 times more likely to have a concomitant CRC found as compared to UC specimens without dysplasia. Up to a 25 % synchronous tumor rate and 55 % synchronous dysplasia rate has been demonstrated in other TPC studies [19, 47].

Flat LGD

In patients with LGD and extensive UC for over 8 years, progression to CRC has been reported to be 13 % at 1 year to 33 % at 5 years [3, 5, 6, 10, 12, 15, 18] with a mean time to progression of 1.8–2.3 years [5, 6, 10]. Woolrich determined LGD to be an indicator of future carcinoma in 18 % of 121 patients [8]. A meta-analysis of 20 studies with 508 LGD patients provided a calculated positive predictive value (PPV) of 22 % for flat LGD (fLGD) as a predictor of CRC [48]. Zisman determined nonpolyoid dysplasia, size >1 cm, previous history of indefinite dysplasia and the presence of a stricture as risk factors for LGD progression. He stratified patients showing that CRC risk at 5 years ranged from 1.8 % in patients with no risk factors to over 60 % with three risk factors [3]. Befrits' study, the only study which has shown no progression of LGD to subsequent HGD or CRC was small with only 16 patients with LGD [9]. Multiple retrospective studies and Thomas' meta-analysis did not demonstrate differences in characteristics between patients with and without LGD prior to HGD and/or CRC [6, 15, 48] again showing the difficulty in making care recommendations in the specific patient.

2. Flat LGD warrants colectomy in the otherwise healthy patient due to the increased risk of unrecognized synchronous high risk lesions and the likelihood of developing subsequent HGD or CRC (Strong recommendation based on moderate-high quality evidence).

High Grade Dysplasia

Recent studies on long term HGD surveillance are lacking as patients typically undergo resection due an inordinately high risk of synchronous CRC, as high as 45 % in earlier studies [49, 50]. In a systematic review, 32 % (of 47 patients) with HGD on colonoscopy had CRC discovered on resection pathology [50]. Some smaller studies report lower rates, [27] but sampling errors, the need for repetitive

colonoscopy, and the fear of synchronous CRC or progression over time has led to TPC being the immediate recommendation in the otherwise healthy UC patient with HGD. HGD identified on random biopsies represents an especially concerning circumstance, since overt signs of polyp formation that would focus the attention of the examiner is lacking. Similarly, multiple areas of dysplasia, especially when flat, can only be addressed by colectomy.

3. HGD, multifocality and flat dysplasia are all high risk features for the development of CRC in the UC patient and warrants total proctocolectomy in the surgically fit patient (Strong recommendation based on moderate-high quality evidence).

DALMS

The PPV for DALMs as predictors of CRC is 41 % as calculated by meta-analysis [48]. 43 % of 47 DALM patients in the small systematic review described above were found to ultimately have CRC [50]. Blackstone et al described a series of 12 resected DALMs. CRC was found in 7, including all 5 single polypoid masses. None had invasive carcinoma on preoperative biopsy [7]. Selective resection of DALMs in the form of polypectomy was proposed by one meta-analysis of 10 studies and 376 UC patients, but with a mean follow up of only 2.8 colonoscopies after resection. Many of these studies had very low patient numbers and mean follow up and number of colonscopies varied greatly across the study cohorts included [17]. Kisiel reported higher rates in 77 of 95 DALM patients who underwent polypectomy with cumulative incidences of cancer of 2 % at 1 year and 13 % at 5 years cited [51]. The value of more advanced colon sparing techniques such as endoscopic mucosal resection, has not been fully evaluated in this high risk group of patients. Thus close colonoscopic surveillance is required after colonoscopic excision.

4. DALMS should be viewed as very high risk lesions in the UC patient justifying TPC in most fit individuals. If able to be completely removed colonoscopically, aggressive subsequent surveillance is necessary (Strong recommendation based on moderate-high quality evidence).

ALMS

By definition, ALMs are within areas of the colon without inflammation. Thus they may be treated similarly to sporadic adenomas due to a low risk of CRC. Hurlstone followed ALMs and DALMs in over 180 patients over a median follow-up of

4.1 years as compared with over 1600 non-UC Controls who had undergone endoscopic mucosal resection (EMR) or polypectomy for lesions. Recurrence rates were low in both groups [52]. Torres et al studied ALMs and DALMs in 59 CD and UC patients and found that CRC only developed in DALMs. However, the group was highly selected leading to the recommendation of endoscopic resection with close, 6 monthly surveillance with colonoscopy [30].

5. ALMs can be viewed as typical polyps, amenable to polypectomy (Weak recommendation based on low quality evidence).

A Personal View of the Data

Due to the lack of consistent progression of inflammation to LGD to HGD to CRC, recommendations for surgical management of UC dysplasia leans towards treating the worst case scenario. This is especially the case since UC patients with dysplasia are frequently middle aged with a life expectancy that should not be foreshortened by preventable malignancy. Couple this with the above described poor concordance between pathologists and one is frequently led to the recommendation of early resection when any form of dysplasia is found on colonoscopy, but especially when HGD or flat dysplasia is found on random sampling. The high incidence of unexpected synchronous CRC when TPC is done for dysplasia further justifies an aggressive surgical approach.

Recently, chromoendoscopy has suggested itself to be a more sensitive and accurate method of following the equivocal patient; however this has not been thoroughly studied. Similarly the use of EMR for DALMs is also understudied, but really is only considered in highly specialized centers by very committed caregivers, and then only with intense colonoscopic follow up (every 6 months). This surveillance itself becomes an added burden, with attendant complications, costs and potential difficulty with patient compliance.

Thus, in the surgically fit patient we advocate TPC in all patients with any grade of pathologically confirmed dysplasia [45]. In the patient with LGD, this may sometimes require a second colonoscopy (frequently chromoendoscopy) for confirmatory biopsies, possibly after a period of intense medical management to minimize inflammation. However, any single confirmed focus of HGD should send the otherwise healthy and consenting patient directly to surgery. Besides eliminating the risk of CRC, patients are effectively “cured” of their colitis by TPC, with elimination of most medications and their attendant side effects and costs, improvement in bowel habit (especially with the IPAA) and elimination of burdensome surveillance colonoscopies [53]. The more difficult dilemma is the surgical high risk or elderly patient or patient refusing surgery, who has a less compelling indication for surgery, a single focus of LGD for example. After thorough counselling, such a patient can be considered for close surveillance using chromoendoscopy and/or EMR if a lesion

is visualized. If the dysplasia is colonic (not rectal), and localized as can be best determined, a subtotal colectomy and ileorectal anastomosis, or even segmental colectomy will decrease the risk of synchronous or metachronous lesions, and will be surgically less morbid. The patient will still need close colonoscopic surveillance, however. Similarly, a segmental resection (or even TAC/IRA) for DALM is possible in the higher risk patient. It avoids a stoma, but any procedure less that TPC needs preoperative confirmation of a dysplasia free rectum which then requires continued surveillance after this more limited surgery.

Editor's Note The concepts and controversies surrounding the identification and management of dysplasia in IBD are evolving rapidly. It appears that most areas of dysplasia are actually grossly visible with high definition scopes and enhancement techniques (e.g., chromoendoscopy). If lesions can be clearly defined, they can be more readily removed endoscopically and followed carefully with serial endoscopy.
The authors have outlined an aggressive approach, especially to the management of low grade dysplasia; many IBD specialists may espouse a more nuanced view with careful endoscopic surveillance offered as an alternative for many of these patients.

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Chapter 11
Post-operative Prophylaxis in Patients with Crohn's Disease

Jonathan Erlich and David T. Rubin

Introduction

Crohn's disease (CD) is a chronic relapsing inflammatory condition, characterized by abscesses, fistulization and stricturing that can affect any part of the gastrointestinal tract, but most commonly affects the terminal ileum and proximal colon. Up to 80 % of CD patients will require at least one abdominal surgery in their lifetime [1]. Unfortunately, surgery is not curative and recurrence is the norm, rather than the exception. Endoscopic recurrence occurs in upwards of 70–90 % of patients within 1 year of surgery [2, 3]. Clinical recurrence is seen in approximately one third of patients within 3 years of surgery [4]. Additionally, up to 50 % of patients will require a repeat surgery within 5 years, while up to 70 % will require a repeat operation within 20 years of their original procedure [4–7]. While prevention of post-operative recurrence is a significant challenge in clinical practice, it is essential for not only the maintenance of the patient's health status and quality of life, but also for the prevention of disease relapse and future surgeries [8]. Having a multidisciplinary approach involving collaboration between surgeons and gastroenterologists is critical for optimizing post-operative care; however patients often delay their follow-up with their gastroenterologist, leaving the surgeon as the sole manager of the patient's post-operative treatment. Communicating a well-organized and clear

J. Erlich
University of Chicago Medicine, Section of Hospital Medicine,
5841 S. Maryland Ave, MC 5000, Room 304, Chicago, IL 60637, USA

D.T. Rubin (✉)
University of Chicago Inflammatory Bowel Disease Center,
5841 S Maryland Ave, MC4076, Chicago, IL 60302, USA
e-mail: drubin@medicine.bsd.uchicago.edu

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plan shortly after resection is especially important because patients who are at high risk of recurrence may be less likely to accept treatment as they enjoy their surgically-induced "remission [9]."

In this chapter, we describe the clinically relevant risk factors for post-operative recurrence as well as the medical options available for prevention. Finally, we provide a practical guide on how to approach the post-operative Crohn's patient based on an individualized, evidence-based plan.

We conducted a Pubmed search from 2005 to 2016 using a combination of the search terms "Crohn's disease", "postoperative", "prophylaxis", "recurrence", "relapse", "prevention", "risk factors", "anastomosis type", and "treatment". Selected embedded references that were published prior to 2005 and considered seminal papers by the authors were also included.

PICO table

Patients	Intervention	Comparator	Outcome
Patients with Crohn's disease following surgical resection	Medical prophylaxis	Endoscopic surveillance	Disease recurrence, need for reoperative surgery

Recurrence in Post-operative Crohn's

The recurrence rates of CD after surgery are very high, especially in those not receiving medical prophylaxis. Endoscopic findings that indicate recurrence of disease include aphthous erosions, deep linear ulcers, mucosal inflammation, fistulae and strictures [10]. Typically, the prevailing phenotype of a patient's disease are thought to be consistent before and after resection, meaning that patients who initially had penetrating disease as an indication for their surgery will often experience penetrating disease when they recur [11].

The most common site of recurrence is at the surgical anastomosis, especially the proximal side [2]. Luminal contents, specifically intestinal flora, appear to play an important role in the pathogenesis of recurrence. While a sustained remission is common among patients with a diverting ileostomy even without medical therapy, those patients who undergo re-anastomosis often have disease recurrence shortly following the procedure [12–14].

Risk Factors for Relapse

Identifying possible risk factors for recurrence in Crohn's patients is essential for optimizing care for the postoperative patient. Risk stratifying patients based on these factors allows tailoring of therapy to help avoid both over- and under-treatment of patients.

Patient Factors

Smoking cigarettes has been the most consistently identified patient-related risk factor for disease recurrence. Compared to non-smokers, smokers have increased rates of endoscopic recurrence and clinical relapse, shorter time to clinical relapse and increased risk of requiring additional surgical intervention [15–19]. There also appears to be a dose effect, with heavier smokers having an increased risk of recurrence compared to milder smokers [20, 21]. Additionally, studies have shown that patients who quit smoking have significantly reduced surgical re-intervention rates, which are comparable to that of non-smokers [18, 22, 23].

There is interest in whether certain genetic variants or profiles of the gut microbiome are potential risk factors for post-operative recurrence, as both are known to be important in the pathogenesis of IBD. Whereas mutations in NOD2 have been identified as a marker for the need for resection in CD cohorts, it has not been shown to have a consistent association with post-operative relapse. However, a recent study identified an association between CAD8 homozygosity and an increased risk of surgical recurrence [24, 25]. Another recent study suggested that microbiota profiles at the time of surgery may have some prognostic value in identifying those patients at risk for developing earlier disease recurrence [26]. Both of these areas of inquiry require further research to help clarify their roles in the pathogenesis of disease recurrence.

Gender, age, age at diagnosis, and prior family history are not consistent risk factors in the literature [27–30].

Crohn's Disease Behavior

Perforating-type disease, perianal disease and previous surgery for CD have been shown to be associated with increased risk of disease recurrence [11, 31–33]. An association between the presence of granulomas in the resected specimen and recurrence has also been consistently demonstrated [13, 28, 30, 34]. The evidence for duration of disease prior to surgery as a risk factor for recurrence is inconsistent [35, 36].

Surgical Factors

Certain perioperative events, such as sepsis, blood transfusions and post-operative complications have not been associated with CD recurrence. While clearing margins of macroscopic disease is imperative, there appears to be no relationship between microscopic CD found at the resection margin and disease recurrence [37]. As laparoscopic surgery has become more popular, there has been interest in whether the technique reduces post-operative disease recurrence. Whereas

laparoscopic technique can offer advantages in the surgical management of CD, including reduced duration of hospital stay, reduced cost and lower morbidity, studies have shown no significant difference in endoscopic or surgical recurrence rates when compared to open procedures [38, 39].

Type of anastomosis has been considered an important potential risk factor for CD recurrence. Due to the subsequent wide lumen created with side-to-side anastomosis, which in theory would prevent early stenosis, subsequent fecal stasis and secondary ischemia, it has been postulated that this technique offers some outcome benefits. Unfortunately, observational studies have not supported this [40]. In a multicenter randomized controlled trial by Mcleod et al., anastomotic type did not affect the recurrence rate of CD after ileocolonic resection [41]. Despite this, other studies have suggested that side-to-side anastomosis may reduce post-operative complications and surgical recurrence [42–44]. Of note, the Kono-S anastomosis, which is a novel antimesenteric functional end-to-end handsewn anastomosis, is a technique with improved endoscopic and surgical recurrence rates; however, long-term outcomes and comparative studies need to be performed in order to confirm its superiority [45].

Myenteric plexitis found during surgery has been consistently shown to be associated with higher rates of endoscopic and surgical recurrence [46–48]. Visceral fat area has also been associated with post-operative recurrence and is believed to have clinical implications with respect to optimizing prophylaxis [49]. Additionally, the European Crohn's and Colitis Organization determined that disease of more than 100 cm should be considered a risk factor for increased incidence of post-operative recurrence [50].

Assessment of Recurrence

Endoscopically identified disease recurrence occurs early and therefore is the preferred measure of relapse in post-operative patients. This is because it precedes clinical symptoms, which do not correlate well with endoscopic findings [51, 52].

The most commonly used endoscopic scoring system to evaluate disease recurrence after resection in CD is the Rutgeerts' score [2]. This is a reliable scoring system that assesses the presence and severity of recurrence in the distal neoterminal [53] (Fig. 11.1). The Rutgeerts' scoring system has become widely used because it has been shown to correlate with subsequent clinical relapse: while less than 5 % of those with scores of i0 and i1 will develop clinical recurrence within 3 years, 14, 40 and 90 % of patients with i2, i3 and i4 scores will develop clinical relapse, respectively [2, 13, 54]. When using this system, it is important to recognize that ulcers are not necessarily due to disease recurrence, and that it is common to have suture-related trauma or marginal ulceration/ischemia at the anastomosis site. Such ulcers should not be included when grading within the scoring system.

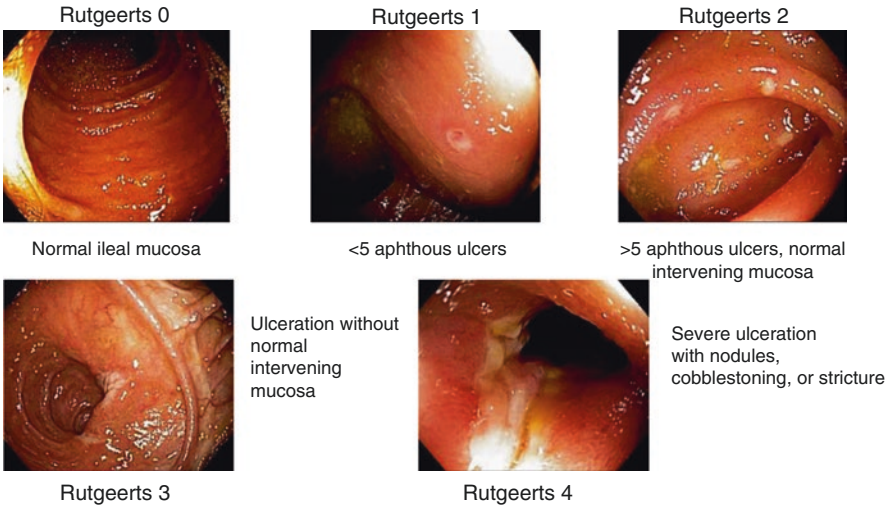

Fig. 11.1 The Neo-TI: the Rutgeert's Score

In terms of timing of evaluation for post-operative recurrence in asymptomatic patients, many guidelines suggest performing a colonoscopy within a year after surgery. More recent evidence has shown that a substantial proportion of endoscopic recurrence occurs within 6 months, many of which were severe with Rutgeerts' score ≥ i3. These findings highlight the importance of earlier evaluation for post-operative recurrence [55].

Non-invasive Methods of Assessing Post-operative Recurrence

While endoscopy is the gold standard for monitoring post-operative recurrence, there is a lot of interest in findings surrogate markers that would avoid the risks, expense and inconvenience inherent in an invasive procedure. Clinical scoring systems, such as the Crohn's Disease Activity Index (CDAI) and the Harvey-Bradshaw index poorly correlate with endoscopic findings [56–58]. Additionally, commonly used biochemical markers of inflammation, such as ESR and CRP, also have not been shown correlate with endoscopic recurrence in post-operative patients [58, 59].

The evidence behind fecal calprotectin (FC) has been very promising for fulfilling the role of a non-invasive method for assessing post-operative recurrence. FC levels correlate well with endoscopic recurrence as measured by the Rutgeerts' score, and patients who have received treatment for their recurrence with subsequent endoscopic improvement have also seen improvement in their FC [58, 60–62]. In a study by Yamamoto and Kotze, a cutoff value of 170 μg/g for FC

Table 11.1 Effectiveness of various methods to assess post-operative endoscopic recurrence

Evaluation method	Efficacy	Quality of evidence
Endoscopy	+++	High
FC	+++	High
SICUS	++	Moderate
WCE	++	Low
ESR/CRP	–	High
Clinical disease scores	–	High

had a sensitivity of 0.83 and a specificity of 0.93 to predict clinical recurrence [62]. In another study, Wright et al. found FC to correlate with endoscopic recurrence and endoscopic severity scores. The authors determined that a cutoff for FC of 100 μg/g had a sensitivity of 0.89 and a negative predictive value of 91 % for disease recurrence. The study concluded that utilizing FC to monitor post-operative patients may allow for 47 % of patients to avoid colonoscopy [58]. Based on these findings, FC may play a valuable role in the post-operative management algorithm, possibly allowing for endoscopy to be reserved for only those patients with abnormal values.

Other non-invasive methods of monitoring postoperative patients have shown promise. In a study by Calabrese et al, small intestinal contrast ultrasonography (SICUS) was shown to have a sensitivity of 92.5 %, specificity 20 % and accuracy of 87.5 % when compared to endoscopy [52]. Additionally, bowel wall thickness was found to correspond with endoscopic severity, although SICUS findings have not been shown to correlate with clinical recurrence [52, 63, 64, [65]. While it's use may be limited by its low specificity, SICUS may have a role in assessing the neoterminal ileum in patients with stenotic lesions not allowing passage of the endoscope [66].

Wireless capsule endoscopy (WCE) also has good sensitivity and specificity in assessing post-operative recurrence. In prospective studies, WCE identified lesions in upwards of 76 % of study subjects that could not be visualized by endoscopy (ibid) [67, 68]. While initial findings are encouraging, further research on WCE role in the post-operative patient needs to be performed (Table 11.1).

Symptoms After Surgery Are Not Necessarily due to Recurrence

It is important to know that common post-operative symptoms, such as diarrhea and pain, may not necessarily be due to CD recurrence. Therefore, prior to initiating treatment for suspected disease recurrence, objective markers of disease should be pursued. Ideally this can be done with endoscopy, although FC may be an acceptable alternative. As clinical symptoms poorly correlate with endoscopic activity, treatment should be based on endoscopic findings or appropriate surrogate markers and not solely on clinical symptoms, in order to prevent both over- and under-treating the patient.

Medical Prophylaxis Options

Following surgical resection, CD patients are often cleared of all of their disease, thus marking an ideal time to prevent further disease from occurring. As discussed above, most patients will unfortunately experience recurrence if not on medical therapy. Many studies have focused on the efficacy of medical therapies in preventing progressive disease, disability and further surgical interventions in the post-operative setting.

Minimal Benefit: Probiotics/5-ASA/Corticosteroids

Given the role that the gut flora plays in the recurrence of disease and evidence of the effectiveness of antibiotics in preventing disease, there has been growing interest in the use of probiotics to alter the microbiota and prevent recurrence. However, multiple studies have failed to show any benefit in the use of probiotics in the post-operative setting [69, 70]. 5-ASA medications are appealing for post-operative treatment, due to their favorable safety profile, ease of administration and low cost, however the results have been inconsistent and their effect on clinical and endoscopic recurrence is minimal at best [71–73]. Furthermore, neither systemic nor local corticosteroids have been shown in the literature to be effective at reducing post-operative recurrence [74, 75].

Moderate Benefit: Antibiotics/Immunomodulators

Due to evidence suggestive of the role of bacteria in disease recurrence, many studies have evaluated the effectiveness of antibiotics in preventing relapse. Whereas ciprofloxacin has not been shown to prevent relapse, nitroimidazole antibiotics (metronidazole and ordinazole) decrease the risk of clinical and endoscopic recurrence [76–78]. Rutgeerts' et al. demonstrated that only 3 months of treatment with metronidazole led to a decrease in recurrence that extended to 12-months following surgery compared to those taking placebo [79]. Studies have shown a further reduction in recurrence rates when metronidazole is used in combination with azathioprine compared to either medication used alone [80]. Additionally, antibiotics have been shown to be cost-effective for preventing post-operative recurrence, even in low-risk patient, although widespread use may be limited by high rates of intolerance [81].

Immunomodulators (IMM) appear to have a modest effect on preventing post-operative recurrence. Thiopurines (azathioprine and 6-MP) have been found to be more efficacious than placebo at reducing clinical relapse and severe endoscopic recurrence at 1 year [77, 82]. They have also been shown to reduce the risk of endoscopic recurrence compared to mesalamine [77]. Long term data has suggested that

thiopurine treatment for over 36 months decreased the need for additional surgical intervention when compared to use of less than 36 months or no treatment at all [83]. In a comparative cost-effectiveness analysis, Azathioprine and 6MP had the most favorable incremental cost effectiveness ratio [84]. Because of the strong evidence of its effectiveness, the AGA has recommended that thiopurines should be used in those with "high risk" for recurrence or in whom postoperative recurrence would be deleterious [85].

High Benefit: Biological Therapy

Biologics have been growing in popularity over the past 10 years and have been found to be the most effective at reducing post-operative recurrence risk. An early small study by Regueiro et al. demonstrated that endoscopic recurrence was reduced from 84.6 % in the placebo arm to 9.1 % in the infliximab treated group at 1 year [86]. In the larger PREVENT study, Regueiro et al. again showed that infliximab decreases endoscopic recurrence compared to placebo, however the reduction of clinical recurrence, which was the primary endpoint, did not reach statistical significance. Of note, adverse event rates, including infections, were similar between the groups [87].

Adalimumab has also been studied and is considered to be equally efficacious at reducing recurrence [88]. Savarino et al. reported that the adalimumab was highly effective at prevention of endoscopic and clinical recurrence at 2 years. Endoscopic recurrence of CD was seen in only 6.3 % of patients receiving adalimumab compared to 64.7 % and 83.3 % of patients who received azathioprine and mesalamine monotherapy, respectively [8]. In the recent Postoperative Crohn's Endoscopic Recurrence (POCER) study, 79 % of high-risk patients who received adalimumab remained in endoscopic remission compared to 55 % of patient receiving a thiopurine [89].

While the focus of this chapter is on post-operative prophylaxis, it is important to know that for patients who experience endoscopic recurrence, biologics have been shown to be superior at reducing endoscopic scores and clinical relapse compared to immunomodulators or 5-ASA [61, 86, 90].

There is currently no data in the post-operative setting or certolizumab pegol, natalizumab or vedolizumab.

Table 11.2 The effectiveness for preventing endoscopic recurrence with associated level of evidence of potential therapies for post-operative prophylaxis

Therapy	Effectiveness	Level of evidence
Probiotics	–	High
Corticosteroids	–	Moderate
Mesalamine	+	Moderate
Nitroimidazole antibiotics	++	High
Ciprofloxacin	–	Moderate
Immunomodulators	++	Moderate
Anti-TNF	+++	High

Authors' Approach to Post-operative Crohn's Patients

While the costs of over-treatment cannot be ignored, under-treatment may place the patient at risk for disease recurrence, as most post-operative patients without prophylaxis will experience recurrence within a year. Despite evidence of its far superior effectiveness in preventing relapse, initiating biological therapies as prophylaxis even for high risk patients may be prohibitively expensive and exposes more patients unnecessarily to potential side-effects [81, 84]. Responsible choice of therapeutic approach therefore must be individualized for each patient. Studies have demonstrated the benefit of early evaluation of recurrence within 6 months of surgery. The recent prospective, randomized POCER study demonstrated that tailoring prophylaxis to risk category coupled with early disease assessment and subsequent treatment "step-up" if recurrence occurred significantly reduced disease relapse and led to increased macroscopic normality compared to those who did not receive the early evaluation [89].

Given the strength of the evidence, we have adopted an approach that all patients who can tolerate metronidazole receive 3 months of treatment at a dose of 350 mg TID following surgery. Low-risk patients are those with long-standing disease (>10 years), who are undergoing their first surgical intervention for a short (<10 cm) fibrostenotic lesion. It is believed that disease recurrence progresses more slowly in these patients and therefore chronic prophylactic therapy is not required at the outset. For high-risk patients, those who smoke, have penetrating or perianal disease, history of multiple prior resections and those with evidence of granulomas or myenteric plexitis in the resected sections, initial combination therapy with an anti-TNF and an IMM should be considered. All smokers should be counseled on its contribution to disease recurrence and be offered assistance with quitting or access to a smoking cessation program. For moderate risk patients, those who do not fit into the other categories mentioned, we recommend treating with IMM monotherapy in the post-operative period.

While early monitoring of disease recurrence has been shown to be beneficial, there is no standard approach on how to do so. In our practice, we measure fecal calprotectin in patients 3 months post-surgery, as levels of FC are known to stay elevated for the first 2 months. Given its high NPV, for patients with FC values <100 mg/kg, we continue them on their current therapy and either repeat FC or perform colonoscopy at 6 months. While some evidence suggests that patients with FC > 100 should have a colonoscopy at 6 months, we risk stratify these patients depending on their level of calprotectin. In the study by Sorrentino et al., patients who had no post-operative recurrence had FC levels <200 mg/kg. Therefore, for patients with FC between 100 and 200, we continue their current medical therapy and perform a colonoscopy at 6 months [8]. For patients with FC levels >200 mg/kg, we optimize or escalate their medical therapy at that time and then perform a colonoscopy at 6 months.

At colonoscopy, patients with i0 or i1 Rutgeerts' score are continued on their current medical therapy, while for patients with i2 or higher, therapy is initiated,

optimized or escalated. This may be accomplished by starting IMM or anti-TNF therapy and optimizing their dosing using therapeutic drug monitoring. A careful assessment of the history, examination and need for therapeutic drug monitoring should be considered when deciding which option to implement.

Once a patient has had their medical therapy optimized and their disease status is stable, it is necessary to assess them every 6–12 months with a measure of disease recurrence, either with FC or colonoscopy. If objective evidence of recurrence occurs, we recommend further optimization of therapy using the algorithm discussed above.

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Part II
Colon Cancer

Chapter 12
Follow-Up in Patient's After Curative Resection for Colon Cancer Surveillance for Colon Cancer

Clifford L. Simmang

PICO table

Pt Population	Intervention	Comparators	Outcomes studied
Pts after curative resection of colorectal cancer	Intensive follow up	Clinical followup	Early detection of recurrence, salvage rates, cost

Introduction

According to the American Cancer Society, 134,490 new cases of colon and rectal cancer will be diagnosed in 2016. The effect is nearly equal between men and women, with 70,820 diagnosed in men, and 63,670 diagnosed in women [1]. Colon and rectal cancer is the fourth most common cancer, however it is the second most common cause of cancer deaths [1]. At least, one third (25–49 % reported) of patients treated with stage II or stage III colon cancer will experience a recurrence, and this has remained fairly steady over the past 20 years [1–3].

The purpose of surveillance following potentially curative surgery for colorectal cancer, is the early identification of recurrent cancer in those patients who might potentially be cured by secondary surgical intervention. Secondly, surveillance also enables screening for metachronous primary cancers and polyps. The diagnosis of an asymptomatic recurrence is more likely to result in attempts at curative reoperation [4]. Even with an intensive investigative program, up to 50 % of asymptomatic recurrences may not be detected [4]. Several studies have also demonstrated that asymptomatic recurrences of colorectal cancer are more amenable to a surgical resection with negative margins (R0) [5].

C.L. Simmang, MD, MS
Chief Medical Officer and Vice President of Medical Affairs,
Baylor Scott and White Medical Center at Grapevine, Grapevine, TX, USA
e-mail: clsimmang56@gmail.com

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Table 12.1 Surveillance recommendations-curative colon and rectal cancer

Intervention	Frequency		
	1–2 years	3–5 years	>5 years
H & P	3–6 months	6 months	Annual
CEA	3–6 months	6 months	None
Colonoscopy	1 year[a]	3 years[b]	5 years[c]
Flexible Sigmoidoscopy rectal cancer	6–12 months	Annual	None[d]
CT scan	Annual	Annual	Annual

[a]3–6 months if not cleared at surgery
[b]Continue at 3 years if adenoma is identified
[c]If cleared at 3 years
[d]Follow colonoscopy

Although there is extensive literature of evaluating the benefit of surveillance strategies for colorectal cancer, there remains ongoing debate. The cost of intensive follow-up is unclear but remains central to the discussion [5].

Search Strategy

An electronic search of the PubMed database was performed from 1996 to 2016. This search terms included "cancer follow-up", "colon surgery" and "postoperative surveillance for colon cancer" with 444 matches. The National Comprehensive Cancer Network (NCCN) [6], along with society guidelines from the American Society of Colorectal Surgeons (ASCRS), American Cancer Society of Clinical Oncology (ASCO) were reviewed. In addition the search included the Cochrane database, Google search and the Ontario evidence based series 26–2 on follow-up care surveillance protocol and secondary measures for survivors of colorectal cancer.

Results

Guidelines

The vast majority of studies exploring the benefits of surveillance have been conducted on patients with resected stage II or stage III disease. Intensive postoperative surveillance programs have been justified in the hope that early detection of asymptomatic recurrences will increase the proportion of patients potentially eligible for curative therapy [7]. Although individual randomized trials have not demonstrate a survival benefit, meta-analyses suggest a modest but significant survival benefit from intensive surveillance after resection of colorectal cancer [8–13]. It does seem clear patients with a recurrence detected by more intense surveillance are more

likely to undergo curative resection, whereas the actual reported survival advantage is more variable.

For a starting template, we began with the National Comprehensive Cancer Network guidelines version 2.2015(6) which reccommend;

1. History and physical every 3–6 months for 2 years and then every 6 months for a total of 5 years
2. CEA every 3–6 months for 2 years, then every 6 months for a total of 5 years
3. CT scan of the chest, abdominal and pelvis annually up to 5 years, especially for patient's at high risk for recurrence. High risk patients would include those with lymphatic, venous or perineural invasion, with poorly differentiated tumors, or patients presenting with obstruction or perforation.
4. Colonoscopy at 1 year when the colon was cleared prior to or at the time of surgery – repeat in 3 years and then every 5 years.
5. If colonoscopy not performed at the time of surgery, then colonoscopy in 3–6 months.
6. PET CT scan is not routinely recommended

Most guidelines are based on the above recommendations. We will now review each of the recommendations.

History and physical examination – low quality evidence – strong recommendation

Recommendation – Office visit with history and physical every 3–6 months for 2 years and every 6 months for a total of 5 years

While the benefit of office visits has not been well established, up to one-half of symptomatic patients may not report their symptom(s) until it is time for the visit with her physician [14, 15]. In addition, this provides an opportunity to discuss the results of surveillance testing. The evidence is limited to suggest that the physician visits provide psychological support and reassurance for patients three, but is a good time to reinforce healthy behaviors such as physical activity.

CEA testing –moderate quality evidence – strong recommendation

Recommendation – CEA every 3–6 months for 2 years and then every 6 months for a total of 5 years- should correlate with the office visit

The use of CEA has been extensively studied. The rationale for postoperative CEA monitoring is to detect an asymptomatic recurrence. Its greatest use has been in patients that have an elevated CEA before surgery which returns to normal after surgery. The strongest argument in favor of CEA testing is that resection of limited metastases, particularly involving the liver, leads to long-term relapse free survival in as many as 40 % of patients that undergo an attempted resection [7].

An asymptomatic elevation of the CEA increases the likelihood of a complete resection and will be associated with better long-term outcomes. Of note, approximately 30 % of all colorectal cancer recurrences are not associated with a CEA elevation. A false-negative CEA result is more commonly observed in poorly

differentiated tumors. Even in patients with a normal preoperative CEA, there may be an elevated CEA in over 40 % of recurrences.

When an elevated CEA is detected, it should be confirmed by retesting. False positive elevations are seen in up to 50 % of patients at some time during their surveillance and follow-up. Also the CEA level is elevated in cigarette smokers. However a progressively rising CEA confirmed on retesting is indicative of metastatic or recurrent disease. These patients need to undergo further evaluation and testing.

Colonoscopy – High quality evidence – strong recommendation
Recommendation –

Colonoscopy at 1 year when the colon was cleared prior to or at the time of surgery – repeat in 3 years and then every 5 years thereafter.

If colonoscopy not performed prior to or at the time of surgery, for instance due to an obstructing lesion, perform a clearing colonoscopy at 3–6 months after surgery.

Flexible sigmoidoscopy or proctoscopy may be performed every 6 months for the first 2 years and annually for up to 5 years, following resection for rectal cancer. When poor prognostic factors are present suggesting a higher risk of local recurrence, proctosigmoidoscopy may be considered every 6 months for 3–5 years.

Synchronous colon cancers occur in 2–5 % of patients with colorectal cancer [16]. Further, all patients with a history of colorectal cancer are at increased risk for developing adenomatous polyps. The National Polyp Study demonstrated a 76–90 % reduction incidence of colorectal cancer when surveillance colonoscopy was used in the setting of adenomatous polyps.

Periodic colonoscopy then enables detection of metachronous cancers at a more favorable stage and even better, the prevention of metachronous cancers by identifying and removing adenomatous polyps. In an analysis of 9029 patients performed by the American Cancer Society-Multi Society Taskforce for Colorectal Cancer, 137 (1.5 %) developed metachronous cancers detected by colonoscopy. This incidence compares favorably with screening colonoscopy.

The guidelines on the frequency for endoscopic surveillance following rectal cancer was traditionally based on a high pelvic recurrence rate. The use of more uniform surgical techniques including total mesorectal excision and the use of neoadjuvant therapy have resulted in local recurrence rates of less than 10 %. The American Society of Clinical Oncology, the American Cancer Society and the US Multisociety Taskforce all have issued different recommendations. The American Society for Clinical Oncology, for example, no longer recommends proctosigmoidoscopy every 6 months in patients treated with adjuvant radiation for rectal cancer, but does recommend proctosigmoidoscopy every 6 months for 2–5 years for patients with rectal cancer not treated with radiation.

CT scan – medium quality evidence – strong recommendation
Recommendation – CT scan of the chest, abdomen and pelvis yearly for 5 years

The current recommendation for CT scan of the chest, abdomen and pelvis has evolved over the past several years. Much of the data has come from surveillance studies where patients underwent more intense versus less intensive follow-up. In one meta-analysis 9, the survival benefit was most significant in patients that had had undergone both CT imaging and CEA measurement.

The most common sites for systemic recurrence for colorectal cancer are the liver and the lungs. 80 % of recurrences will develop in the first 2–3 years. No study has directly compared the evidence regarding the benefit of CT scans every 6 months versus annually. Very high risk patients, such as those with prior liver metastases, N2 disease, or an indeterminate lesion on prior imaging may be imaged every 6 months [3].

There is less evidence for chest surveillance than for abdominal (liver) imaging. However in one European trial, there were seven asymptomatic patients with normal CEA levels [17] who had their pulmonary recurrences diagnosed only by CT scan, and therefore would have gone undetected without surveillance chest CT. The CT detected group had a significantly longer median survival from time of recurrence compared with their symptomatic counterparts (26.4 versus 12.6 months), but not significantly longer than the CEA detected group (19.2 months). The largest proportion of resectable recurrences were found using chest CT, even though a larger proportion of recurrences was found with abdominal imaging.

MRI and PET Scans

These imaging modalities are not routinely recommended. MRI may be considered in a patient that has a contraindication to intravenous contrast. Both MRI and PET scanning may be indicated for an equivocal abnormality found on a CT scan (Table 12.1).

Overall Utility

Many have questioned the cost-effectiveness of surveillance programs. A Cochrane systematic review revealed no effect on overall survival, no difference in disease specific survival as well and no difference in detection of recurrence [18]. The cost has been reported anywhere from $1–$4 million for life saved. On the other hand, the data described above clearly suggests that those patients who have a recurrence detected prior to symptoms have a higher resectability rate for cure with an associated higher 5 year survival rate

Personal Review of the Data

We believe that surveillance gives patients the best opportunity to detect a recurrence while it is still curable. In our practice, we generally follow the guidelines as outlined above. A careful, individualized evaluation of the patient's risks for recurrence as well as their comorbidities/ability to tolerate additional treatment will impact the recommendation for surveillance.

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Chapter 13
Management of Patients with Acute Large Bowel Obstruction from Colon Cancer

Marc A. Singer and Bruce A. Orkin

Introduction

Although colorectal cancer remains the third most common malignancy worldwide [1], it is highly treatable in its early stages. Unfortunately, 10–29 % of patients with colorectal cancer will present with a large bowel obstruction [2–5]. This poses a challenging clinical dilemma for patients and physicians alike.

Bowel obstruction is highly morbid condition. Intervention to relieve the obstruction is appropriate for the large majority of patients. Patients with newly diagnosed colorectal cancer will benefit from relief of the obstruction, allowing time to adequately evaluate comorbidities and complete tumor staging. Modern systemic chemotherapy may afford patients with metastatic disease up to 2 years survival [6]. Therefore palliative procedures to relieve obstruction are an important component of the management of obstructed colorectal cancer patients, even in the setting of stage IV disease.

Surgery has traditionally been the primary treatment of malignant large bowel obstruction. More recently, endoscopic stenting has become a viable alternative and has grown in popularity. Endoscopic insertion of a self-expanding metallic stent (SEMS) to relieve the obstruction was first described as a palliative procedure, but was quickly adopted as a bridge to surgery. An endoscopic palliative procedure is an attractive option if it relieves the obstruction, with a low morbidity and requirement for stoma. Similarly, stents as a bridge to surgery allow for conversion of an emergency operation to a safer, elective, one-stage operation (Table 13.1).

M.A. Singer, MD, FACS, FASCRS (✉) • B.A. Orkin, MD, FACS, FASCRS
Section of Colon and Rectal Surgery, Rush University School of Medicine,
Professional Office Building, Suite 1138, 1725 West Harrison Street, Chicago, IL, USA
e-mail: marc_singer@rush.edu

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Table 13.1 PICO table

P (patients)	I (intervention)	C (comparator)	O (outcomes)
Patients with obstructing colorectal cancer	Surgery	Self expanding metallic stents	Technical success, morbidity, bridging to surgery, oncologic outcomes, survival

Methods: Search Strategy

This review is based on the results of a search of the English language literature published in databases including PubMed, Ovid, Google Scholar, and the Cochrane Library. Publications were included from inception through December 2015. Search terms included "stent," "stenting," "colon," "rectum," "colorectal cancer," "obstruction," "prospective," "palliation," "randomized," and "review." Relevant completed and ongoing trials cited on www.clinicaltrials.gov were also reviewed. Emphasis was placed on publications since 2010, so as to provide the most relevant practices and up to date information. Systematic reviews, randomized trials, and prospective comparative trials were reviewed in detail, and summarized in the Results Table. Level of evidence and strength of recommendation according to the GRADE system were assigned to each [7]. Case series and technical reports were reviewed and referenced as needed.

Results

Emergency surgery has long been the standard treatment for obstructing colorectal cancers, despite the high risk of mortality and complication rates approaching 50 % [4, 8–16]. Long-term survival for patients undergoing emergency operations for malignant obstruction is inferior to those undergoing elective operations [17, 18] This is likely due to a combination of both patient specific factors related to the emergency nature of the operation, as well as more advanced stage tumors tending to present with obstruction [12, 19–21].

Even in the setting of advanced pathology, medically suitable patients may benefit from resection of the primary tumor. In addition to relieving the obstruction, palliative resection appears to convey a survival benefit in patients with metastatic disease [21–24]. The absolute survival advantage is modest, but may be important to a patient with a limited life expectancy.

After resection, a decision must be made between primary anastomosis and creation of an intestinal stoma. A large number of patients treated with a "temporary" stoma will never undergo stoma closure. Further, primary reconstruction avoids the hidden costs of a stoma to the patient, such as appliances, new clothing, and loss of work [25].

Surgeons must honestly counsel patients and families that in the setting of cancer, especially metastatic, that there is a 20–50 % likelihood of the stoma being permanent [26–29]. For this reason, surgeons should construct every stoma with the same attention to detail as if it were a permanent stoma. Emergent colostomies are well known to carry a high rate of stoma specific complications [30].

Self-Expanding Metal Stents (SEMS)

Endoscopically deployed self-expanding metal stents can be used to restore intestinal continuity in patients with obstructing colon tumors. First introduced as a palliative treatment for unresectable malignancies in the early 1990s, [31] the practice rapidly evolved into a bridge towards one stage curative resections. The purported benefits include transformation from an emergent to an elective operation with reduced morbidity, mortality, length of stay, cost, rate of stoma formation, and increased minimally invasive techniques and survival [32–34].

Multiple case reports and institutional series have demonstrated the safety and efficacy of self-expanding metal stents to treat obstructing colorectal tumors. The large majority of treated tumors are left sided or rectal tumors. These tend to obstruct more often than right sided tumors, which are more commonly treated with right colectomy. Rectal tumors can be stented, however stents placed into the distal rectum are at risk of causing pain, tenesmus, or prolapsing through the anus. Most endoscopists can achieve a very high degree of technical success, on the order of 90–95 % [35, 36]. Success is dependent upon tumor size and location, but also the skill and experience of the endoscopist. Some authors have suggested a learning curve of 20–30 procedures [37–39]. Common procedural complications include perforation, migration, and late occlusion due to tumor in growth or stool impaction. A recent review of over 4000 procedures documented a perforation rate of 7.4 % [35]. Covered stents are more resistant to tumor in growth and late obstruction, while uncovered stents carry a lower rate of migration.

Stenting has grown in popularity as it provides a less invasive treatment for obstruction. Biagi et al. [40] demonstrated that the time to initiation of adjuvant chemotherapy effects survival, and stents have at least the theoretical benefit of enabling a far more expeditious initiation of treatment. Two general strategies have developed from the early experience: stenting as definitive palliation, and stenting as a bridge to surgery [41]. The minimally invasive nature of stenting makes it an attractive option for either goal, but this must be balanced by the effectiveness, morbidity, mortality, cost, rate of stomas, etc. A large number of publications have addressed these issues. The largest numbers of these are single center experiences and retrospective reviews. There are few high quality prospective or comparative trials. For this reason, systematic reviews and meta-analyses are useful approaches to evaluation of the relative value of stenting versus surgery.

Stenting as Palliation

The data supporting the safety and effectiveness of stenting to relieve obstruction is plentiful, however this is mostly low quality data in the form of small case series and retrospective reviews. Few authors have directly compared palliative stenting to surgical resection. There are no randomized controlled trials to support colectomy for right sided cancers, but this remains the widely accepted standard of care. Stenting of right sided lesions is technically feasible, [42–45] and may be considered for palliation. This review will primarily consider data regarding stenting of left sided

lesions. There have been several recently published systematic reviews specifically examining stenting compared to surgery in the palliative setting.

In 2011, Lee et al. [46] reported the long term outcomes of palliative stenting in patients with incurable obstructing cancers by conducting a retrospective review of 71 patients treated with stents and 73 patients treated with palliative surgery during 2000–2008. Stenting was as successful as surgery in relieving the obstruction (96 vs 100 %; p = 0.12). Fewer early complications occurred in patients treated with stents (16 vs 33 %; p = 0.015), which included a 5.6 % perforation rate with stenting. Primary patency of the stents was shorter than surgery, but patency after a second endoscopic intervention was comparable to surgery (patency 229 vs 268 days; p = 0.239). There were more late complications in the stenting group, but there were similar rates of major complications (p = .07). The number of patients requiring stomas was reduced in the stent group (18 vs 51 %; p < 0.001). The time to chemotherapy was significantly reduced in the stented patients (16 vs 31 days; p < 0.001). Overall survival was similar between groups. The authors concluded that stenting is an effective therapy for initial palliation, reduces time to chemotherapy and stoma requirements, with comparable longer term efficacy.

Young et al. [47] recently published an Australian randomized controlled trial of stenting vs surgical decompression in patients specifically diagnosed with malignant, incurable colon obstruction. The primary outcome measure was change in quality of life. 52 patients (26 each arm) were enrolled. Stenting was technically successful in 73 % of patients, with a 79 % rate of clinical success, and zero perforations. The quality of life scores (QLQ-CR29) were reduced in both groups, however there was less reduction in quality of life scores in the stent group from baseline to 12 months (p = 0.01). Mortality and median survival were similar (5.2 vs 5.5 months). The rate of stomas in the stent group was drastically reduced (27 vs 92 %). The stented patients also enjoyed a shorter length of stay and return of bowel function. The rate of patients proceeding to chemotherapy was the same in both groups (42 %). The morbidity was similar between groups (38 vs 54 %).

Due to the relative lack of high quality prospective or comparative data, multiple authors have written systematic reviews and performed meta-analyses combining multiple small cohort studies. In 2012, Zhang et al. [48] performed a meta-analysis including eight trials evaluating stenting vs surgery for palliative treatment of incurable disease. Outcomes of 601 patients (232 stent, 369 surgery) were detailed. There were fewer stomas created in the patients undergoing stenting compared to surgery (34 vs 51 %; p = 0.04). Mortality (6 vs 5 %; p = 0.47) and permanent stoma rate (17 vs 26 %; p = 0.52) were similar between groups. Complications were lower in the stent group (21 vs 50 %; p = 0.001). There were no significant differences in recurrence or survival (57 vs 56 %; p = 0.39).

Zhao et al. [49] published a meta-analysis in 2013 which reviewed 13 trials, including 3 randomized controlled trials (RCTs) comparing palliative stenting to surgery. These trials included 837 patients with 404 stented and 433 undergoing surgery. The 30-day mortality favored stenting (4.2 vs 10.5 %; p = 0.01). Early complications also favored stenting (14 vs 34 %; p = 0.03-stent perforation rate was 10.1 %). However, late complications were lower with surgery (32 vs 13 %; p < 0.0001). Clinical relief of obstruction was similar (93 vs 99.8 %; =0.0009). The post procedure length of stay (LOS) favored stenting (9.6 vs 18.8 days; p < 0.00001). The requirement for stoma

significantly was reduced by stenting (13 vs 54 %; $p<0.00001$). The time to postoperative chemotherapy also was improved by stenting compared to surgery (15.5 vs 33.4 days). Survival time was similar (7.6 vs 7.9 months; $p>0.05$). The authors concluded that stenting provided similar survival in the palliative setting, with reduced 30-day mortality, LOS, need for stomas, and time to chemotherapy.

In 2014, Liang et al. [50] published a similar systematic review and meta-analysis, but included 9 studies (3 RCT) including 410 total patients (195 stented, 215 surgery). The technical success of stenting was 94 %, with clinical success at 94 %. The stent related perforation rate was 3.7 %. The mortality (7.1 vs 11.6 %; $p=0.22$) and short term complications were similar (26 vs 35 %; $p=0.22$). Stenting again demonstrated a higher long rate of complications (OR 2.34; $p=0.03$).

Takahashi et al. [51] recently reviewed the available data from controlled trials of stenting vs surgery as palliation for unresectable cancers. This review included 10 studies, with 793 patients (stenting 375, surgery 418). Similar outcomes to the previous reviews were noted for mortality (2.1 vs 8.6 %; $p<0.01$) and stoma creation (11 vs 41 %; $p<0.01$). Stenting did improve early complications (12.3 vs 29.7 %; $p<0.01$), and longer term survival. Stenting complications included perforations (7.4 %), migration (8.4 %), and obstruction (13 %). Stenting caused a higher rate of total late complications (24 vs 14 %; $p=0.03$).

Stenting as a Bridge to Surgery

Early reports [52] of stenting as a bridge to surgery offered patients an opportunity for a safe one stage operation, with a significantly lower rate of colostomy formation. Multiple European centers began to adopt and refine this treatment strategy. In 2011, Jimenez-Perez et al. [53] detailed the experience of 182 patients prospectively enrolled into two large European multinational registries. Procedural success was achieved in a remarkable 98 % of patients. Clinical success with resolution of obstructive symptoms was realized in 94 % of patients. Perforation occurred in 1.7 % of patients, and overall stent complications were observed in 7.8 % Elective surgery was performed in 90 % of patients at a median of 14 days later. A stoma was required at the time of surgery in only 6 % of surgical patients. This experience detailed the successful application of the bridge to surgery strategy, with a high degree of technical success, and a low rate of stoma formation. It did not however describe oncologic results or long term outcomes of these patients.

Meisner et al., [54] also in 2011, similarly documented the short term safety and efficacy of stenting as a bridge to surgery. They examined 447 patients enrolled prospectively in 2 registries at 39 hospitals. In this cohort, the technical success of stenting was 95 %, with clinical success (relief of obstruction) in 91 %. Perforations occurred in 3.9 %. Successful procedures led to elective surgery in 90 % of patients at a mean of 16 days after stenting. Stomas were created in only 6 % of these patients. Thirty day mortality was 9 %, primarily due to perforation and cancer-related death. This growing experience continued to suggest that stenting as a bridge to surgery was reasonably safe in patients with obstructing colon tumors.

The first prospective randomized controlled trial comparing stenting as a bridge to surgery vs immediate surgery was published in 2011 by Pirlet et al. [55]. The primary outcome measure was the need for a stoma for any reason. This trial was performed at nine centers. Only 30 patients were enrolled in each group. Surprisingly, 43 % of the stented patients required a stoma compared to 57 % of the immediate surgery patients (p = 0.30). Both groups had similar morbidity, mortality, and length of stay. A bridging stent did not reduce the need for stoma, however the technical success of stenting in this trial was only 47 % (perforation rate was 6.7 %), considerably lower than most other prospective groups. In fact, of the patients that underwent a technically and clinically successful stenting, none required a stoma at the time of surgery. Therefore, this trial can be interpreted to suggest that if endoscopic stenting is successful, then the need for stoma is eliminated. But the rate of perforation was much higher and the rate of successful stenting was much lower than in other contemporary studies, suggesting a lower level of experience and expertise or possibly patient selection bias.

Despite early concern for perforations, the Dutch continued to examine stenting as a bridge to surgery. A cooperative trial at 25 hospitals randomizing 98 patients to stenting (47) or surgery (51) was reported in 2011 [56]. Enrollment in this trial was suspended due to increased morbidity in the stenting group at interim analysis. Stoma rates at latest follow up were similar (69 vs 60 %), although the initial stoma rate was lower in the stent group (51 vs 75 %). The initial trend of increased morbidity in stoma patients was not confirmed in 98 patients with long-term follow up.

In 2013, Kavanagh et al. [57] published described the short and medium term results of a retrospective review of patients who underwent either stenting as a bridge to surgery or immediate surgery between 2005 and 2011. The final analysis included 22 patients in the bridging group and 26 in the emergent surgery group. Initial stoma rates were similar (48 vs 42 %; p = 0.23). The permanent stoma rates were also similar. There were no early mortalities and early morbidity was similar (59 vs 65 %). Stenting was successful in 91 % of attempts with a 5 % perforation rate. The rate of patients starting chemotherapy within 8 weeks was similar in each group (22 vs 15 %; p = 0.13). The cancer specific survival and overall survival were also similar between groups. The authors concluded that stenting is an effective bridge to surgery, resulting in a similar stoma rate, primary anastomosis rate, morbidity, and mortality.

In 2013, Ghazal et al. [58] published a prospective randomized trial comparing stenting as a bridge to surgery compared to immediate total abdominal colectomy with ileorectal anastomosis. Sixty patients were randomized. The rate of technical success for the stent group was 97 %, and was followed by elective resection 7–10 days later. Morbidity was reduced in the stent group (13 vs 50 %; p = 0.012). Anastomotic leak was 3.3 % in the subtotal colectomy group. There were no mortalities. The subtotal colectomy patients experienced more frequent bowel movements postoperatively. Cancer recurrence was similar between groups (17 vs 13 %; p = 0.228). In this study, the authors concluded that stenting as a bridge to segmental resection was safer, with fewer bowel movements postoperatively.

Gianotti et al. [28] published their results from 134 prospectively evaluated patients with malignant obstruction. They were treated with either stenting as a bridge to surgery (n = 49), stents as palliation (n = 34), or with immediate surgery (n = 51). Here the technical success of stenting was again quite high at 95 % with a clinical success in

98 % of patients. Perforation rate was a remarkably low 1 %. Complications were significantly reduced in stented patients compared to surgical patients (33 vs 61 %; p = 0.005), as was length of stay (10 vs 15 days; p = 0.001). Mortality was 2 % in both groups. The rate of stoma formation was significantly reduced in the stented patients (6 vs 22 %; p = 0.01). Interestingly, the stented patients had improved overall survival.

Although prospective, randomized comparative data on stenting remains sparse, additional studies with larger cohorts have recently been published. In 2015, Saito et al from Japan described a prospective cohort of 518 patients stented from 2012 to 2013 [59]. Stenting as a bridge to surgery was performed in 312 of these patients. The technical and clinical success rates were 98 and 92 %. Perforation identified during stenting was 1.6 %, and an additional 1.3 % perforations were identified at the time of surgery, yielding an overall perforation rate of 3.8 %. Surgery was electively performed in 297 (95 %) patients, with a median time to surgery of 16 days. The primary anastomosis rate was 92 %, and the overall stoma rate was 10 %. Mortality was 0.7 %, and postoperative morbidity was 16 % (including a 4 % anastomotic leak rate). This is the largest multicenter prospective cohort of patients managed with stenting as a bridge to elective surgery. The vast majority of patients were successfully stented and subsequently underwent a one stage operation with low morbidity.

Because there are relatively few prospective trials evaluating stenting as a bridge to surgery, multiple authors have performed systematic reviews in the last 5 years in an effort to draw meaningful conclusions from pooled data. In 2011, Sagar et al. [60] provided a Cochrane review with a meta-analysis including 5 RCT trials with 207 patients. The primary objective was to evaluate the clinical success rate of stents compared to emergency surgery. Surgery offered a higher rate of relief of obstruction, but stenting offered a shorter length of stay. There were similar rates of complications. However, the included trials had several different definitions of return of GI function and resolution of obstruction.

In 2012, Tan et al. [61] performed a meta-analysis of 4 RCT which included a total of 234 patients. Summarized technical and clinical success rates for stenting were 71 and 69 %, with a perforation rate of 6.9 %. Stenting as a bridge to surgery resulted in a significantly higher rate of primary anastomoses (RR 1.58, 95 %CI 1.22–2.04; p < 0.001), and lower overall stoma rate (RR 0.71; p = 0.004). There were no differences in the rates of permanent stomas, mortality, anastomotic leak, or surgical site infection. It should be noted that 3 of the included trials were terminated early due to complications (2 in their stenting group, and 1 in their surgery group).

Cirocchi [62] published a meta-analysis in 2013 of 3 RCTs specifically comparing stenting as a bridge to surgery vs immediate surgery for left colon and rectal cancers. The clinical success rates were 53 % for stenting vs 99 % for surgery. Mortality was similar between groups (8 vs 9 %). Overall complications were similar (48 vs 51 %), but the stented patients had a somewhat lower rate of stoma formation (45 vs 62 %).

In 2014, Huang [63] performed a systematic review of 7 RCTs which included 382 patients (stenting 195, surgery 187). The technical success of stenting was 77 %. There were no differences in mortality (11 vs 12 %), but the stented patients experienced fewer complications (33 vs 54 %; p = 0.03). Also, there was a higher rate of primary anastomoses (67 vs 55 %; p < 0.01) and lower permanent stoma rates with stenting as a bridge to surgery (9 vs 27 %; p < 0.01).

Most recently, in 2015 Matsuda described the effect of stenting on long term oncologic outcomes in a systematic review, [64] which included 11 studies. These were a combination of prospective, retrospective, and RCTs with a total of 1136 patients (432 stents as bridge to surgery, and 704 emergency surgeries). Overall survival, disease free survival, and recurrence rates were similar between groups. Five year overall survival was available in eight reports, with generally similar results between groups (57 vs 67 %, P = 0.66), however the data was heterogeneous. Five year disease free survival reported in 5 trials was also not significantly different between groups (48 vs 59 %; p = 0.43). Eight trials reported recurrence rates, with no significant differences. The authors concluded that stenting as a bridge to surgery was oncologically comparable to emergency surgery with respect to overall survival, disease free survival, and recurrence.

This issue of oncologic safety has been specifically addressed by several authors who focused on defining the oncologic risks of stenting as bridge to surgery compared to immediate resection. It is possible that a delay in surgery, procedure related perforation, or occult perforation may lead to increased tumor recurrence. A 2015 Danish study [65] sought to clarify if self-expanding metal stents used specifically as a bridge to surgery were safe and useful by examining a population-based database with procedures performed from 2005 to 2010. Patients that survived 30 days postoperatively were analyzed (581 stent, 3333 resection). Five-year survival was improved in the stented patients (49 vs 40 %; adjusted mortality ratio 0.98, 95 %CI 0.90–1.07), however the 5-year recurrence was greater (39 vs 30 %; adjusted incidence rate ratio 1.12, 95 % CI 0.99–1.28). The authors concluded that stenting and emergent resection have similar 5-year survival, but stenting may cause increased recurrence. Other authors have suggested that there may be an increased rate of tumor spillage from stent perforations, and that there may be a higher rate of metastatic disease or shorter survival if a perforation occurs [66–68].

Conclusions

Review of this literature seems to indicate that although it may be possible that stent perforation can increase recurrence or metastatic disease, it is much clearer that stenting as a bridge to surgery significantly reduces perioperative complications. A reduction in complications, in turn, has been correlated with improved survival in a recent analysis of more than 12,000 patients [69]. Therefore, patients with a high risk of perioperative complications may be best suited for stenting as a bridge [70, 71]. To be efficacious and maintain a reasonable level of safety, institutional rates of successful stent placement should be 90 % or better, and the rates of stent-related perforation should be 5–7 % or lower.

It is unlikely that a large scale RCT comparing stenting as a bridge to surgery will be conducted due the requirement of a very large sample size, difficulty with technical standardizations, and need for long-term cancer follow up. It would also be very difficult to standardize the surgical arm of such a trial – segmental resection vs Hartmann's procedure vs total colectomy, stoma, etc. Therefore, meta-analyses, as imperfect as they are, may be the best source of data and recommendations.

The American Society of Colon and Rectal Surgeons (ASCRS) 2013 Practice Parameters for the Management of Rectal Cancer [72] addresses the issue of stenting. The authors reiterate that stenting should not be considered in the setting of perforation, massive bleeding, or lack of technical expertise. Technical success may be achievable, but is at risk for failure due to migration, pain, and incontinence when placed in the rectum. The authors do conclude that a stent may function as a bridge to surgery, and facilitate a primary anastomosis, or as a component of palliative treatment in the setting of metastatic disease. Surgeons were cautioned about the limited duration of patency of stents in light of the improving survival of patients on modern palliative chemotherapy. The recommendation was graded as a strong recommendation in favor of stenting based on low quality evidence.

Currently, trials of stenting versus surgery are being conducted at Nanfang Hospital in southern China, and at the Chinese University of Hong Kong (www.clinicaltrials.gov). In addition, other trials in progress are comparing devices such as covered versus uncovered stents.

The Approach to the Patient with Obstructing Colon Cancer

When a patient with an obstructing colorectal cancer presents, the first decision that must addressed is the goals of care. Some patients may prefer to seek hospice care with comfort measures only, especially in the setting of metastatic disease. If the patient elects to pursue treatment, then the next decision is how to acutely manage the obstruction. The primary options are stenting or surgery. Most right-sided colon lesions are treated with right colectomy. These patients should undergo a brief period of resuscitation and optimization, followed by right colectomy with either primary anastomosis, ileostomy and mucous fistula, or anastomosis with proximal loop ileostomy, depending on the condition of the patient and the colon.

For left-sided colon lesions, endoscopic stenting is an attractive option. If the endoscopist has experience with stenting and there are no compelling reasons to proceed immediately to the operating room, such as perforation, then stenting should be considered. If successful, a thorough metastatic workup and medical optimization can proceed. If the patient has incurable disease, the stent may serve as definitive palliation. Patency can be expected for many months and may be repeated if needed. Occasionally, resection may be performed subsequently if the metastatic disease is stabilized and the primary tumor is symptomatic. If the patient appears to have potentially curable disease, stenting is also a good initial approach. Stenting as a bridge to surgery does appear to reduce the need for a stoma and reduces the rate of postoperative complications. Although not all stents are technically successful and there is a 5–7 % rate of perforation, stenting has the distinct advantage of conversion of an emergency operation into an elective operation with the ability to stage and stabilize the patient. Patients and their families should clearly understand that stenting is not universally successful, that there are complications, and that, if unsuccessful, immediate surgery would be necessary, as would have been offered otherwise.

Published data of stenting compared to surgery (2010–2015)

Publication	Design	Patients	Technical success of stenting	Stenting results		Surgery results		Quality of evidence (GRADE)
Palliative stenting – prospective trials								
Young (2015) [47]	RCT	26 Stent 26 Surgery	73 %	Mortality	8 %	Mortality	15 %	High
				Morbidity	28 %	Morbidity	54 %	
				Perforation	0	Perforation	0	
				LOS	7 days	LOS	11 days	
				Stoma	27 %	Stoma	92 %	
				Postop chemotx	42 %	Postop chemotx	42 %	
				Survival	5.2 months	Survival	5.5 months	
Palliative stenting – systemic reviews								
Takahashi (2015) [51]	Meta-analysis	10 trials 375 stent 418 surgery	95 %	Mortality	2 %	Mortality	9 %	High
				Morbidity	12 %	Morbidity	30 %	
				Perforation	7 %	Stoma	41 %	
				Stoma	11 %	Late complications	14 %	
				Late complications	24 %			
				Survival	improved			
Liang (2014) [50]	Meta-analysis	9 trials 195 stent 215 surgery	94 %	Mortality	7 %	Mortality	12 %	High
				Morbidity	26 %	Morbidity	35 %	
				Perforation	3.7 %			
Zhao (2013) [49]	Meta-analysis	13 trials 404 stent 433 Surgery	93 %	Mortality	4 %	Mortality	11 %	High
				Morbidity	14 %	Morbidity	34 %	
				Perforation	10 %	Perforation	–	
				LOS	10 days	LOS	19 days	
				Stoma	13 %	Stoma	54 %	
				Time to Chemotx	16d	Time to Chemotx	33 d	
				Survival	7.6 months	Survival	7.9 months	

Stenting as a bridge to surgery – prospective trials								
Saito (2015) [59]	Prospective cohort	312 stent	98 %	Mortality	0.7 %			Moderate
				Morbidity	16 %			
				Perforation	3.8 %			
				Initial stoma	8 %			
				Final stoma	10 %			
				Bridged to surgery	95 %			
Erichsen (2015) [65]	Prospective cohort	581 stent 3333 surgery		5-year survival	49 %	5-year survival	40 %	Moderate
				Recurrence	39 %	Recurrence	30 %	
Ghazal (2013) [58]	RCT	30 stent bridge to segmental colectomy 30 subtotal colectomy with ileorectal	97 %	Mortality	0	Mortality	0	Moderate
				Morbidity	1 %	Morbidity	50 %	
				LOS	13 days	LOS	8 days	
				Recurrence	17 %	Recurrence	13 %	
						More frequent bowel movements		
Gianotti (2013) [27]	Prospective cohort	49 stent as bridge; 34 stent as palliation 51 surgery	95 %	Mortality	2 %	Mortality	2 %	Moderate
				Morbidity	33 %	Morbidity	61 %	
				Perforation	1 %	LOS	15 days	
				LOS	10 days	Stoma	22 %	
				Stoma	6 %	5 year survival	55 %	
				5 year survival	80 %			
Gorissen (2013) [73]	Prospective cohort	62 stent 43 surgery	90 %	Morbidity	8 %	Morbidly	21 %	Moderate
				Mortality	3 %	Mortality	9 %	
				Stoma	23 %	Stoma	37 %	
				5-year survival	71 %	5-year survival	56 %	
				Chemo	42 %	Chemo	26 %	

(continued)

Published data of stenting compared to surgery (2010–2015)

Publication	Design	Patients	Technical success of stenting	Stenting results		Surgery results		Quality of evidence (GRADE)
Alcantara (2011) [74]	RCT	15 stent 13 surgery	100 %	Morbidity	13 %	Mortality	8 %	Moderate
				Mortality	0	Morbidity	54 %	
				Perforation	0	Anastomotic leak	31 %	
				Stoma	7 %	Stoma	0	
				5-year survival	57 %	5-year survival	69 %	
				LOS	13 days	LOS	10 days	
Pirlet (2011) [55]	RCT	30 stent 30 surgery	47 %	Mortality	9 %	Mortality	4 %	High
				Morbidity	49 %	Morbidity	53 %	
				Perforation	7 %	Stoma	57 %	
				Stoma	43 % (0 % in patients successfully bridged with stent)			
Van Hooft (2011) [56]	RCT	47 stent 51 surgery	70 %	Mortality	11 %	Mortality	10 %	Moderate
				Morbidity	53 %	Morbidity	45 %	
				Perforation	13 %	Initial stoma	75 %	
				Initial stoma	51 %	Final stoma	60 %	
				Final stoma	69 %			
				Bridge to surgery	94 %			
Ho (2012) [75]	RCT	20 stent 19 surgery	75 %	Morbidity	35	Morbidity	58	Moderate
				Mortality	0	Mortality	16	
				Perforation	0	Stoma	32 %	
				Stoma	10 %	LOS	13	
				LOS	14			

Stenting as a bridge to surgery – systematic reviews								
Matsuda (2015) [64]	Meta-analysis	11 trials 432 stent 704 surgery		5 year survival	57 %	5 year survival	67 %	Moderate
				Recurrence	31 %	Recurrence	27 %	
Huang (2014) [63]	Meta-analysis	195 stent 187 surgery	77 %	Mortality	11 %s	Mortality	12 %	High
				Morbidity	33 %	Morbidity	54 %	
				Permanent stoma	9 %	Permanent stoma	27 %	
Cennamo (2013) [76]	Meta-analysis	178 stent 175 surgery	74 %	Mortality	8.4 %	Mortality	8 %	High
				Morbidity	36 %	Morbidity	46 %	
				Perforations	8 %	Stoma	48 %	
				Stoma	25 %			
Tung (2013) [77]	RCT	24 stent 24 surgery	83 %	Mortality	0	Morality	0	Moderate
				Morbidity	8 %	Morbidity	33 %	
				Stoma	0	Stoma	25 %	
				5 years survival	48 %	5 years survival	27 %	
				Chemotx	75 %	Chemotx	54 %	
Cirocchi (2013) [62]	Meta-analysis	3 trials 97 stent 100 surgery		Mortality	8.2 %	Mortality	9 %	Moderate
				Complications	48 %	Complications	51 %	
				Stoma	45 %	Stoma	62 %	
				Clinical success	53 %	Clinical success	99 %	
Zhang (2012) [48]	Meta-analysis	8 trials 232 stent 369 surgery	87 %	Mortalitys	6 %	Mortality	5 %	Moderate
				Morbidity	21 %	Morbidity	50 %	
				Primary anastomosis	78 %	Primary anastomosis	43 %	
				Stoma	34 %	Stoma	51 %	
				Permanent stoma	17 %	Permanent stoma	26 %	
				5 year survival	57 %	5 year survival	56 %	

(continued)

Published data of stenting compared to surgery (2010–2015)

Publication	Design	Patients	Technical success of stenting	Stenting results		Surgery results		Quality of evidence (GRADE)
Tan (2012) [61]	Meta-analysis	4 trials 116 Stent 118 Surgery	71 %	Mortality	7 %	Mortality	6 %	Moderate
				Perforation	6.9 %	Primary anastomosis	44 %	
				Primary anastomosis	66 %	Stoma	64 %	
				Stoma	44 %	Permanent stoma	44 %	
				Permanent stoma	32 %			
Sagar (2011) [60]	Cochrane/ Meta-analysis	5 RCT 102 stent 105 surgery	86 %	Mortality	2.3 %	Mortality	2.3 %	High
				Morbidity	39 %	Morbidity	46 %	
				Perforation	5.9 %	LOS	17 days	
				LOS	11.5 days	Relief of obstruction	99 %	
				Relief of obstruction	78 %			

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Chapter 14
Utility of Primary Tumor Resection in Asymptomatic, Unresectable Metastatic Colon and Rectal Cancer

Michael Pezold, Geoffrey K. Ku, and Larissa K. Temple

Introduction

One in five patients diagnosed with colorectal cancer (CRC) present with synchronous metastatic disease, and of these, only 13 % survive to 5 years [1]. Curative resection of the primary tumor and metastases can improve 5-year overall survival (OS) to 30–50 % [2]. Unfortunately, about three-quarters of patients with metastatic CRC present with unresectable disease to the liver [3]. In this setting, the principal treatment is chemotherapy, with an overall median survival in randomized-controlled trials of >20 months [4, 5]; in fact, a recent phase III study suggested that patients who were able to receive all currently available systemic treatment options had a median OS of nearly 30 months [6].

While receiving chemotherapy, about 10–20 % of patients may develop symptoms from the primary colonic tumor (e.g. obstruction, perforation, and severe bleeding) that necessitate acute intervention [7–11]. Upfront resection of the primary colon cancer prior to the development of symptoms could potentially prevent morbidity, and improve outcomes. Early retrospective data has suggested a survival benefit with primary colon resection, combined with chemotherapy, in the presence

M. Pezold, MD, MS
Department of Surgery, New York Presbyterian-Weill Cornell Medicine, New York, NY, USA

G.K. Ku, MD
Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

L.K. Temple, MD, MS (✉)
Colorectal Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA
e-mail: templel@MSKCC.ORG

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Table 14.1 Clinical question

P	Patient population	Unresectable, metastatic colon cancer with an asymptomatic primary tumor
I	Intervention	Primary tumor resection (colectomy) followed by 1st line chemotherapy,
C	Comparator	1st line chemotherapy with primary tumor resection only if/when patient becomes symptomatic
O	Outcomes	Overall survival, Hazard Ratio

of unresectable metastases [8, 12]. However, up to half of the patients in these analyses did not receive chemotherapy after surgery, and these patients had no survival benefit when compared to those receiving chemotherapy alone [12].

As a surgeon, it is difficult to draw conclusions from the literature, which is limited to retrospective data, with considerable susceptibility to selection bias. Further complicating the decision to pursue upfront surgery is the fact that there have been significant survival gains over the last decade as a result of multi-drug regimens and targeted therapies [13–20]. Depending on one's perspective, the improved survival associated with modern-era systemic therapy may either obviate the need for resection by providing significant reduction in tumor size and control of local symptoms, or may result in a greater number of patients developing symptoms from the primary tumor because they live longer, thereby requiring surgery. No good data exists regarding the likelihood of curative resection after chemotherapy in patients who present with initially unresectable disease; thus, the clinical choices in this setting are primarily colon resection followed by chemotherapy, or chemotherapy alone. In this chapter, we examine emerging data regarding primary tumor resection with chemotherapy in patients with unresectable metastatic disease and an asymptomatic primary, versus patients receiving upfront multidrug chemotherapy (Table 14.1).

Search Strategy

A detailed search of the Embase-Medline databases was conducted for current medical literature published from 2010 to 2015. The following search terms were employed to identify relevant articles: ("colon" OR "colorectal") AND ("cancer" OR "carcinoma" OR "adenocarcinoma") AND ("metastatic" OR "Stage IV" OR "Stage 4") AND "asymptomatic" AND ("surgery" OR "colectomy" OR "resection"). Duplicate articles were excluded. We included 14 articles, published from 2010 to 2015, that were identified in a Cochrane review and meta-analysis on this specific topic, and were not identified in our initial literature search [21, 22]. The title and abstracts of English-language articles were assessed for relevance. We excluded articles for the following reasons: not relevant, no comparator group (trend

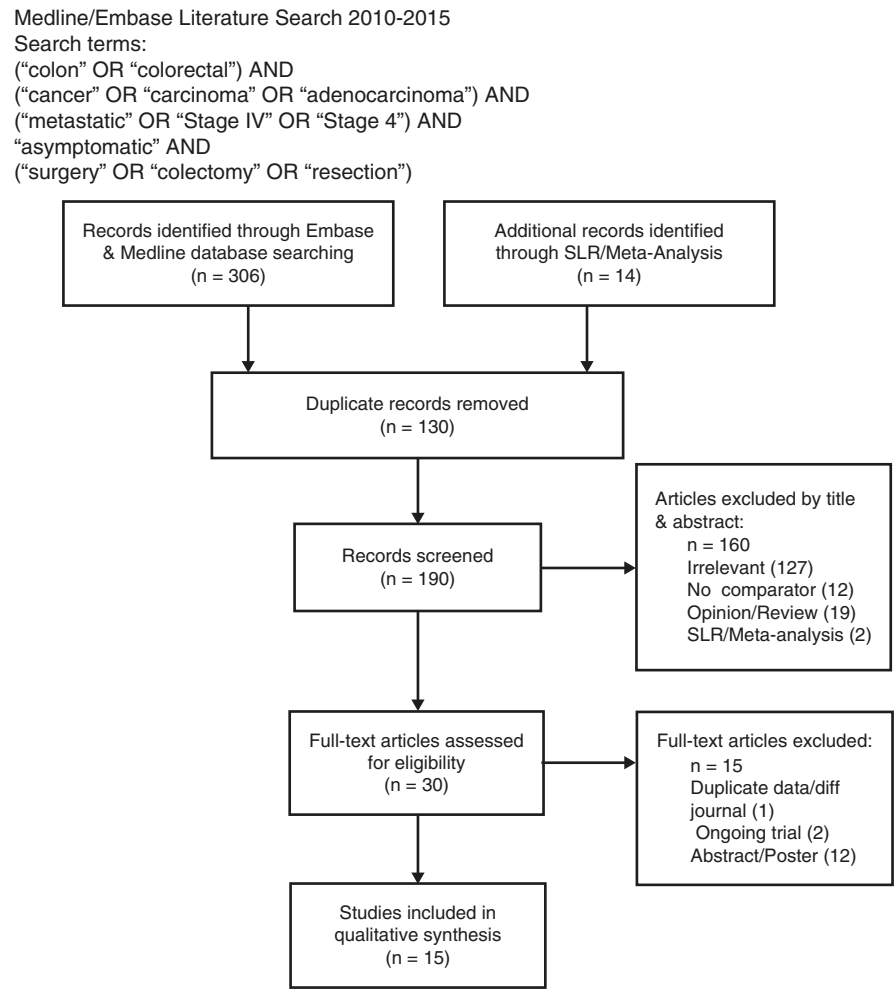

Fig. 14.1 PRISMA diagram, systematic literature search results

analysis), review/opinion articles without primary data, and systematic literature reviews/meta-analyses. A total of 30 articles met the inclusion criteria for full review. Full-text articles were excluded if they were limited to an abstract/poster, contained data duplicated in a different journal, or reported on ongoing trials without reporting any preliminary data. Fifteen manuscripts remained for analysis, five of which were identified from the Cochrane Review and meta-analysis. The literature review process, following PRISMA guidelines, is detailed in Fig. 14.1. Selected articles were abstracted for several variables including study design, time interval, patient population, chemotherapy, survival, and quality (Table 14.2).

Table 14.2 Literature search results

First author	Year	Study design	Interval	Patient population	Chemotherapy regimen(s)	Patients (n)		Median overall survival (mo)		Survival	Acute surgery (*NR*)	Quality of evidence
						R	*NR*	*R*	*NR*	*HR*	%	
Seo	2010	Retrospective cohort	2001–2008	umCRC + APT	FL ± Ox/Iri ± Bev/Cetux	196	83	22	14	–	8.4	Low
Chan	2010	Retrospective cohort	2000–2002	mCRC	Not reported	286	125	14	6	–	–	Very low
Venderbosch	2011	Retrospective review of RCT (CAIRO I)	2003–2004	mCRC	CAPOXIRI	258	141	16.7	11.4	0.63	–	Very low
	2011	Retrospective review of RCT (CAIRO II)	2005–2006	mCRC	CAPOX/Bev ± Cetux	159	289	20.7	13.4	0.65	–	Very low
Karoui	2011	Retrospective cohort, propensity scored	1998–2007	umCC ± APT	FL ± Ox/Iri ± Bev/Cetux	85	123	30.7	21.9	–	19	Low-Mod
Verberne	2011	Retrospective cohort	2002–2006	mRC ± APT	Not reported	26	21	26	17	0.5	–	Very low
Cetin	2013	Retrospective cohort	2006–2010	umCRC + APT	CAPOX/IFL/ FOLFIRI ± Bev	53	46	23	17	–	4.4	Low
Boselli	2013	Retrospecitve cohort	2010–2011	umCRC + APT	FOLOX ± Bev	17	31	4	5	–	–	Very low
Ferrand	2013	Retrospective review of RCT (FFCD 9601)	1997–2001	mCRC (mCC)	FL	156	56	16.3 (15.2)	9.5 (11.1)	–	7	Low

Yun	2014	Retrospective cohort, propensity matched	2000–2008	umCRC + APT umCRC + APT	± FL ± Ox/ Iri ± Bev/ Cetux	113 (286)	113 (198)	17.2	14.4	–	4.5	Moderate
Watanabe	2014	Retrospective cohort	2002–2009	umCRC + APT	FL ± Ox/ Iri ± Bev/ Cetux	46	112	19.9	19.0	–	21	Low
Yoon	2014	Retrospective cohort, propensity matched	2000–2007	umCRC ± APT	FL/Cape ± Ox/ Iri ± Bev/ Cetux	51 (195)	51 (66)	16.5	12	0.68	-	Low-Mod
Matsumoto	2014	Retrospective cohort	2005–2011	umCRC + APT	Fl ± Ox/ Iri ± Bev/ Cetux	41	47	23.9	23.6	0.72	25.5	Low
Tsang	2014	Retrospective cohort (SEER)	1996–2007	mCRC	Not reported	8599	3117	21	10	–	–	Very low
Tarantino	2015	Retrospective cohort, propensity scored (SEER)	1998–2008	mCRC	Not reported	22858	17575	–	–	0.40	–	Very low
Ahmed	2015	Retrospective cohort	1992–2005	mCRC + APT	Not reported	521	313	18.0	8.1	0.52	–	Very low

APT asymptomatic primary tumor, *Bev* bevacizumab, *Cape* capecitabine, *CAPOX* capecitabine/oxaliplatin, *CAPOXIRI* capecitabine/oxaliplatin/irinotecan, *Cetux* cetuximab, *FL* fluropymidine/leucovorin, *FOLFOX* leucovorin/infusional 5-FU/oxaliplatin, *FOLFIRI* leucovorin/infusional 5-FU/irinotecan, *Iri* irinotecan, *mCC* metastatic colon cancer, *mCRC* metastatic colorectal cancer, *mRC* metastatic rectal cancer, *Ox* oxaliplatin, *umCC* unresectable metastatic colon cancer, *umCRC* unresectable metastatic colorectal cancer.

Results

Our literature search identified 15 recently published retrospective studies, in which patients received primarily multi-drug chemotherapy. No prospective observational or randomized controlled trials (RCTs) have been published to date, and secondary analyses of these trials are limited.

Four RCTs were initiated to address this question, although two have already closed due to poor accrual [23, 24]. The Dutch Colorectal Cancer Group (CAIRO4) and the German SYNCHRONOUS trial group have opened multicenter, randomized, superiority trials comparing primary tumor resection + fluoropyrimidine-based regimens with targeted therapy, vs. fluoropyrimidine-based regimens with targeted therapy alone [25, 26]. The results of these trials are not anticipated for several years, but will obviously have a significant impact on surgical decision-making. Until that time, the data from our literature search represents the body of knowledge available on which surgeons may base decisions. Many studies report upfront resection vs. no resection, but do not address the more important question of upfront surgery and chemotherapy vs. chemotherapy alone. Among both groups, there were limited or no data regarding chemotherapy received, and need for acute surgery while on chemotherapy. Recognizing these limitations, a review of the current literature does provide some guidance to the practicing surgeon who is attempting to decide whether or not to resect the primary colon tumor before initiating chemotherapy in patients with unresectable metastatic disease.

Overall Survival

Twelve of the 15 studies identified in our search demonstrated better OS with primary tumor resection vs. no resection in patients with metastatic colon cancer, with a median survival benefit of 7 months. At face value, these results suggest superior OS with primary tumor resection prior to the development of symptoms in patients with unresectable metastatic CRC. Yet on closer analysis, there are serious limitations to these findings, and they should therefore be interpreted with ample skepticism.

To reduce the impact of selection bias and potential confounders, four studies used propensity score modeling, with variable results. Two groups from Korea used propensity scores to match patients who underwent initial primary tumor resection + chemotherapy vs. chemotherapy alone. The smaller of these studies found a statistically significant OS benefit with primary tumor resection (16.5 vs. 12 months, $p = 0.048$) [21], whereas the other, much larger study found no statistical difference in OS between these groups (17.2 vs. 14.4 months, $p = 0.27$) [27, 28]. In the remaining two studies, the data were not sufficiently defined or granular, and the results are less compelling [29, 30]. A French publication reported that OS was superior with primary tumor resection + chemotherapy vs. chemotherapy (30.7 vs. 21.9 months, $p = 0.031$) even after propensity analysis; however, a significant pro-

portion of patients in both groups had obstructive primary tumors at initial presentation (38.8 % vs 26.5 %), and it remains unclear if the survival advantage was from primary resection vs. stent placement or chemotherapy [29]. Similarly, a large U.S. SEER Database analysis demonstrated a dramatic survival advantage with primary tumor resection vs. no resection (HR = 0.40, $p < 0.001$) even after propensity matching (for such factors as age, grade, baseline carcinoembryonic antigen level), but potential confounders such as chemotherapy, performance status, comorbidity, and metastatic disease extent/resectability were not reported [30]. In the end, after controlling for confounding and sufficiently defining the target population, the data did not suggest a significant survival advantage with upfront surgery in asymptomatic patients.

Chemotherapy and Survival

A central criticism of earlier retrospective studies comparing primary tumor resection vs. initial chemotherapy has been the reliance on 5-fluorouracil (5-FU)/leucovorin monotherapy, which was the only chemotherapy agent available prior to the early 2000s. To restrict our literature search to modern chemotherapeutic regimens, we limited our investigation to studies published from 2010 to the present. Despite these efforts, seven of the selected articles included patients receiving 5-FU/leucovorin or the oral 5-FU pro-drug capecitabine alone [27–29, 31–34], and five studies failed to report whether chemotherapy was even administered [30, 35–38]. Furthermore, considerable heterogeneity in chemotherapy regimens existed in all but three of the studies. In these three studies, patients received only irinotecan- or oxaliplatin-based chemotherapy, with or without the monoclonal antibodies bevacizumab (anti-vascular endothelial growth factor) and cetuximab (anti-epidermal growth factor receptor) [39–41]. One of these studies retrospectively analyzed two RCTs and demonstrated a 5-month survival benefit with primary tumor resection and subsequent palliative chemotherapy; however, this study was limited by the fact that patients in the chemotherapy-only group had a statistically greater metastatic disease burden [39]. In the two remaining studies, primary resection followed by chemotherapy vs. chemotherapy alone did not significantly improve OS [40, 41].

The delay in initiating chemotherapy has frequently been considered a drawback to primary tumor resection. In the three studies reporting time-to-chemotherapy in asymptomatic patients who underwent upfront surgery, the data demonstrate a median 4–5 week delay in chemotherapy initiation, compared to patients who had upfront chemotherapy [31, 33, 41]. In addition to this delay, the data suggest that a significant proportion (15–50 %) of asymptomatic patients who undergo upfront surgery do not proceed to chemotherapy most likely due to debilitation from surgery [28, 33, 34, 37, 41] and only one of these studies showed an improved OS with upfront surgery [37]. Two publications included patients for either strategy only if they had received some chemotherapy; one of the two studies reported that primary tumor resection was associated with a significantly better OS (30.7 vs. 21.9 months, $p = 0.03$ [29]; 23 vs. 17 months, $p = 0.32$ respectively) [40]. These

data suggest that OS is potentially optimized in patients who have upfront surgery *when* they are able to receive postoperative chemotherapy. Identification of those patients who will be able to proceed from surgery to chemotherapy in an expeditious manner remains challenging.

Metastatic Disease Burden and Survival

Careful patient selection for upfront surgery is critical, as the disease burden of metastatic CRC has a dramatic influence on candidacy for curative resection and OS. Of the studies that reported a survival benefit with primary tumor resection [27, 29–32, 35–40], more than half did not report the extent or resectability of metastatic disease [30, 32, 35–39]. For example, two studies attempting to identify an optimal strategy through examination of SEER data reported that patients with stage IV CRC lived significantly longer after primary resection [30, 35]. However, neither study described the extent and resectability of metastatic disease, receipt of chemotherapy, or symptoms related to the primary tumor.

In a retrospective analysis of two Dutch RCTs (CAIRO I and II), OS was better with resection compared to no resection (16.7 vs. 11.4 months, $p = 0.004$; 20.7 vs. 13.4 months, $p < 0.0001$), although there was evidence to suggest that patients who did not have surgery were more likely to have an abnormal LDH, more extrahepatic disease, and oligo-metastases, all independent predictors of poor survival [39].

Amongst the eight manuscripts that provided sufficient documentation of the burden of unresectable metastatic disease, the majority of studies found that primary tumor resection did not provide a significant survival advantage over chemotherapy [27–29, 31, 33, 34, 40, 41]. Only two demonstrated a significant difference in median OS with upfront primary resection vs. initial chemotherapy (30.7 vs. 21.9 months, $p = 0.03$) [29], (21 vs. 10 months, $p < 0.001$) [27]. In a study by Chan et al., patients receiving chemotherapy first were significantly more likely to be of older age, to have adjacent organ invasion, extensive liver metastases, poorer performance status, and a rectal primary tumor, all of which are poor prognostic features. In the studies showing no survival benefit, three were of relatively small sample size ($n < 100$), and two limited primary resection to patients with non-traversable tumors only [33, 34, 40, 41]. However, in the overwhelming majority of studies with documented unresectable metastatic disease, OS was not significantly different between groups.

Further Considerations

While there is no compelling evidence that supports upfront surgery vs. chemotherapy with respect to survival benefit, surgeons face additional issues when deciding between primary surgery and chemotherapy. These deserve further discussion.

Acute Surgery During Chemotherapy

Removal of the primary tumor in an elective setting prior to the development of obstruction, perforation or severe bleeding should theoretically result in lower morbidity and mortality. Within our selected studies, 4–25 % of patients receiving chemotherapy first developed symptoms requiring acute surgery [22, 24–28]; and except for differences in the study sizes, no discernible trend could be found between low- and high-incidence studies with respect to patient population, chemotherapy received, or time interval. In three of the four largest studies (n > 200 patients), less than 10 % of patients required acute surgery while on chemotherapy; the most frequent indication was obstruction, and rarely tumor perforation or bleeding [28, 31, 32]. If the theoretical primary benefit of upfront resection is to avoid acute surgery at a later time, somewhere between five and ten patients would receive an unnecessary intervention in order to prevent acute surgery in one patient. Thus, the prevention of acute surgery with elective resection is less common than is purported. Additionally, one cannot ignore the potential delay in chemotherapy initiation, and the potential deterioration in performance status associated with serious surgical complications. From a prevention standpoint, primary tumor resection does not provide a significant benefit for most patients.

Postoperative Complications: Elective Versus Acute Surgery

Colorectal resection, even in the elective setting, is plagued by a variety of complications, and can delay the initiation of chemotherapy. Understandably, acute surgery comes with an even greater risk for complications that may significantly delay or prevent the re-institution of palliative chemotherapy. No study in our search reported on the delay or completion of chemotherapy associated with complications. Three studies reported complications after surgery [31, 33, 34], one of which provided data only on complications after elective resection, thus preventing inter-group comparisons [31]. The results from the remaining two publications failed to show a difference with regards to the incidence of complications, after either elective or acute surgery [33, 34]. The smaller of the two studies found similar rates of severe complications (Clavien-Dindo Grade 3 and 4) [34]; paradoxically, the larger study found that elective surgery was associated with more complications [33]. Although primary tumor resection should intuitively be associated with the lower morbidity of elective surgery, no study has actually demonstrated any such difference in morbidity between elective vs. acute surgery.

Systemic Inflammation and Primary Resection

Emerging evidence suggests that the benefits of primary tumor resection may involve more than the prevention of primary tumor symptoms. Tumor-associated systemic inflammation is associated with significant reductions in survival in patients with

solid-tumor cancers [42]. Increased neutrophil-to-lymphocyte ratio (NLR) is a well-established biomarker of systemic inflammation, and can be calculated with a simple complete blood count. However, none of the manuscripts identified in this search included NLR in their analyses. Two retrospective studies of patients with metastatic CRC who underwent primary tumor resection in the setting of asymptomatic disease, demonstrated a persistent survival benefit with a low NLR or reversal of NLR from high to low [43, 44]. Both studies stratified outcomes by NLR level; reversal of NLR with tumor resection was associated with an 11-month survival benefit compared to a persistently high NLR. These two studies were limited by the fact that they were retrospective analyses, lacked comparator groups, and did not clarify the extent of metastatic burden (other than reporting the presence of oligo-metastases). Nevertheless, these observations are intriguing and should be validated prospectively.

Recommendations

No definitive evidence supports upfront primary tumor resection in patients with unresectable, metastatic CRC and an asymptomatic primary who plan to receive multi-drug chemotherapy. Existing evidence for or against primary tumor resection is severely limited by data that is mostly retrospective and observational. There is considerable potential for selection bias when healthier patients with predicted better survival pursue surgery. No recent studies support primary tumor resection for the prevention of future symptoms, as none have clearly shown a diminished morbidity with upfront surgery. A meta-analysis and Cochrane Review have demonstrated no survival benefit with primary tumor resection in asymptomatic patients.

Given the paucity of data, the National Cancer Center Network (NCCN) Guidelines for colon cancer do not endorse resection of a primary tumor in the setting of unresectable synchronous liver and/or lung metastasis, unless the patient is at imminent risk for obstruction or severe bleeding [45]. Furthermore, the guidelines recommend synchronous or staged resection in the setting of resectable disease. Although the emerging retrospective evidence linking improved survival to lower systemic inflammation after primary resection in CRC is intriguing, many more basic science and clinical investigations are warranted. Randomized controlled trials are needed in order to clarify the benefits of primary tumor resection in asymptomatic individuals; biomarker and correlative analyses are essential to the attempt to identify a subpopulation that might benefit from initial surgery.

Personal View of the Data

My current practice embraces chemotherapy first in asymptomatic patients with unresectable, metastatic colon cancer, except in the cohort with lung-only metastases, as these patients tend to have more indolent metastatic disease. Less than 7 % of

patients at our institution ever require surgery for their primary tumor while receiving initial chemotherapy [11]. In this setting, multi-drug chemotherapy has proven effective and safe in the long-term treatment of metastatic disease. Moreover, in a subset of patients, current multimodality therapies have substantially improved our ability to obtain a curative resection at a later date. Given the survival benefits of a staged or synchronous resection, treatment should focus on improving the probability of resection. Clinical judgment, however, should ultimately direct decision-making, with the goal of optimizing survival and quality of life. In determining a treatment plan, I very carefully evaluate the patient for symptoms, reviewing colonoscopy reports and CT scans. In patients who present with anemia, I generally find that the symptoms can be managed medically, and this improves within 2–4 cycles of chemotherapy. In patients with mild obstructive symptoms, I tend to recommend upfront chemotherapy with careful observation, and find it quite common to see resolution of symptoms within 2 cycles of treatment. This approach is supported by data on our patients with locally advanced rectal cancer, in whom we routinely administer oxaliplatin-based induction chemotherapy and observe high radiographic, clinical and pathologic complete response rates [46]. For patients with significant symptoms and/or evidence of proximal dilation on CT scan, I recommend resection, bearing in mind the increased risk of complications and potential delay in chemotherapy. Although the data do not support primary tumor resection in patients with unresectable disease, there is considerable equipoise between strategies, and there is need for a randomized trial in the future.

Recommendations

- Patients with unresectable, metastatic colon cancer and an asymptomatic or minimally symptomatic primary tumor should not undergo resection of the primary tumor (Evidence quality low, weak conditional recommendation)

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Chapter 15
Management of Large Sessile Cecal Polyps

Brett Howe and Richard L. Whelan

Overview/Introduction

The subject matter of this chapter are large sessile adenomas of the cecum. The audience is presumed to be general or colorectal surgeons who regularly perform colonoscopy. This chapter is intended for a Western audience. It is important to note that the literature referenced in this chapter pertains to large bowel adenomas and is not necessarily specific to cecal lesions.

It is important to realize from the outset that there is presently a huge gulf between the Far East and the Western Hemisphere regarding the treatment of large sessile polyps. The high incidence of gastric cancer in Japan led to aggressive screening programs that were applied nationwide in an effort to detect premalignant lesions and cancers at an early stage. The technique of Endoscopic Mucosal Resection (EMR), now a piecemeal resection method, was initially used to obtain large gastric biopsies. Endoscopic Submucosal Dissection (ESD), which allows en bloc excision of mucosal lesions with normal tissue margins after submucosal injections to 'lift' the lesion off of the muscularis propria, was next developed for the management of early gastric cancer [1]. After learning and mastering these methods in the thick walled stomach a subset of Japanese endoscopists ventured into the large bowel more than a decade ago. Presently, large sessile polyps in all parts of the colon are routinely removed via ESD methods in Japan and other countries in the Far East with completion rates ranging from 80 to 91.5 %, a bleeding rate between 0 and 1.5 %, and perforation rates of 1.4–10.4 % [2–8].

B. Howe, MD • R.L. Whelan, MD (✉)
Mount Sinai School of Medicine, Mount Sinai West Hospital,
New York, NY, USA
e-mail: rwhelan@chpnet.org

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It should be noted that there are experts who believe that EMR (and not ESD) is the preferred method for removal of large sessile polyps outside the operating room setting [9–11]. Certainly, EMR is, by far, the more commonly used polypectomy method world wide. A clear disadvantage of EMR is that piecemeal resection makes it impossible to confirm complete resection via pathologic analysis.

It is also important to understand that there is also a large gap between the Far East and West as regards the ability to accurately distinguish between adenomas, advanced dysplastic lesions, and superficial cancers based on a lesion's surface appearance in the absence of tissue biopsies. Currently used methods include chromoendoscopy (use of surface dyes to reveal polyp surface anatomy and pit patterns), narrow band imaging, and magnification (via endoscope up to 150 X). A separate endoscopic examination may be performed wherein some or all of the above methods are applied to a large polyp and many photos obtained; in many centers this data is reviewed by experts at a polyp staging conference [akin to a tumor board] at which time a consensus diagnosis is made. The ability of these methods to distinguish between adenomas with varying degrees of dysplasia, SM-1 cancer, and SM-2 cancer has been verified in numerous large case series [12–16]. The end result is that in Japan far fewer colectomies are done for large benign sessile colorectal adenomas and noninvasive highly dysplastic lesions.

At present, a relatively small subset of Western gastroenterologists, are learning and employing these techniques in a limited number of centers. In an effort to avoid colectomy and its attendant morbidity and mortality, several combined surgical and endoscopic polyp removal methods have also been developed and utilized [17–19]. Nonetheless, the vast majority of large sessile lesions in the U.S. are still treated via segmental colectomy, most often a standard oncologic resection. An assumption of this chapter is that, where safe and feasible, avoidance of colectomy is desirable.

It should also be noted that the endoscopic and combined endoscopic/laparoscopic skill sets and experience of surgeons varies greatly in the U.S. and that we are on the threshold of substantial changes in this arena. This reality makes general recommendations applicable to all settings impossible. Each surgeon must look within their medical/surgical community and, perhaps, refer patients to interventionalists familiar with advanced polypectomy methods or combined laparoscopic/endoscopic methods. Alternately, having made the commitment to learn one or more of these newer methods, appropriate training and skills acquisition must take place prior to embarking on the employment of these techniques. The learning process is facilitated by identifying an interested and experienced surgical colleague who is willing to participate in these cases. The consent process must be honest and fully explain the potential benefits and complications of the new methods. When performed by surgeons, in the authors' opinion, these procedures are best carried out in the operating room. Also, it is advised that a broad consent be obtained that gives permission for either endoscopic or laparoscopic surgical removal of the polyp, via wedge resection or standard colectomy. In the authors institution, these cases are covered by an Institutional Review Board (IRB) approved protocol and an IRB consent is obtained prior to surgery [19].

Treatment Options

Polyp treatment options include: (1) EMR (standard piecemeal snare polypectomy with/without saline lift), (2) ESD polypectomy, (3) laparoscopic-facilitated colonoscopic piecemeal polypectomy, (4) "wedge" partial circumference cecectomy, (5) standard segmental bowel resection. As mentioned, although ESD experts perform the procedure in the endoscopy suite, presently, in the U.S., the small number of surgical endoscopists performing ESD or EMR for the large and most challenging polyps do so in the operating room usually under general anesthesia. In this way, after the ESD is completed, a laparoscopy can be performed to inspect the bowel for perforations or weaknesses which, if found, can be closed with seromuscular sutures. Alternately, if the ESD/EMR attempt fails, then the polyp can be removed surgically (wedge or segmental resection). Of note, it is mandatory that CO2 gas be used for endoscopic insufflation of the large bowel when ESD or EMR is performed in conjunction with laparoscopy in order to avoid bowel distension and loss of the operative field.

A brief discussion of these methods follows:

EMR and Laparoscopic Inspection

It is strongly advised that a submucosal lift be established prior to snare polypectomy EMR. The lift makes full thickness perforation less likely by increasing the distance between the muscularis propria and the lesion. Also, failure of a part of the lesion to lift alerts the endoscopist to the possibility that a cancer may be present and invading into the deep muscular layer (vs. scarring from a prior removal attempt). It is important that a concerted effort be made to fully remove the polyp during the first attempt since subsequent efforts will be more difficult and associated with a higher perforation risk due to scarring between the mucosa and muscularis propria. As regards bleeding, rates between 3.1 and 11.3 % have been reported in EMR series [20–22]. After successful completion of the EMR, a laparoscopy may be performed to evaluate the bowel wall integrity and repair or to reinforce the bowel wall if needed. In failed cases a laparoscopic bowel resection can be carried out.

ESD and Laparoscopic Inspection

The following tools are necessary for ESD: lifting solution, sclerotherapy catheter, needle knife (variety available), dissection cap (fits on scope tip and facilitates submucosal dissection), polypectomy snare (specialty snares available), and, importantly, a high frequency electrosurgical current generator (HFEC, that

provides pulsed, adjustable currents). A More detailed description of the method can be found elsewhere. Briefly, the patient is positioned so that the lesion is "up". After injection of the lifting solution (usually with methylene blue added) the resection margin is superficially marked with the knife (HFEC soft coagulation setting) after which the mucosa is fully scored for about 25–35 % of the circumference. Next the cut mucosal edge is undermined with the knife creating a submucosal pocket into which the scope tip (with dissection cap affixed) is inserted; the submucosal dissection is then continued beneath the lesion. As needed, the circumference of the specimen is completely scored. Gravity assists by retracting the partly detached polyp. A snare may be used to complete the resection. Clips may be used to close to the mucosal defect. As for EMR, laparoscopic inspection and repair of the bowel wall (vs wedge or ileocolectomy if major injury is found) may be performed after ESD completion.

Laparoscopic-Facilitated Colonoscopic Polypectomy Method

Milsom, Franklin, and Lee have championed this method carried out in the operating room wherein a piecemeal colonoscopic EMR is carried out after submucosal lift with the help of simultaneous extrinsic manipulation of the polyp and colon segment via laparoscopic instruments. After polypectomy the bowel wall is inspected (after submersion under water) via laparoscope and endoscope. Full thickness injuries and smaller perforations are repaired laparscopically with seromuscular sutures. The specimens are removed transanally. If necessary, a laparoscopic segmental colectomy can be performed. This method requires an experienced laparoscopist in addition to an expert endoscopist. The laparoscopic bowel manipulation is challenging and more dangerous than usual because the colon (and possibly the small bowel) is fully insufflated which notably decreases the operative working space [17–19].

Laparoscopic "Wedge" Partial Circumference Full Thickness Resection

This method is an option for well placed cecal lesions. A laparoscopic linear GIA type stapler is used to resect a portion of the cecum containing the polyp (identified via tattooing and simultaneous colonoscopy). It is critical that the ileocecal (IC) valve be protected and that the polyp be fully removed. The authors recommend that the stapler be applied only after the colonoscope has been inserted into the terminal ileum (protects the valve and TI). After closing the stapler, the colonoscope is withdrawn into the right colon and the stapler's position assessed. After resection, the cecal specimen must be removed from the abdomen and then opened and inspected.

If the margin is in question, frozen sections should be obtained. If a clean margin is not obtained then either more cecum need be removed or an ileocectomy performed. Practically, it is very difficult to wedge resect polyps that lie between the appendiceal orifice and the IC valve because either the IC valve may need to be partially resected or the polypectomy is incomplete [17, 19].

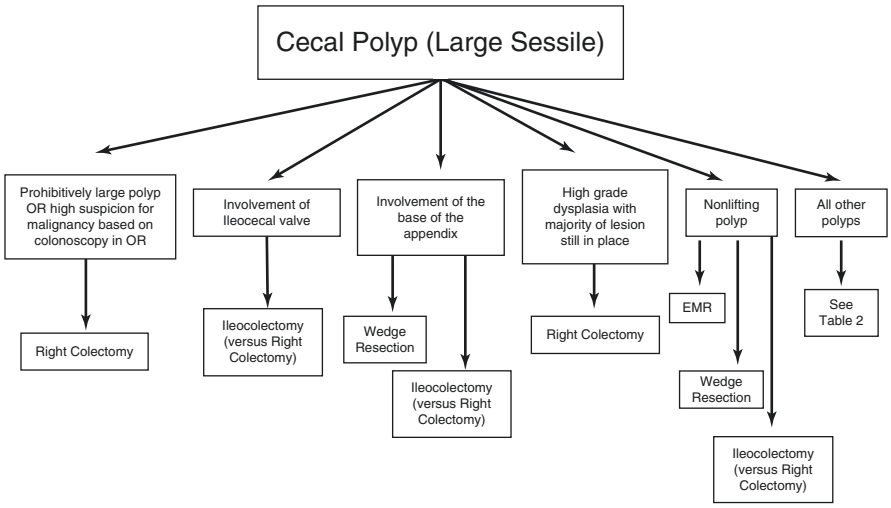
Standard Segmental Bowel Resection

Performed laparoscopically, when necessary. The main question here is whether to do a limited ileocectomy (as for Crohn's disease) vs a standard oncologic right hemicolectomy. It is the author's preference to do a right hemicolectomy because of the risk that an invasive cancer will be found on final pathology.

Treatment Algorithm

It is also not possible to provide a simple algorithm for the treatment of sessile cecal polyps because specific characteristics of the polyp (size, degree of dysplasia, failure to lift, etc.) and the specific location of the polyp (involvement of ileocecal valve or appendiceal orifice) may dictate treatment. Table 15.1 provides the treatment option(s) for each of these situations.

Table 15.1 Treatment algorithm for large sessile cecal polyps



Polyp Characteristics

Very large size is a relative contraindication for endoscopic removal (the skill set of the endoscopist is also a factor); polyps that involve the great majority of the cecum are best dealt with via bowel resection.

Regarding large sessile polyps for which prior biopsies show high grade dysplasia and where the majority of the polyp remains in place; the two largest series suggest that there is a 30–41% chance of there being invasive cancer on final pathology [23, 24]. Given the present inability of the vast majority of Western endoscopists to make the distinction between a highly dysplastic polyp and a cancer based on the surface appearance or other means, the authors recommend a standard oncologic right colectomy for patients with large sessile adenomas with high grade dysplasia.

Polyps that do not fully "lift" with submucosal injection also pose a problem. Failure to lift may signify either the presence of cancer invading into the muscularis propria or a scar that is the residua of prior polypectomy attempts. The treatment options in this situation are: EMR via snare, wedge partial circumference full thickness resection, or ileocolectomy (vs right hemicolectomy).

Location

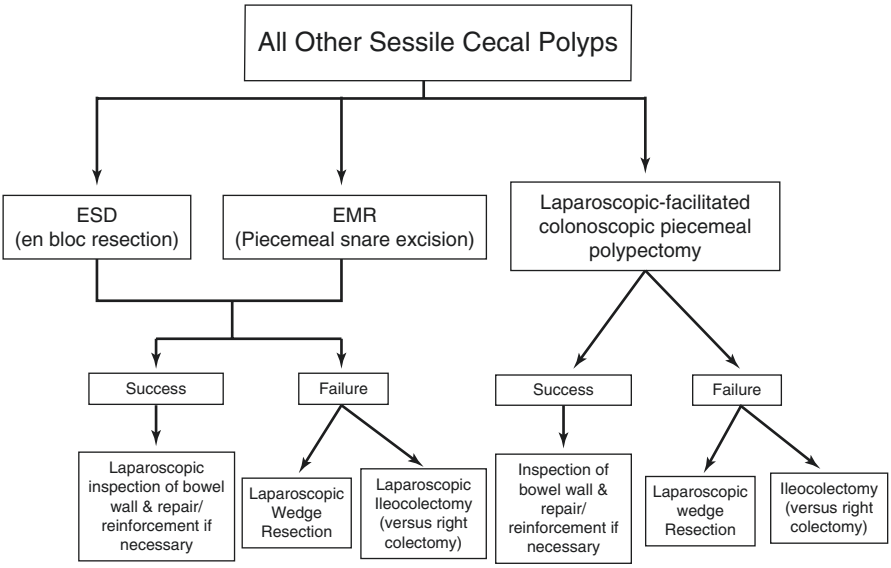
ESD and complete EMR are not options for lesions involving the ileocecal valve or appendix base since the inner polyp edge and margin may not be visible or accessible. The appropriate treatment for the former is an ileocolic bowel resection (vs right colectomy) whereas for the latter a wedge resection may be possible vs. an ileocolectomy.

Algorithm (for Polyps That Do Not Fall into the Above Categories) (Table 15.2)

As stated, an assumption has been made that surgical endoscopists would perform these advanced colonoscopic procedures in the operating room in conjunction with laparoscopy. Since there are multiple advanced colonoscopic methods that can be used and because the preference and experience of each surgeon will largely determine the method chosen, the algorithm includes all 3 methods.

The ESD and EMR methods are listed side by side in the table since the algorithm for each is the same. After successful polypectomy, laparoscopy is done to interrogate the bowel for perforations and to repair the bowel wall with seromuscular sutures, if necessary. If the polypectomy is not successful, a wedge resection would be carried out, if feasible. Laparoscopic-assisted colectomy is reserved for

Table 15.2 Treatment algorithm for large cecal polyps amenable to combined endoscopic/laparoscopic treatment



failed polypectomy patients for whom wedge resection is not an option or if the bowel has been injured beyond repair during endoscopic polyp removal.

Proponents of the laparoscopic-facilitated colonoscopic method (Milsom, Franklin) would follow the right most track on Table 15.2; in these cases, the laparoscopy would be done simultaneously so that the polyp can be presented to endoscopist during the polypectomy. After successful colonoscopic polypectomy the bowel wall is inspected and laparoscopically repaired if need be. A laparoscopic wedge resection or ileocolectomy is reserved for patients in whom the colonoscopic removal attempt fails.

Conclusion

It is appropriate to utilize advanced colonoscopic methods to remove large benign polyps in order to avoid colectomy and its attendant morbidity. Numerous methods are available, however, in the authors opinion, ESD is the current gold standard. Since ESD has not yet been widely embraced by gastroenterologists in the U.S., the combined colonoscopic and laparoscopic methods discussed in this chapter have been devised and employed by surgeons in the West. Use of these methods holds the promise of organ preservation in patients in whom the current alternative is a segmental colectomy. Having said this, it is likely that in a decade or so these lesions will be excised endoscopically in the endoscopy suite without the need for concomitant laparoscopy.

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Chapter 16
Stage II Colon Cancer: Towards an Individualized Approach

Blase N. Polite

Introduction

Like many oncologists, the sight of a stage II colon cancer patient on my schedule draws a sigh. I know the discussion will be long and the concepts confusing even to the statistically literate; and at the end of the day, I will have to leave it up to the patient to make the decision because neither guidelines nor data in the vast majority of the cases clearly point to the correct answer of whether they should or should not receive chemotherapy. The problem is that stage II colon cancer is a wastebasket of likely different cancers biologically with SEER 5-year survival rates ranging from 66 % in stage IIA cancers to 37 % for stage IIC disease [1]. In this chapter, I will present the current state of science for stage II colon cancer with the hopes of allowing the practitioner to better risk stratify patients and thereby select those who are most likely to benefit or not benefit from adjuvant chemotherapy. I will conclude with my recommendations for specific cases with the strength of that recommendation based on the science.

Search Strategy

PICO table

Pt population	Intervention	Comparators	Outcomes studied
Pts with stage 2 colon cancer	Chemo	Observation	Disease free survival, overall survival

B.N. Polite, MD, MPP
Section of Hematology/Oncology, University of Chicago Biological Science Division, Chicago, IL, USA
e-mail: bpolite@medicine.bsd.uchicago.edu

N. Hyman, K. Umanskiy (eds.), *Difficult Decisions in Colorectal Surgery*,
Difficult Decisions in Surgery: An Evidence-Based Approach,
DOI 10.1007/978-3-319-40223-9_16

I searched the PubMed data base using the following MeSH terms: Colonic Neoplasms/drug therapy, Colonic neoplasms/pathology, Colonic neoplasms/surgery, chemotherapy/adjuvant, gene expression, DNA mismatch repair, fluorouracil, oxaliplatin, irinotecan, meta-analysis, randomized controlled trials. References of relevant articles were searched for missed studies. I also reviewed major abstracts relevant to these topics presented at the ASCO annual meeting and ASCO GI symposium from 2012 to 2015. Finally, I cross checked my references with those in the UpToDate article entitled "Adjuvant chemotherapy for resected stage II colon cancer." [2]

Results

Non-risk Stratified Patients

Table 16.1 lists the most relevant studies which have attempted to answer the utility of chemotherapy in stage II colon cancer. While not a perfect study, only the QUASAR trial [3] comes close to being a truly randomized trial of stage II colon cancer patients with reasonable power to answer the question of a chemotherapy benefit. All the other studies are either underpowered or are pooled subset analyses of randomized trials. Most of these are very well done scientifically, including a meta-analysis done by the Cochrane group [4], but suffer from biases inherent in pooled analysis. To this mix we also add registry data which are the weakest of all the study types in the table because of uncontrolled threats to internal validity. In the QUASAR trial, 5-FU chemotherapy resulted in a statistically significant improvement in overall survival and disease free survival. The absolute magnitude of the survival benefit was 3.6 % (95 % CI: 1–6 %) meaning you would have to treat 28 patients with chemotherapy to save one life. No other study confirms this survival advantage statistically, but most suggest a magnitude of benefit which is not inconsistent with the QUASAR results either for overall survival (OS) or at least for disease free survival (DFS) [4–11]. The exception to this are 2 registry studies from the United States and British Columbia which fail to show any advantage to chemotherapy and may even suggest it is detrimental [12, 13]. The two trials utilizing more modern oxaliplatin-based chemotherapy do not appear to show a significant improvement over 5-FU alone for stage II colon cancer patients, although they are underpowered to answer this question with any certainty [6, 11].

Risk-Stratification-Clinical and Pathologic Factors

It is important to clarify terminology surrounding risk stratification, namely the distinction between a prognostic versus a predictive factor. Prognostic factors relate to the expected outcome of patients with those factors. Predictive factors are ones which determine how well a patient will respond to a particular therapy or

Table 16.1 Role of chemotherapy for stage II colon cancer

Study	Trial type	Stage II cancer Pts	Therapies	RFS (95 % CI)	OS (95 % CI)	Strength
QUASAR [3]	RCT	2,146	5-FU vs surgery alone	0.78 (0.66–0.93)	0.82 (95 % CI: 0.7–0.95)	High
NACCP [10]	RCT (subset)	468	5-Fu vs surgery alone	71 % vs. 65 % (OR crosses 1)	5 year: 78 % vs 70 % (OR crosses 1)	Moderate
INT-0035 [9]	RCT	318	5-Fu vs surgery alone	7 years: 79 % vs 71 % (p = 0.1)	7 year: 72 % vs 72 % (p = 0.83)	Moderate
Nordic [8]	Pooled RCT	812	5-FU vs surgery alone	NR	79 % vs 79 % (p = 0.81)	Moderate
IMPACT-B2 [5]	Pooled RCT	1016	5-Fu vs surgery alone	5 year: 76 % vs 73% (p = 0.061)	5 year: 82 % vs. 80 % (p = 0.057)	Moderate
Gill et al. [7]	Pooled RCT (IMPACT-B2 + 2 additional trials)	1440	5-FU versus surgery alone	5 year: 76 % vs. 72 % (p = 0.049)	5 year: 81 % vs 80 % (p = 0.1127)	Moderate
MOSAIC [6]	RCT (subset)	899	FOLFOX vs 5-FU	5 year: 83.7 % vs 79.9 % (p = 0.258)	6 year OS: 86.9 vs 86.8 (0.986)	Moderate
NSABP C-07 [11]	RCT (subset)	699	FLOX vs 5-FU	5 year: 82.1 % vs. 80.1 %	89.7 vs 89.6	Moderate
Cochrane [4]	Meta-analysis	7097	Chemo vs. surgery alone	HR 0.83 (0.77–0.92)	HR 0.96 (0.91–1.02)	Moderate
SEER-Medicare [13]	Registry	6,234[a]	Chemo vs surgery alone	NR	5 year: 70 % vs. 69.5 %	Moderate
BCCA data base [12]	Registry	1,697[a]	Chemo vs surgery alone	5 year: 87.1 % vs. 92 % (p = 0.18)	5 year: 82.9 vs 83.3 (p = 0.561)	Moderate

NR not reported

[a]Stage II with no poor prognostic feature (obstruction/perf, T4, poor/undiff histology, >12 LN, emergent surgery)

intervention. A common fallacy to which we are all susceptible is that patients with the worst prognosis are the ones most likely to benefit from aggressive treatment. It is sometimes the case but often it is not. In stage II colon cancer, the most commonly recognized prognostic factors are as follows: T4 disease, inadequate lymph node sampling (<12 lymph nodes), poorly differentiated histology (in MSI-L/S patients), perforation, obstruction, lymphovascular invasion, perineural invasion, and positive resection margins [14]. It is very important that the reader pay special attention to the high grade tumor histology and the importance of interpreting this in the context of the mismatch repair (MMR) or microsatellite instability (MSI) status of the tumor. As we will go into detail below, tumors with MMR deficiency or MSI-H phenotype are often high grade yet have an excellent prognosis.

Whether these adverse risk factors are predictive of benefit to chemotherapy is less clear. The strongest data to suggest a benefit of chemotherapy in high risk groups comes from the British Columbia Cancer Agency (BCCA) registry which found a significant survival advantage for patients with T4 tumors who received 5-FU chemotherapy (HR 0.5 95 % CI: 0.33–0.77) [12]. In contrast neither a US Intergroup meta-analysis nor a SEER registry study could discern any differential chemotherapy advantage for high versus low risk groups [7, 13]. In the MOSAIC study utilizing oxaliplatin-based therapy, there was a suggestion of a disease free survival advantage in the high risk stage II group with 5 year DFS of 82.3 % versus 74.6 % (HR 0.72; 95 % CI: 0.5–1.02) for FOLFOX versus infusional 5-FU alone [6].

Risk-Stratification-Molecular Factors

The strongest data for both a prognostic and predictive factor exists for a deficiency in the mismatch repair pathway. It is beyond the scope of this chapter to explain the nuances of MMR deficiency and testing for it; but in brief, patients with defective MMR tumors either have a germline loss of one of the MMR proteins (MLH1, MSH2, MSH6, PMS2) or epigenetic silencing of the MLH1 promoter [15]. The former is associated with Lynch syndrome and the later often in the setting of a CpG Island methylator phenotype (CIMP). Defective MMR tumors can either be tested for using a PCR panel of 5 reference microsatellite sites; if at least 2 show instability then the tumor is characterized as MSI-H. More often in the clinical setting, immunohistochemistry testing (IHC) is used to stain for the presence or absence of one of the MMR proteins. By convention in the literature, we call a tumor as defective MMR (dMMR) if they are either MSI-H or have an absence of an MMR protein by IHC.

Table 16.2 lists the major studies which have explored the prognostic and predictive value of MMR testing in stage II colon cancer. The majority of these studies clearly show that those with dMMR stage II tumors have a superior prognosis compared to those with pMMR with hazards of recurrence or death often 50 % lower [16–20]. In the study by Sargent, et al. [19] patients with dMMR tumors who received chemotherapy had a hazard of death which was nearly three times those who were on observation (HR 2.95; 95 % CI: 1.02–8.54). The reason why this may be the case is speculative, but we know patients with dMMR often have an intense

Table 16.2 Role of dMMR as prognostic and predictive marker for stage II colon cancer

Study	dMMR colon patients	Therapies	DFS (vs pMMR)	DFS w/chemo vs w/o chemo	OS (vs pMMR)	OS w/chemo vs w/o chemo
Sargent et al. [19]	102 (stage II)	5-FU vs surgery alone	0.51 (95 % CI: 0.29–0.89)[a]	HR 2.3 (95 % CI: 0.84–6.24)	0.47 (0.26-0.83)[a]	2.95 (95 % CI:1.02–8.54)
Jover et al. [27]	76 (38 stage II)	5-Fu vs surgery alone	6 year: 71 % vs 63 % (p=0.3)	6 year: 57.7 % vs 67.6 % (p=0.6)[b]	76 % vs 71 % (p=0.5)	69.2 % vs 73.5 % (p=0.8)[b]
Kim et al.(NSABP c01-c04) [28]	98 (II and III)	5-Fu vs surgery alone	HR 0.77 (95 % CI: 0.4–1.48)[a]	Interaction p=0.68[b]	HR 0.82 (95 % CI: 0.44–1.51)	Interaction p=0.62[b]
Klingbiel et al. (PETACC-3) [18]	86 (stage II)	FOLFIRI vs 5FU	HR 0.26 (95 % CI: 0.1–0.65)	HR 1.27 (0.65–2.49)	HR 0.16 (0.04–0.64)	HR 1.47 (0.65–3.36)
Hutchings et al. (QUASAR) [17]	167 (stage II)	5-Fu vs surgery alone	RR 0.44 (95 % CI: 0.29–0.67)	2 year: 2.2 % vs 5.1 % Interaction p=0.55	NR	NR
Gavin et al (NSABP C07-C08) [16]	207 (93 stage II)	FOLFOX	HR 0.48 (95 % CI: 0.3–0.7)	Interaction 0.97	HR 0.64 (95 % CI: 0.46–0.89)	Interaction p=0.848

dMMR defective DNA mismatch repair, *pMMR* proficient mismatch repair, *NR* not reported

[a]Includes only patients not treated with chemotherapy

[b]Includes stage II and III

immune response to their tumors and are in fact the only colon cancer cohort to date where immune checkpoint inhibitors appear to be effective in the metastatic setting [21]. It is suggested that chemotherapy may blunt this immune response. This hypothesis is further corroborated by recent data suggesting that if there is a chemotherapy benefit for these patients, it is only for those with germline tumors which tend not to express the hyper-mutated phenotype [22]. These findings of a detrimental impact have not been corroborated by the other studies listed in Table 16.2. However, no study has found a clearly beneficial impact of chemotherapy for this cohort, who have an otherwise excellent prognosis. It is important to note that all of these studies are severely limited by power to test for the interaction between dMMR status and chemotherapy effect.

Several studies have also looked at other molecular mutations in the BRAF and KRAS genes including interactions of these factors with dMMR status as well as those with CpG Island methylator phenotype [16, 17, 23, 24]. No clear consensus has emerged with one study suggesting a BRAF mutation is prognostic for poorer overall survival in all stage II patients [16] and another in only those with pMMR status [23]. An additional study suggested a poorer survival for KRAS mutant tumors but not BRAF [17]. In none of the studies were KRAS, BRAF, or CIMP predictive of benefit from chemotherapy and as such have not found their way into our treatment algorithms.

Risk-Stratification-Gene Expression Profiling

Genomic Health (Redwood City, CA), developed an 12 gene recurrence panel and tested an 11 gene treatment benefit panel marketed as the Oncotype DX Colon Cancer Assay [20]. The recurrence score was able to segregate patients with stage II colon cancer into low, intermediate and high risk groups with those in the lowest risk group (44 % of patients) having a 13 % 3 year risk of recurrence and those in the highest risk group (26 % of patients) having a 21 % risk of recurrence. The recurrence score remained prognostic even after controlling for other pathologic and clinical characteristics. A further validation study using CALGB 9581 patients and a more contemporaneous cohort of patients treated with oxaliplatin in the NSABP C-07 study found similar results [25, 26]. Unfortunately, in none of these studies was the recurrence score or the treatment score able to predict the patients most likely to benefit from chemotherapy. That is, the gene panel is prognostic but not predictive, meaning the proportional benefit from chemotherapy was similar regardless of recurrence score. Can such a test be useful? The answer is, yes if small differences in absolute benefit are important to your patient. For example, assuming a 20 % proportional benefit to chemotherapy (consistent with the QUASAR data) a patient with a low risk score would expect about a 2.6 % absolute benefit from chemotherapy whereas one in the high risk group a 4.2 % absolute benefit. I have found very few patients who find these types of differences helpful in their decision making but it is a discussion that I have especially in my T3N0 pMMR patients.

Recommendations Based on the Data

1. All stage II patients should be tested for dMMR either by IHC or PCR and those with dMMR should not receive chemotherapy (evidence quality high, strong recommendation)
2. Patients with T4 tumors, high grade (pMMR), <12 LN sampled, or with perforation should receive 5-FU-based chemotherapy (evidence quality moderate, moderate recommendation)
3. Patients with T4b tumors should receive oxaliplatin based chemotherapy (evidence quality weak, moderate recommendation)
4. Patients with T3N0 pMMR tumors should be offered Oncotype DX testing to aid in decision making (evidence quality moderate, weak recommendation).

A Personal View of the Data

Stage II colon cancer confronts us with the battle of the head versus the heart. Only for dMMR patients are the two well aligned where I believe the data compel us not to offer these patients chemotherapy. For pMMR T3N0 patients with no high risk features (High grade and <12 lymph nodes positive being the main ones I pay attention to in this setting) I remain at true equipoise. I am comfortable with whatever decision my patients make and see my role as trying to ensure they understand the risks and benefits so that they can make a truly informed decision. It is in the stage IIB and IIC patients I struggle most. My heart (or my gut) wants to treat all IIB patients with fluoropyrimidine- based chemotherapy and all IIC with FOLFOX. I rationalize that the IIC patients have a worse 5 year survival than IIIB patients and therefore should be treated as aggressively, but I am at a loss to point a single piece of strong evidence to support this. Nevertheless, that is my practice.

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Part III
Rectal Cancer

Chapter 17
Rectal Cancer: Management of T1 Rectal Cancer

Woon Kyung Jeong and Jose G. Guillem

Introduction

The widespread implementation of screening colonoscopy has led to a parallel increase in the detection of early staged rectal cancer including T1N0M0 lesions. Rectal cancers at this stage have invaded into the submucosal layer of the rectal wall without metastasis to lymph nodes and other organs and have been traditionally managed with a transabdominal radical resection (RR). However, since a RR is associated with significant postoperative morbidity, local excisional approaches (LE) such as transanal excision (TAE), transanal endoscopic microsurgery (TEM), and transanal minimally invasive surgery (TAMIS), have been adopted. Whether the oncological results of a less morbid LE approach is comparable to a more morbid RR approach for T1N0M0 rectal cancer is the essential question of this chapter.

When confronted with a patient with a presumed T1N0M0 rectal cancer based on preoperative physical exam and imaging studies, both LE and RR options have to be considered and the pros and cons of each approach and their associated long-term and short-term oncological outcomes and functional consequences and implications for the specific patient at hand carefully discussed.

W.K. Jeong • J.G. Guillem (✉)
Colorectal Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
e-mail: guillemj@MSKCC.ORG

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Search Strategy

P (patients)	I (intervention)	C (comparator)	O (outcomes)
Patients with T1 rectal cancer	Local excision	Radical resection	Oncologic outcomes, quality of life

A literature search in Pubmed, Embase, and Scopus databases was performed. The terms used for the search included: "T1 rectal cancer"; "early staged rectal cancer"; "local excision"; "radical resection"; "recurrence"; "sexual function"; "anorectal function" and "quality of life". Only articles written in English and published between 2010 and 2015 and reporting original data or meta-analysis on T1 rectal cancer were selected. Important and evidence-based studies published before 2010 were also included.

Results

We found two meta-analyses which met our search criteria and included most of the significant data on the topic (Table 17.1) [1, 2]. Of these two studies, one was larger (2896 patients from 13 studies [1] versus 860 patients from seven studies [2]) and reported detailed preoperative diagnostic workup and oncologic data including lymphovascular invasion and surgical margin status as well as the use of neoadjuvant and/or adjuvant therapy [1]. However, these two meta-analyses included studies that were retrospective and non-randomized [3–15], and some of the retrospective studies included small numbers of patients. The one prospective randomized study on this topic which was included in both meta-analyses only enrolled 50 patients [16].

Oncologic Outcomes

Local Recurrence

In our review of these two meta-analyses, rates of local recurrence were higher in patients undergoing a LE when compared to patients undergoing a RR (4–33 % versus 0–6 %, respectively) [1, 2].

Distant Metastasis

Of these two meta-analyses, only one compared distant metastasis rates between LE and RR and showed no significant differences (0–8 % versus 0–4 %, respectively) [2]. However, it is important to point out that this study included only patients undergoing TEM and did not include TAE or TAMIS.

Table 17.1 Comparison of meta-analysis studies on T1 rectal cancer

Study	Year	Study design	Patients (LE/RR)	Local recurrence	Distant metastasis	DFS	OS	Morbidity	Mortality	Quality of evidence
Kidane et al. [1] (TAE, TEM, TAMIS vs. RR)	2015	Meta-analysis	2896 (1315/1581)	LE > RR (relative risk, 2.36; 95 % CI, 1.64–3.39)	n/a	5-years DFS, LE < RR (relative risk, 1.54; 95 % CI, 1.15–2.05)	5-years OS, LE < RR (relative risk, 1.46; 95 % CI, 1.19–1.77)	LE < RR (relative risk, 0.20; 95 % CI, 0.10–0.41)	LE < RR (relative risk, 0.31; 95 % CI, 0.14–0.71)	moderate
Lu et al. [2] (TEM vs. RR)	2015	Meta-analysis	860 (303/557)	LE > RR(OR, 4.62; 95 % CI, 2.03–10.53)	no difference (OR, 0.74; 95 % CI, 0.32–1.72)	no difference(OR, 1.12; 95 % CI, 0.31–4.12)	no difference(OR, 0.87; 95 % CI, 0.55–1.38)	n/a	n/a	moderate

LE local excision, *RR* radical resection, *DFS* disease-free survival, *OS*, overall survival, *TAE*, transanal excision, *TEM*, transanal endoscopic microsurgery, *TAMIS*, transanal minimally invasive surgery, *CI*, confidence interval, *OR*, overall risk, *SEER*, surveillance, epidemiology, and end results, *HR* hazard risk

Overall Outcome

In one meta-analysis, disease-free survival rate was higher in patients undergoing a RR [1]. However, in the other meta-analysis, no significant difference was noted in disease-free survival between the two surgical treatment options [2]. This may be due to the fact that in the latter met-analysis, only 2 studies reporting disease-free survival were included.

With regard to overall survival, one meta-analysis showed better results for RR over LE [1]. The other meta-analysis did not, even though it did demonstrate a significantly higher local recurrence rate in patients undergoing a LE (odds ratio, 4.62; 95 % confidence interval, 2.03–10.53) [2]. The authors do not provide an explanation for this. However, it is possible that salvage radical surgery and adjuvant chemotherapy and/or radiation therapy may have eradicated some of the locally recurrent rectal cancer and impacted survival in a positive manner. However, other studies suggest that failure following a local excision may not be salvageable in a significant number of cases [17].

Quality of Life

Of the two meta-analyses, only one reported on morbidity and noted a higher morbidity rate for RR over LE [1]. LE was associated with a much lower need for permanent stoma [1]. However, a number of the studies included were from over 20 years ago when sphincter sparing TME was not as established as it is today.

There is a paucity of literature comparing sexual or anorectal functions following RR and LE and none are prospective randomized studies. Therefore, the two meta-analyses [1, 2] did not discuss this topic. One study not included in the two meta-analysis, however, did compare the quality of life after TEM and TME in sex- and age-matched patients and reported no significant differences in quality of life between TEM and TME; but more frequent defecation disorders were observed after TME [18]. A trend toward better sexual function after TEM was also reported. However, a greater portion of patients in the TME group were T3 and received preoperative radiotherapy (18 % versus 0 %) which probably had a negative impact on sexual function.

Other Studies

There are several recently published papers comparing local excision to radical resection that were not included in our analyses for specific reasons. One study included T1 and T2 rectal cancers and did not provide a subset analysis on T1 cancers [19] and the other included endoscopic polypectomy in the LE group [20]. One single institution study comparing LE to RR was not included in either of the meta-analyses [21]. It was a small sample (n = 124), retrospective study which demonstrated

a local recurrence rate of 11 % in the LE group versus 1.6 % in the RR group, but no difference in the disease-free and overall survival between the two groups. Our institutional experience at Memorial Sloan-Kettering Cancer Center (MSKCC) on a larger cohort (n = 282) with a similar length of follow-up demonstrated an inferior disease-specific survival for patients with a T1 rectal cancer undergoing a LE relative to those undergoing a RR (87 % versus 96 %) [12].

In summary, the best available data suggest that a RR offers an oncologic advantage over a LE approach for early staged (T1N0M0) rectal cancer. This is probably related to the increased likelihood of a local recurrence noted after a LE approach, which is not always salvageable.

Evidence Based Recommendations

A review of the published oncological results demonstrates that a RR provides the best oncologic outcome for a T1 rectal cancer. LE is an option for patients with T1 rectal cancer without high risk features who either are not suitable for a RR or are willing to accept the oncological risks in the interest of avoiding the functional consequences of a RR. There should not be enlarged mesorectal lymph nodes suspicious for metastasis on preoperative images nor evidence of poor differentiation (PD), lymphovascular invasion (LVI), perineural invasion (PNI), or submucosal (Sm) invasion >1 mm on pathological analysis. If one of these high risk features in noted, a RR is recommended [22, 23]. If such a patient were to insist on having a LE rather than the recommended RR, they have to understand that local recurrence rates after LE of a T1 rectal cancer range between 12 and 29 % with long-term follow-up, despite applying careful selection criteria for LE [5, 10, 15, 24, 25]. If a local recurrence develops and a salvage surgery is pursued, it would likely be extensive as one study reported the need for multivisceral pelvic resection in 33 % and total pelvic exenteration in 5 % of patients undergoing a RR after a recurrence following a LE of T1 rectal cancer [17].

1. Patients with a T1N0M0 rectal cancer that are otherwise fit should be offered a radical resection incorporating mesorectal excision.
2. Patients with a T1N0M0 rectal cancer not able to undergo a radical resection may be offered a local excision understanding the increased risk for failure with possible limited salvage options.

   Grade of data: moderate quality

A Personal View/Approach

If a patient is found to have a biopsy proven rectal adenocarcinoma that clinically looks and feels like it is not deeply invasive (mobile, non tethered, exophytic rather

than ulcerated) and possibly amenable to a LE, a careful review of the pathology as well as local [endorectal ultrasonography (ERUS) or rectal magnetic resonance imaging (MRI)] and distant [computed tomography (CT) of chest, abdomen and pelvis] staging has to occur in order to further determine if indeed a LE approach is appropriate. The presence of any adverse pathological features (PD, LVI, PNI, or Sm invasion >1 mm) would be associated with an increased likelihood of mesorectal lymph node involvement and in an otherwise healthy individual with good anorectal sphincter function (good baseline tonicity, squeeze, no paradoxical motion of puborectalis sling, etc.), a RR would be offered. In an elderly individual with significant co-morbidities and/or poor anorectal function, a LE approach would be a safer initial approach (lower morbidity, mortality, and probable better function) than a RR but would be associated with a possible increased risk of local and distant failure. A more challenging scenario is the otherwise healthy individual with a very distal (1 cm above upper part of anorectal sphincter) invasive (T1N0M0 on imaging) rectal adenocarcinoma with good pathological features who is interested in a restorative curative resection. In this situation, the patient has to be informed that if LE is pursued initially and pathology identifies a T2 lesion and he/she were to pursue a subsequent salvage RR, this may or may not be feasible since the prior suture line fibrosis of LE would compromise creation of coloanal anastomosis and function.

Numerous other clinical scenarios exist based upon the local and distant staging of the rectal cancer, the presence or absence of poor pathological features, the distalmost location of the lesion relative to the upper most portion of the anorectal sphincters, the function of the anorectal sphincters, the presence or absence of co-morbidities, etc. Optimal matching of the treatment plan to the individual patient requires that all the above variables be taken into consideration and that the patient and family be informed and engaged in a discussion where short and long term wishes, risks, gains and losses are clearly discussed and agreed upon.

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Chapter 18
Management of T_2 Rectal Cancer

Peter A. Cataldo

Introduction

What's "best" for the cancer, may not always be "best" for the patient. This is particularly true for T_2 rectal cancer; more specifically for *patients* with rectal cancer. More radical treatments may in certain circumstances, result in higher disease free survival, but not in improvements in overall survival, and certainly not a better functional result or enhanced quality of life. In selecting treatment options one must understand multiple important factors regarding the tumor and the patient in whom it resides.

Regarding patient factors: (1) Some patients wish to do "everything possible" to minimize any risk of tumor recurrence, while others want to avoid a colostomy "at all costs". (2) Some patients' anorectal function is poor enough that a radical resection with permanent colostomy will result in the best chance for cure *and* provide the best functional outcome. (3) In others, even a well performed low anterior resection for a mid or proximal tumor will result in an unacceptable deterioration in anal function, and significantly impact quality of life. (4) Finally, in some individuals with significant comorbidities curing the cancer may be an unnecessary goal as life span is already severely limited.

Regarding the tumor: (1) Location is everything; proximal T_2 rectal tumors are very different from distal T_2 tumors. (2) Accurate tumor staging is often difficult prior to surgical resection. Differentiating T_1 from T_2 lesions may be impossible for MRI and difficult for endorectal ultrasound [1, 2]. Even radiologists experienced in MRI evaluation of rectal cancer find it difficult to differentiate between advanced T_2 lesions and early T_3 cancers. (3) Diagnostic imaging, both MRI and endorectal ultrasound, may be little better than "flipping a coin" when predicting metastatic

P.A. Cataldo
Colon and Rectal Surgery, University of Vermont College of Medicine,
Burlington, VT, USA
e-mail: Peter.Cataldo@uvmhealth.org

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lymphadenopathy in association with early rectal cancers. Large lymph nodes may look worrisome but are often benign, while up to 50 % of metastatic lymph nodes are less than 5 mm and missed on both MRI and ultrasound [3, 4].

As one critically evaluates the literature, particularly when comparing radical to local surgical treatment, there is subtle, unintentional selection bias that is ubiquitous, incredibly important, and rarely mentioned. Authors compare patients undergoing local excision for T_2 (lymph node status estimated by inaccurate imaging; with a 50 % false negative rate) N_0, with individuals undergoing radical TME for pathologically staged T_2 N_0 (with microscopic evaluation of regional nodes), commonly in a retrospective analysis. In these studies, authors often implicate occult lymph node metastases as responsible for the local recurrence following local excision. If this is truly the case (which is likely), then many patients in the local excision group are truly T_2 N_+. Therefore, as we compare local with radical resection, it's important to realize a percentage of patients in any "local excision group" have Stage III rectal cancer while essentially none of the patients in the radical resection group are Stage III. As described above, it is often inaccurate staging that leads to increased recurrence in the local excision group rather than inadequate treatment.

Why is the choice between local and radical resection so important, and so often discussed in rectal cancer while it's rarely mentioned and of little clinical importance in colon cancer? The consequences of radical resection in the vast majority of colon cancers is minimal, such that there is no real functional benefit to local excision. In addition, laparotomy or laparoscopy is required for both local and radical resection. Regarding rectal cancer, radical resection requires a transabdominal approach while local excision is accomplished via an endoluminal approach with no cutaneous incision and minimal complications, often as an outpatient procedure. Importantly, the functional consequences of a successful radical resection include significant diminution of anorectal, urinary and sexual function, and a significant percentage of these individuals will require a permanent or temporary stoma [5–9].

In treating rectal cancer of any stage, three modalities are commonly considered; surgery, radiation, and chemotherapy. Some individuals may require all three, each associated with its own unique consequences. As more modalities are used, complications and long term consequences increase. Chemotherapy is a "systemic" treatment designed to decrease systemic recurrence, and is generally associated with systemic consequences. Both surgery and radiation are local therapies, and are predominately associated with local consequences. The combination of radiation and surgery particularly compounds complications and functional consequences.

Patient population	Intervention	Comparators	Outcomes
Patient with T_2N_0 rectal cancer	Local excision with chemoradiation	Radical resection Chemoradiation alone	Oncologic outcomes Functional outcomes

Search Strategy

A literature search was conducted including the following databases: MEDLINE (using PubMed) and the Cochrane Library. Publications not written in English were excluded. Titles and abstracts of retrieved studies were reviewed for relevance and eligibility. Results from the most recent meta-analyses were also included in this review. Full texts of all eligible studies were retrieved and evaluated.

Surgical Decision Making

Extensive literature review revealed very few trials that actually compared local and radical resection for T_2 rectal tumors. In fact, there is only one prospective trial that compared local excision (transanal endoscopic microsurgery) with radial resection following neoadjuvant chemoradiation for T_2N_0 rectal cancer [10]. There are no trials that compare local excision to "watch and wait" following chemoradiation for T_2 lesions. There are several "database" reviews that compare both local and radical resection, but suffer from the traditional shortcomings associated with database queries [11, 12]. Therefore, decision making for patients with T_2N_0 rectal cancer remains difficult and cannot generally be based on level I data. It must come from review of trials that separately evaluate local excision, radical resection, and observation therapy.

The tables that are compiled below are a result of contemporary literature review in the management of early rectal cancer. Unfortunately, direct comparisons between treatment modalities are rare. The best an informed surgeon can hope for is to review this data and apply it individually to each patient, looking at functional data, oncologic results, stoma and complication rates.

Table 18.1 depicts local recurrence, cancer specific survival, morbidity, and length of follow-up for available techniques. Table 18.2 looks at permanent stoma rates following local excision, radical resection and chemoradiation alone. Table 18.3 looks at response rates, local recurrence and overall survival following "watch and wait" therapy.

Recommendations

There is little debate in the literature regarding treatment of proximal T_2N_0 rectal cancer. All individuals who are medically fit should undergo radical resection, most commonly anterior resection with total (or tumor specific) mesorectal excision, and anastomosis. Current trials suggest this will result in high survival rates, a low incidence of local recurrence, and minimal functional consequences. Neoadjuvant or adjuvant treatment is not necessary.

Table 18.1 Oncologic intervention and results [10–12, 14, 18–24]

Trial	Stage	Intervention	N	Local recurrence (%)	Cancer survival (%)	F/U (months)	Morbidity (%)
LeZoche et al.	T_2N_0	Pre-op chemoXRT & TEM Pre-op chemoXRT & TME	35 35	5.7 2.8	94 94	84	13.8 16.7
Guerrieri et al.	T_2N_0	Pre-op chemXRT and TEM	139	10	92	225	9.2
Chen et al.	T_2N_0	TEM (selective XRT) LAR (selective chemo)	30 30	7.1 0	100 100	18 18	21 20
You et al.	$T_{2–3}N_0$	Pre-op chemo XRT & TEM	60	10	85.9	36	7.5
ACOSOG Z6041	T_2N_0	Pre-op chemoXRT & local excision	79	4	88.2	56	16
You et al.	T_2N_0	LE Radical resection	164 866	22.1 15.1	67.6 76.5	60	5.8 14.6
SEER Database	T_2N_0	LE (selective radiation) Radical resection	332 2,362		81 90.5	60	
Swedish Rectal Cancer Trial	Stage I, II, III	Pre-op XRT & Surgery Surgery alone	454 454	9 26	72 62	156	26 19
German Rectal Cancer Trial	Stage II and III	Pre-op chemXRT & Surgery Surgery & post-op chemoXRT	404 395	7.1 10.1	68.1 67.8	134	36 34
Dutch Rectal Cancer	Stage I, II, III	XRT & Surgery Surgery alone	924 937	5.6 10.9	64.2 63.5	60	

For distal T_2N_0 tumors, local recurrence increases, as do stoma rates, functional consequences and morbidity and mortality. Literature review suggests cancer specific survival, and overall survival are broadly similar for radical resection, local excision with neoadjuvant or adjuvant chemoradiation, or chemoradiation followed by “watch and wait”. Older studies have suggested local recurrence rates are higher

Table 18.2 Stoma rates following various treatment interventions [10, 14, 18–24]

Trial	Intervention	N	Permanent stoma
LeZoche, et al.	Pre-op chemoXRT &TEM Pre-op chemoXRT & TME		0 26
Guerrieri et al.	Pre-op chemoXRT & TEM	139	0
Chen et al.	TEM LAR	30 30	0 0
Yu et al.	TEM	60	0
ACOSOG Z6041	Pre-op chemoXRT & LE	79	9
Swedish Rectal Cancer trial	Preop XRT & Surgery Surgery alone	454 454	55 59
German Rectal Cancer Trial	Pre-op chemoXRT & Surgery Surgery & post-op chemoXRT	404 395	34 30
Dutch Rectal Cancer Trial	Pre-op XRT & surgery Surgery alone	924 937	33 29

Table 18.3 Outcomes following non-operative management of rectal cancer [15, 25–27]

Trial	N	Tumor stage	Clinical complete response (%)	Local recurrence (%)	Follow-up (months)	Disease free survival (%)
Appelt et al	40	Stage I, II, III	73	15.5	24	75
Smith et al. MSKCC	32		22	19	17	88
Maas et al. Netherlands	21	Stage I, II, III	11	4.8	25	93

for local excision when compared to radical resection; however, the majority of these studies evaluated traditional transanal techniques [12]. More recent data, although small case series, have identified equivalent local recurrence rates when comparing TEM to radical resection [13, 14]. More large scale, multicenter trials will be necessary to confirm comparable local recurrence rates. There is clear evidence that local excision alone is inadequate treatment for T_2 rectal cancer, resulting in unacceptable local recurrence rates and subsequent decreases in cancer specific survival [12]. There is currently sufficient data to suggest that traditional transanal excision is technically inferior to advanced techniques for local excision (most data evaluates TEM, but more date is becoming available for TEO, TAMIS, and SILS approaches) [13]. There is no debate that permanent stoma rates, functional (defecatory, urinary, and sexual) consequences, and morbidity and mortality are significantly higher following radical resection.

Regarding "watch and wait" observational therapy following chemoradiation, oncologic outcomes are similar to radical resection for the select group of patients with a complete clinical response [15, 16]. These are observational trials, predominately from one center. There are no prospective randomized data available. There are no trials comparing observational therapy with local excision.

Based on this literature review, treatment must be individualized. The main benefits associated with radical resection are accurate pathologic staging, the avoidance of chemotherapy and radiation, and possibly lower rates of local recurrence. These benefits come at the cost of higher complication rates, greater functional consequences, and higher permanent stoma rates.

The benefits of local excision are obvious; avoidance of laparotomy or laparoscopy, outpatient surgery, minimal morbidity and mortality, fewer functional consequences, and avoidance of a permanent stoma. However, local excision requires neoadjuvant chemoradiation and may be associated with higher rates of local recurrence. In addition, accurate pathologic staging cannot be achieved.

Author's Approach

It can't be emphasized enough that treatment for T_2N_0 rectal cancer must be individualized. A detailed history identifying a patient's desires, fears, physical, and social limitations is essential for developing a treatment plan. As previously stated, I separate proximal and distal T_2N_0 rectal cancer into two distinct treatment groups. All medically fit patients with proximal lesions undergo radical resection without neoadjuvant therapy.

For distal lesions, decision making is more complex. Enrollment in open clinical trials is offered if appropriate. After discussion, if patients are most concerned about tumor recurrence and need to have definitive evidence regarding mesorectal lymph node spread, they undergo radical resection (either LAR or APR depending upon tumor location). Perineal dissection for all APRs is performed prone with a cylindral excision [17]. For patients more concerned about anorectal function, a multimodality approach is used. Pathology is reviewed, patients with poor differentiation or lymphovascular invasion identified on biopsy (this is uncommon) are counseled that radical resection is preferred.

For others, treatment begins with neoadjuvant chemoradiation (after discussions in a rectal cancer multidisciplinary tumor conference). Five fluorouracil based chemotherapy, *without* oxaliplatin, combined with 5040 rads over 5 weeks is most common. Patients are then evaluated 4 weeks following completion of chemoradiation with physical examination and flexible sigmoidoscopy. Photographs of the tumor site are taken and stored electronically. If there is significant tumor response, patients undergo 2–4 more cycles of chemotherapy and then subsequent repeat endoscopic evaluation of the tumor. If there is little or no treatment response, radical resection is recommended. If no tumor is identified or if the tumor continues to decrease in size, patients complete 4 months of chemotherapy. After completion of the entire neoadjuvant regimen, patients have another endoscopic rectal evaluation, and CT chest, abdomen and pelvis. Provided there is no metastatic disease, patients will either undergo TEM or careful observation. TEM was used for all patients in the past but recovery is very slow with significant delays in wound healing if local excision is performed following radiation [18]. Now only patients with actual or a question of a small residual rectal tumor undergo TEM. Patients with a cCR are

individualized to observation vs TEM depending upon patient and physician preference. This is an area of cancer management that is changing rapidly and will likely change significantly in the next decade.

For individuals who have little or no response to neoadjuvant therapy, local excision is not an option. These patients are at *very high risk* for local recurrence following TEM and radical resection is recommended. Only patients that are medically unfit or refuse radical resection are considered for TEM, and are at risk to fail this treatment plan.

Conclusions

T_2N_0 rectal cancer comprises a heterogeneous group of patients with varied worries, goals, and expectations. In addition, risk of recurrence, both local or systemic, may be influenced by factors beyond TNM Stage, such as lymphovascular invasion, degree of differentiation, and response to neoadjuvant therapy. Importantly, multiple treatment options exist, each with different risks of recurrence and with different effects on post treatment quality of life. Current surgical literature is inadequate to provide an absolute "standard" treatment regimen at the present time Therefore, treatment must be tailored to match the patient's personal needs (desire to avoid a colostomy, concerns regarding anorectal, urinary, and sexual function, and need to know accurate lymph node status) in addition to curing the cancer. This can only be successfully accomplished by taking the time to thoroughly learn the patient's goals and to assess subtle tumor factors in order to assure the treatment is not worse than the disease.

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Chapter 19
Clinical Complete Response after Neoadjuvant Chemoradiotherapy in Rectal Cancer: Operative or Non-Operative Management?

Miranda Kusters and Julio Garcia-Aguilar

PICO table

Patient population	Intervention	Comparator	Outcomes
Patients with complete response after neoadjuvant treatment of rectal cancer	Non-operative management	Surgery (TME)	Cancer recurrence, morbidity, disease-free survival, overall survival

Introduction

Surgical excision of the rectum and its mesorectal envelope has been the mainstay of rectal cancer treatment for over a century [1]. Despite advances in surgical technique and perioperative care, total mesorectal excision (TME) remains an operation associated with some mortality, significant morbidity, and sequelae that permanently impair quality of life [2].

Some patients with locally advanced rectal cancer (LARC) have a pathologic complete response (pCR) to neoadjuvant chemoradiotherapy (nCRT). Patients with pCR have lower local recurrence (LR) and improved survival rates compared to non-pCR patients, raising the question of whether they truly need surgery [3]. As most of the mortality, morbidity, and long-term sequelae from multimodality therapy are related to excision of the rectum, avoiding TME selectively in patients who obtain a sustained response to nCRT will improve the quality of life, with the added benefit of avoiding overtreatment.

M. Kusters
Department of Surgery, Catharina Hospital, Eindhoven, The Netherlands

J. Garcia-Aguilar, MD (✉)
Colorectal Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA
e-mail: garciaaj@mskcc.org

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While the evidence suggesting that some rectal cancers can be treated with radiation alone is almost a century old, it is Angelita Habr-Gama from Sao Paulo who should be credited with suggesting that rectal cancer patients with clinically complete responses (cCR) to neoadjuvant chemoradiation could achieve long-term local tumor control without surgery [4].

These ideas were initially received with disbelief, but reports from other institutions have confirmed that surgery can be avoided in select rectal cancer patients treated with nCRT. However, the evidence supporting this treatment approach is based on small institutional series of heterogenous groups of patients who were staged using different imaging modalities, treated according to diverse radiation and chemotherapy regimens, evaluated at different times after completion of the neoadjuvant therapy, selected for observation using different criteria, and followed for relatively short periods of time. In spite of these limitations, clinicians are starting to accept a paradigm shift for this select group of rectal cancer patients, often pushed by patients motivated to avoid the consequences of a low colorectal anastomosis or a permanent colostomy. The treatment plan after neoadjuvant therapy that consists of close active surveillance, rather than surgery, is called watch-and-wait or non-operative management (NOM).

Uncertainties about Tumor Response to Neoadjuvant Therapy

While the above-mentioned studies all suggest that most patients with cCR after neoadjuvant chemotherapy can achieve prolonged local tumor control without surgery, a number of questions must be answered before NOM can be considered a standard option for patients with LARC.

The proportion of patients responding completely to neaodjuvant chemoradiation seems small and the optimal time to assess clinical response unknown. Tumor response depends on radiation dose, but doses beyond 54 Gy are rarely used in LARC patients. Adding other drugs effective in colon cancer as radiosensitizers beyond fluorpyrimidines has been found to be ineffective or prohibitively toxic [5–8]. Tumor response to chemoradiation is closely associated with time, and in patients undergoing TME after nCRT, the proportion of tumors with pCR increases with the time interval between chemoradiation and surgery [9]. As prolonging the interval to surgery and postoperative systemic chemotherapy may be unsafe in patients at risk of LR, attempts have been made to deliver systemic chemotherapy immediately before or after chemoradiation [10]. Delivering systemic chemotherapy before rather than after surgery has been shown to increase tumor response without delaying the treatment of potential micrometastatic disease. In these patients, the assessment of the clinical response, with the potential recommendation of NOM or surgery, is performed at the completion of both chemoradiation and systemic chemotherapy [10, 11]. This approach has resulted in pCR rates as high as 38 % in patients with clinical stage II and III disease and has the added advantage of increasing compliance with adjuvant systemic chemotherapy as well as shortening ileostomy time for patients after low anterior resection [10].

The lack of a reliable and uniform method of distinguishing post-treatment scar from residual tumor in the bowel wall or regional lymph nodes is the main obstacle to NOM in patients treated with neoadjuvant therapy. Most authors agree that digital rectal examination, endoscopy, and imaging studies should be used (Table 19.1). A flat white scar with or without telangiectasia and a normal digital exam are good predictors of pCR, while the presence of superficial ulceration or a palpable modularity on digital rectal exam considered an indicator of incomplete response [12, 13]. While clinical assessment tends to underestimate tumor response, there is always a possibility that tumors are concealed in or behind an apparently normal scar in the rectal wall [14]. Endorectal ultrasound, computed tomography (CT), and positron emission tomography with [^{18}F]fludeoxyglucose provide a rough estimate of tumor regression but are not sensitive enough to identify pCR [15]. Conventional MRI morphological sequences (e.g. T2- and T1-weighted images) cannot differentiate residual tumor from surrounding fibrosis, but diffusion-weighted (DW) MRI sequences may improve the diagnostic performance of morphological MRI sequences in differentiating pCR from residual tumor [16]. The criteria used to grade response undoubtedly influence the observed clinical outcomes: a strict definition reduces the proportion eligible but increases the chance of NOM success, while looser criteria increase the number of eligible patients but also risk of local tumor regrowth and distant metastasis. Currently, there are no validated criteria defining clinical and radiological tumor response, but a new set of criteria categorizing response in a 3-tier system is currently being tested in a prospective clinical trial [17].

Table 19.1 Criteria of complete response, near-complete response, and incomplete response [13]

	Complete response	Near-complete response	Incomplete response
Endoscopy	Flat, white scar Telangiectasia No ulcer No nodularity	Irregular mucosa Small mucosal nodules or minor mucosal abnormality Superficial ulceration Mild persisting erythema of the scar	Visible tumor
Digital rectal exam	Normal	Smooth induration or minor mucosal abnormalities	Palpable tumor nodules
MRI-T2W	Only dark T2 signal, no intermediate T2 signal AND No visible lymph nodes	Mostly dark T2 signal, some remaining intermediate signal AND/OR Partial regression of lymph nodes	More intermediate than dark T2 signal, no T2 scar AND/OR No regression of lymph nodes
MRI-DW	No visible tumor on B800-B1000 signal AND/OR Lack of or low signal on ADC[a] map Uniform, linear signal in wall above tumor is ok	Significant regression of signal on B800-B1000 AND/OR Minimal or low residual signal on ADC map	Insignificant regression of signal on B800-B1000 AND/OR Obvious low signal on ADC map

[a]ADC, apparent diffusion coefficient

A number of patients with apparent cCR develop tumor regrowth during follow-up. As most regrowth occurs in the bowel wall, repeated endoscopic exams are essential. Any suspicious changes in the scar should be biopsied. MRI should also be performed regularly to detect nodal disease. Changes in the size, contour, heterogeneity, or restriction of diffusion should raise the possibility of relapse. Repeated exams and continuous monitoring are often necessary to confirm recurrence.

Ultimately, finding reliable predictors of response to neoadjuvant therapy would help identify patients most likely to benefit from NOM and reduce toxicity for those who will likely have poor response. Tumor size and stage seem to predict response, with smaller, early-stage tumors being more likely to yield pCR. The search for molecular predictors of tumor response has not yielded any breakthrough findings so far. We have previously shown that rectal tumors with a KRAS mutation are less likely to respond to nCRT [18]. However, these findings await validation by studies of large independent cohorts.

Treatment Options for Patients with a cCR after Neoadjuvant Therapy: Observation or Surgery?

Unfortunately, there is no level 1 evidence regarding the oncological and functional outcomes of NOM versus standard TME after a cCR. Ideally, a randomized study should be performed, with a non-inferiority design for the non-operative arm. However, there are 2 reasons why this kind of study is difficult to perform. First, a non-inferiority study requires investigators to demonstrate that survival will not be compromised in NOM. Such a study requires a large sample size that will be difficult to achieve. Second, it is unlikely that patients who are told that NOM is an alternative option potentially offering similar oncological results would opt for randomization with a chance of undergoing surgery anyway.

Meta-analyses are also not available. Thus, the only types of studies we can analyze are retrospective series or prospectively followed patient series. Our search terms on PubMed were “complete response,” “rectal cancer,” “non-operative management,” “watch and wait,” and “wait and see.” We will discuss the oncological and functional results in the next chapters.

Evidence Supporting NOM

In this overview, we included studies in which patients with a cCR as established by digital rectal examination, endoscopy, and MRI were compared to a cohort of patients who had a resection and demonstrated pCR on pathologic examination. There is also one study in which patients were managed by NOM after cCR diagnosis established by MRI alone. In our opinion this is not the standard of care, so we did not include this study [19]. Table 19.2 shows the oncological outcomes of the 5 comparative studies in order of publication.

Table 19.2 Studies in which oncological outcomes for NOM in patients with cCR were compared to those for OM in patients with pCR

Reference	No of cCRs (NOM)	No of pCRs (OM)	Difference in T-stage[a]	Difference in distance of tumor[a]	Difference in adj. chemo[a]	Overall survival		p-value	Disease-free survival		p-value	Evidence level
						NOM	OM		NOM	OM		
Habr-Gama et al. [20]	71	22	Equal	Equal	Equal	5-year 100 %	5-year 88 %	0.01	5-year 92 %	5-year 83 %	0.09	3b
Maas et al. [4]	21	20	nm	nm	nm	2-year 100 %	2-year 93 %	0.23	2-year 89 %	2-year 91 %	0.77	3b
Smith et al. [21]	32	57	NOM	OM	OM	2-year 96 %	2-year 100 %	0.56	2-year 88 %	2-year 98 %	0.27	3b
Araujo et al. [22]	42	69	NOM	OM	Equal	5-year 72 %	5-year 90 %	0.32	5-year 61 %	5-year 83 %	0.04	4
Li et al. [23]	30	92[b]	Equal	Equal	nm	5-year 100 %	5-year 96 %	0.26	5-year 90 %	5-year 94 %	0.51	4

nm not mentioned

[a]In favor of NOM (non-operative management) or OM (operative management), meaning less advanced T-stage, higher location of the tumor or more adjuvant chemotherapy (adj. chemo)

[b]cCR patients who underwent surgery

The first comparison between 71 NOM patients with a cCR and 22 OM patients with a pCR was reported by Habr-Gama [20]. Patients were well-informed about the risks and benefits of NOM. In a retrospective series of 194 patients with near-complete response, NOM was considered too risky and surgery was performed; 22 (8.3 %) of these patients ended up having a pCR. Regarding clinical parameters and postoperative treatment, there was no significant difference between the NOM and OM patients, although it seemed that there were slightly more T3/T4 tumors in the OM group. The NOM group's disease-free survival (DFS) was similar to that of the OM group; 1-year survival (OS) was significantly better. The authors do not explain this; the question remains whether the deaths were related to the surgery, although no perioperative deaths were reported.

In a small but very carefully selected series of prospectively followed patients by Maas et al., 21 well-informed NOM patients were compared to 20 retrospectively selected OM patients with pCR. Of the 20 OM patients, 5 had cCRs and were treated before the wait-and-see policy was introduced, and 15 had a near-complete clinical response [4]. Although the study's data tables show no differences between the patient groups, no statistics were presented. There was no difference in OS and DFS between the groups.

The third study, by Smith et al., describes 32 NOM patients and 57 OM patients with a pCR [3]. NOM was described to the patients as a non-standard treatment which might compromise oncological outcomes, but the majority opted for this management because of high medical comorbidity or because they did not want to undergo surgery. The OM patients had slightly more proximal tumors and received adjuvant treatment more often but had more advanced tumors compared to the OM-patients. Even so, DFS and OS were not significantly different.

Araujo et al. conducted a retrospective analysis of 42 patients treated with NOM and compared them to 69 patients who had a pCR after resection [22]. NOM was not the standard of care in this institution, so most patients in this group were patients who refused surgery or wanted to postpone it as long as possible. DFS was significantly worse in the NOM group, but the authors also mentioned that this might be due to the fact that there were more distal cancers in this group. DFS was not significantly different if only patients with low rectal cancers were included. The most striking element of this paper is the inclusion of 20 patients in the NOM group (54 %) with residual tumor or ulceration. Although statistically this did not influence DFS, this weakens the study considerably, as in our opinion patients should be referred for surgery in the case of residual disease.

Li et al. published the only series in which patients with cCR who underwent NOM were compared to patients with cCR who underwent surgical management [23]. There seemed to be no difference clinically between the two groups. However, the reasons for treatment selection were not explained by the authors. It is unclear whether there is a time bias due to NOM's introduction at a certain time point or whether there was informed consent for this strategy. For these reasons, we consider it a weak study.

A group from the United Kingdom has recently reported a multi-institutional experience with a NOM approach versus surgical resection in rectal cancer patients treated with chemoradiation [24]. In contrast to the previously discussed series, this

study compared the outcomes of 129 patients with cCR and 228 rectal cancer patients who had surgical resection after neoadjuvant chemoradiation independent of the pathological stage. The neoadjuvant therapy regimens in the two groups were similar. After a median follow-up of 33 months from start of chemoradiation, 44 (34 %) patients with cCR had local regrowths, corresponding to an actuarial 3-year local regrowth rate of 38 %. Similar to previous findings, most local regrowths were in the bowel wall, and most underwent successful salvage treatment. The authors developed one-to-one paired cohorts (109 patients in each group) using propensity-score matching for the key confounders. The 3-year non-regrowth DFS rate (time until death, local recurrence, or distant metastasis, not including local regrowths) was 88 % for the NOM group and 78 % for the surgical group (log rank $P = 0.22$). The colostomy-free survival rates were 74 % and 47 %, respectively. The authors concluded that NOM is oncologically safe in a multi-institutional setting, supporting the standard adoption of NOM. However, the results of this study should be interpreted with caution, as tumors in NOM patients had earlier pretreatment tumor stage, were less likely to have nodal involvement, rarely had unfavorable histological features, and were more likely to have normal carcinoembryonic antigen levels. In addition, comparing patients with and without cCR, independent of the pathological stage, introduces significant bias, as tumor response is associated with improved outcome compared to non-responders.

On the basis of the first 3 studies, although they are based on only level 3b evidence, we can carefully conclude that NOM results in similar oncological outcomes associated with recurrence-free survival and overall survival compared to OM. A prerequisite for NOM is a cCR, *not* a near-complete response. Since about 70 % of patients with cCR would have a pCR after resection, you might expect less favorable oncological outcomes compared to the patients who had a resection and 100 % pCR. Instead, the similar outcomes suggest even more strongly that NOM is oncologically safe.

Local Regrowth and Salvage Therapy vs. Stoma Rates and Operative Mortality

Table 19.3 summarizes local-regrowth, stoma, and mortality rates in the 5 retrospective studies. Overall, the mean time to local regrowth in NOM patients with cCR was 31 months. Local regrowth appeared in an average of 8 % of all patients, although this also includes the Araujo study, which included near-complete responders. Ninety-four percent of all local regrowths could be salvaged, and 4 % of all cCR patients ended up with a permanent stoma. By contrast, 35 % of patients receiving OM had a permanent colostomy. The mean mortality rate after OM was 2 %. Local recurrence after this management was still present in 2 % of the cases, despite the pCR after primary surgery.

As mentioned earlier, the timing and definition of cCR can greatly influence the proportion of patients considered as having a cCR as well as associated local recurrence rates. One should bear in mind that the above-mentioned 8 % local regrowth

Table 19.3 Comparison of the rates of local failure, stoma, and operative mortality after NOM in patients with cCR and after OM in patients with pCR

Reference	Mean interval to LR in NOM (months)	No. of LR cases in NOM (%)	No. of salvage-able LR cases in NOM (%)[a]	NOM patients undergoing salvage therapy		OM		No. of LR cases in OM (%)	No. of peri-operative mortality cases (%)
				No/temporary stoma (% of all NOM patients)	Permanent stoma (% of all NOM patients)	No/temporary stoma (%)	Permanent stoma (%)		
Habr-Gama et al. [20]	60	2 (3)	2 (100)	1 local excision 1 brachytherapy	0 (0)	13 (59)	9 (41)	0 (0)	0 (0)
Maas et al. [4]	22	1 (5)	1 (100)	1 local excision	0 (0)	11 (55)	9 (45)	0 (0)	1 (5)
Smith et al. [21]	11	6 (19)	6 (100)	3 (9)	3 (9)	nm	nm	0 (0)	nm
Araujo et al. [22]	48	5 (12)	4 (80)	1 (2)	3 (7)	56 (81)	13 (19)	4 (6)	3 (4)
Li et al. [23]	22	2 (7)	2 (100)	1 local excision 1 nm	nm	52 (57)	40 (43)	2 (2)	0 (0)
Mean[a]	31	16 (8)	15 (94)		6 (4)		71 (35)	6 (2)	4 (2)

[a]Mean excludes studies in which there were 'nm' (not mentioned) data

rate is for a strongly sub-selected patient cohort. For example, in Maas et al. this cohort represented 21 patients, which was 11 % of the patients treated with chemoradiotherapy. Also, in the later Habr-Gama series, local regrowth numbers varied depending on the group of patients considered. When 68 % of the patients treated with chemoradiotherapy were managed with NOM, long-term sustained response could be achieved in 57 % [25]. These numbers are consistent with the first published prospective trial (NCT00952926) by Appelt et al. [26] This study showed 58 % local tumor control after 2 years in patients with primary low T2/T3 rectal cancers treated with chemoradiotherapy resulting in a cCR. The patients in this study had their assessment at 6 weeks after treatment completion, which is early (resulting in a 78 % cCR rate), also explaining the high local regrowth rate. All local recurrences (9 of 9) after NOM underwent resection with clear resection margins.

Functional Outcomes and Toxicity Associated with NOM

It is generally believed that functional outcomes are better in patients who have undergone NOM than in patients who have undergone a resection, owing to the risk for nerve damage and low-anterior resection syndrome. The only study comparing functional outcomes after NOM versus resection with a pCR is by Maas et al., which confirmed that functional outcomes are better after NOM [4]. Bowel function in patients in the OM group was significantly more affected by food intake, and these patients used pads and colonic irrigation more frequently, had less control over flatus, and reported more changes in their post-diagnosis/treatment bowel habits. Also, patients who had NOM had a lower mean Wexner incontinence score (0.8 versus 3.5) and a lower mean defecation frequency (1.8/day versus 2.8/day) than patients who had a resection. Appelt et al. also described good functional outcomes; there was no self-reported fecal incontinence in 72 % of patients after 1 year and in 69 % at 2 years after NOM. The median Wexner incontinence score was 0 at all time-points [26].

Regarding NOM toxicity, only one study measured it accurately: the prospective study of Appelt et al. [26]. However, in this study brachytherapy was given as a boost to 60 Gy chemoradiotherapy. Rectal bleeding was the most common symptom, reported by 78 % of the patients after 1 year, although this was mild in most patients; 6 % had grade 3 rectal bleeding, which needed transfusion or intervention, at 2 years. The authors hypothesized that this unexpected high toxicity rate might be due to the combination of chemoradiotherapy with a brachytherapy boost, which could be replaced by a boost of external beam radiotherapy. This study describes the short-term toxicity of NOM, but follow-up was too short to determine long-term radiation effects. There are reports of long-term toxicity of the rectum after irradiation of the reproductive organs in patients receiving treatment with old radiation techniques. Still, it is very difficult to weigh long-term toxicity against the morbidity prevented by avoiding an operation.

Non-Operative Management in the Elderly

Most surgery studies focus on young and healthy patients. There is strong evidence however, that in elderly patients and patients with comorbidities, surgery is associated with not only increased in-hospital mortality and 30-day mortality but also above-baseline death rates up to 1 year postoperatively [27–29].

A very thorough analytic decision model study from Smith et al. took into account the 90-day mortality rate and used a probabilistic Markov simulation to model outcomes in patients with a cCR after nCRT for rectal cancer treated with either empiric surgery or a NOM strategy [30]. Several NOM studies and the outcomes in the UK National Health Registries empiric surgery database were used in the model. The primary endpoint was overall survival; secondary outcomes were DFS and quality-adjusted life years. The model was run for 3 categories: 60-year old cohort with mild comorbidities, 80-year-old fit patient cohort with mild comorbidities (Charlson score <3), and 80-year-old cohort with significant comorbidities (Charlson score ≥ 3). The results of the study showed that, because of the increased operative risk associated with elderly and comorbidity patients, conservative management options result in superior survival at 1 year after treatment. Further, equivalent DFS and quality of life can be achieved compared with surgery in patients with a cCR. Even though the potential improvement in survival after 1 year is marginal in younger patients treated with NOM, surgery did not improve DFS and quality of life.

Future Prospective Studies

There are currently several open prospective studies and registries concerned with the question of NOM vs. OM. Many can be found on www.clinicaltrials.gov.

The only one comparing NOM versus resection in cCR is being conducted at the Cancer Institute Hospital in Sao Paulo (NCT02052921), but that trial is suffering from low accrual, which was to be expected due to previously discussed reasons. A prospective study sponsored by Royal Marsden (NCT01047969) seeks to prove the safety of NOM. It has 2 primary outcome measures at 2 years after the end of nCRT: estimation of the percentage of patients for whom surgery can be omitted and the percentage of patients with local failure, defined as positive margin status of the resected tumor or surgically unsalvageable disease.

Further, Memorial Sloan Kettering Cancer Center in New York is currently coordinating a prospective randomized trial that incorporates NOM (NCT02008656) [17]. The primary purpose is to evaluate 3-year DFS in patients with locally advanced rectal cancer randomized between induction chemotherapy with nCRT versus nCRT with consolidation chemotherapy. Patients with a cCR according to clearly defined criteria will undergo NOM. Also, quality of life and functional outcomes will be evaluated and validated. Further, molecular markers will be studied in all patients to see whether there are profiles that can predict a complete response.

Another initiative is the International Watch and Wait Database (www.iwwd.org), a prospective registry in which all patients with a near complete or clinically complete response can be entered in a secure Internet database. Dozens of centers cooperate in this project, and the actual entered patient-number is regularly updated on the website. There are frequent teleconferences between the participating centers to exchange ideas and to coordinate and optimize data analyses. The purpose is to evaluate long-term outcomes of NOM in large numbers of patients, although the differences between the centers will make this statistically challenging.

Expert Opinion

- In patients with cCR, there is more and more evidence that NOM does not compromise DFS.
- Patients with cCR should be referred to specialized surgeons who have considerable experience with cCR in LARC. Experience is essential.
- There is not enough evidence to guide decision-making in patients with near-complete clinical responses.

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Chapter 20
Management of the Patient with Rectal Cancer Presenting with Synchronous Liver Metastasis

Shafik M. Sidani and Maher A. Abbas

Introduction

An estimated 39,610 new cases of rectal cancer (RC) are expected in the United States in 2015 [1]. Synchronous colorectal liver metastasis (SCRLM) occurs in 20 % of patients with locally advanced RC [2, 3]. Median overall survival (OS) for patients with SCRLM is 20–24 months without resection as opposed to 5-year OS of up to 50 % with R0 resection of metastatic disease [4]. Oncologic outcomes continue to improve with the development of new effective chemotherapy regimens and increased hepatectomy rates [5, 6]. Patients with SCRLM constitute a heterogeneous group with varying preoperative fitness, tumor biology, tumor resectability, and symptomatology related to the primary tumor. Potential cure is dependent on the ability to resect all disease, and requires a multidisciplinary approach. Locally advanced RC requires chemoradiation (CRT) with surgery, whereas SCRLM is initially addressed with chemotherapy. Surgery for symptomatic relief is reserved for select cases. The optimal sequence of multimodality treatment to address the primary tumor and associated metastatic disease is under active investigation.

S.M. Sidani (✉) • M.A. Abbas
Digestive Disease Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates
e-mail: shafiksidani@gmail.com

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Search Strategy

An electronic search was conducted using the PubMed database for reports published in the English language between January 1990 and October 2015 using the key words rectal cancer in various combinations with liver metastasis(es), hepatic metastasis(es), staged resection, simultaneous resection, synchronous resection, combined resection, liver-first, chemotherapy, and radiation. Referenced studies from identified reports were reviewed if relevant. The "related articles" function was used to further expand the search. Only studies published between 2000 and 2015 clearly identifying at least 20 patients with RC and synchronous liver metastases were included in the tables summarizing the studies. If more than one study was reported from the same institution, the most recent study focusing on RC was included.

Patient population	Intervention	Comparator	Outcomes studied
Patients with RC and SCRLM	Staged rectum-first approach	Liver-first approach Simultaneous resections approach	Perioperative morbidity Disease free survival (DFS) OS

Results

Evaluation of the Patient with Rectal Cancer and Synchronous Hepatic Metastasis

The initial evaluation of patients with rectal cancer and SCRLM includes determination of symptomatology, colonoscopy, staging, determination of resectability from an oncologic standpoint, and evaluation of the future liver remnant based on imaging before and after multimodality treatment, as well as assessment of fitness for surgery. In addition to imaging of the primary tumor with magnetic resonance imaging (MRI) and endorectal ultrasound [7], computed tomography (CT) is useful to evaluate distant disease. Contrast-enhanced MRI can detect or further characterize small hepatic lesions and is superior to CT in the setting of post-chemotherapy hepatic steatosis [8]. Fluorodeoxyglucose-positron emission tomography (FDG-PET) can detect extrahepatic disease that would preclude curative resection and change management in up to 24 % of cases [9, 10]. Two randomized prospective trials reported conflicting results regarding the utility of FDG-PET [11, 12]. Ruers et al. demonstrated that non-curative surgery was avoided in one of six patients as a result of PET findings [11] whereas Moulton et al. failed to confirm these results [12]. Additional studies have supported the use of FDG-PET in patients with rectal cancer and SCRLM [13–20]. Sensitivity of PET after chemotherapy is reduced due to decreased metabolic activity of residual tumor [21–24].

Liver biopsy can be helpful in select cases with equivocal imaging findings but should not be performed routinely due to the risk of tract seeding [25–28].

Treatment Options

Following a diagnosis of rectal cancer with SCRLM, the treatment plan is formulated with the goal of prolonging survival and maximizing the prospects of a curative resection. Many studies combine both colon and rectal cancer and are compromised by selection bias; no prospective randomized data comparing treatment approaches exists to guide management decisions. Rectal cancer presents additional challenges compared to colon cancer with concerns for local recurrence, potential need for adjuvant or neoadjuvant radiation therapy, and complexity of pelvic surgery. The heterogeneity of scientific data pertaining to chemotherapy and radiation regimens, and the introduction of various drugs during the last two decades add to the challenges of data interpretation [29, 30].

Table 20.1 summarizes studies directly comparing the perioperative results of surgical approaches for colorectal cancer with SCRLM. Table 20.2 shows comparative oncologic outcomes of those studies. Table 20.3 presents outcomes of case series of the different surgical approaches.

Multimodality Treatment Although chemotherapy is generally included in the treatment plan of patients with SCRLM, there is no consensus on timing, benefit, and risk. The EORTC 40983 randomized trial demonstrated improvement in progression free survival but not overall survival when six cycles of neoadjuvant and six cycles of adjuvant FOLFOX were administered perioperatively, compared to surgery alone. Resection rates were equivalent in both groups showing that the window of resectability is not lost with neoadjuvant chemotherapy. Notably, the chemotherapy group had fewer nontherapeutic laparotomy rates (5 % versus 11 %) [76, 77]. Similarly, two meta-analyses comparing surgery with or without chemotherapy demonstrated the benefit of chemotherapy in disease free but not overall survival [78, 79].

Neoadjuvant chemotherapy allows early treatment of micrometastatic disease, and provides upfront information regarding tumor biology and response to adjuvant chemotherapy. Outcomes after hepatectomy are superior in patients with a positive tumor response to neoadjuvant chemotherapy as opposed to nonresponders [6, 80, 81]. This selects out patients with progression of disease on chemotherapy prior to surgery, who have significantly lower disease free and overall survival [82]. Neoadjuvant chemotherapy may also improve resectability in borderline resectable or initially unresectable SCRLM [83–85]. Disadvantages of upfront chemotherapy include the risk of progression of initially resectable disease [86], the dilemma of disappearing liver metastases, as well as liver injury prior to hepatectomy. There is conflicting evidence regarding the safety of neoadjuvant chemotherapy prior to liver surgery [87–92], and the response to treatment should typically be assessed every

Table 20.1 Studies comparing morbidity and mortality of surgical approaches for CRC with SCRLM

Author (year)	N (RC with SCRLM)	Follow-up (months)	Approach, N (RC with SCRLM)	Morbidity (%)	P value	Mortality (%)	P value	RC cases analyzed separately (Y/N)	Quality of Evidence
Weber (2003) [31]	97 (34)	30	SR, 35 (10)	23	0.326	0	NS	N	low
			RF, 62 (24)	32		0			
Chua (2004) [32]	96 (45)	NR	SR, 64 (32)	53	0.25	0	NS	N	low
			RF, 32 (13)	41		0			
Capusotti (2007) [33]	79 (27)	NR	SR, 31 (10)	33	0.037	1	0.392	N	low
			RF, 48 (17)	56		0			
Reddy (2007) [34]	610 (162)	NR	SR, 135 (54)	36	0.86	3	NR	N	low
			RF, 475 (108)	39		1			
Thelen (2007) [35]	219 (78)	70	SR, 40 (6),	18	0.166	10	0.012	N	low
			RF, 179 (72)	25		1.1			
Turrini (2007) [36]	119 (44)	66	SR, 57 (24)	21	0.07	3.5	0.09	N	low
			RF, 62 (20)	31		5			
Yan (2007) [37]	103 (42)	24	SR, 73 (27)	32	NR	0	NS	N	low
			RF, 30 (15)	43		0			
Assumpcao[a] (2008) [38]	141 (57)	31	SR, 21 (21)	20 (for liver resection)	–	2.1	–	Y (all RC)	low
			RF, 36 (36)						
Martin (2009) [39]	230 (53)	NR	SR, 70 (30)	56	0.24	2	NS	N	low
			RF, 160 (23)	55		2			
Moug (2009) [40]	64 (24)	NR	SR, 32 (12)	34	0.69	0	NS	N	low
			RF, 32 (12)	59		0			
Slupski (2009) [41]	89 (24)	NR	SR, 28 (10)	14	0.9	0	NR	N	low
			RF, 61 (14)	13		1			

Author (year)	N (RC with SCRLM)	Follow-up (months)	Approach, N (RC with SCRLM)	Morbidity (%)	P value	Mortality (%)	P value	RC cases analyzed separately (Y/N)	Quality of Evidence
Brouquet (2010) [42]	156 (81)	25	SR, 43 (18)	47	NS	5	NS	N	low
			RF, 72 (35)	51		3			
			LF, 27 (19)	37		0			
Cellini (2010) [43]	74 (74)	23	SR, 30 (30)	NR	–	0	NS	Y (all RC)	low
			RF, 13 (13)	NR		0			
De Haas (2010) [44]	228 (41)	41	SR, 55 (12)	11	0.015	0	0.557	N	low
			RF, 173 (29)	25		0.6			
Luo (2010) [45]	405 (206)	NR	SR, 129 (69)	47	>0.05	1.5	1.000	N	low
			RF, 276 (137)	54		2			
van der Pool (2010) [46]	57 (57)	34	SR, 8 (8)	25R[b], 25 L	0.59R 0.39 L	0	NS	Y (all RC)	low
		40	RF, 29 (29)	31R, 17 L		0			
		28	LF, 20 (20)	20R, 30 L		0			
Vigano (2011) [47]	36 (36)	39	SR, 32 (32)	31	NR	5	NR	Y (all low/ mid RC)	very low
			RF, 4 (4)	25		0			
Abbott (2012) [48]	144 (87)	36	SR, 60 (34)	38	NR	3.3	0.38	N	low
			RF, 84 (53)	41		1.2			
Dexiang (2012) [49]	1061 (357)	19	SR, NR	25	NS	2	NS	N	low
			RF, NR	21		2.4			

(continued)

Table 20.1 (continued)

Author (year)	N (RC with SCRLM)	Follow-up (months)	Approach, N (RC with SCRLM)	Morbidity (%)	P value	Mortality (%)	P value	RC cases analyzed separately (Y/N)	Quality of Evidence
Mayo (2013) [50]	1004 (276)	34	SR, 329 (91)	27	>0.05	2.7	>0.05	N	low
			RF, 647 (170)	25		3.2			
			LF, 28 (15)	39		0			
Slesser (2013) [51]	112 (49)	NR	SR, 36 (19)	25	0.161	6	0.241	N	low
			RF, 76 (30)	45		1.3			
van Dijk (2013) [52]	50 (50)	32	SR, 26 (26)	31	–	0	–	Y (all RC)	low
			RF, 12 (12)						
			LF, 7 (7)						
Fukami (2015) [53]	63 (28)	NR	SR, 41 (16)	22	0.758	0	NS	N	low
			RF, 22 (12)	27		0			
Sabbagh (2015) [54]	52 (52)	42	SR, 15 (15)	58R[b], 15 L	0.06R 0.9 L	0	NS	Y (all low/ mid RC)	low
			RF, 27 (27)	30R, 10 L		0			
			LF, 10 (10)	60R, 20 L		20			
She (2015) [55]	116 (32)	23	SR, 28 (13)	25	0.28	7.1	0.29	N	low
		28	RF, 88 (19)	16		1.1			
Silberhumer (2015) [56]	198 (198)	NR	SR, 145 (145)	41	0.30	0	NS	Y (all RC)	low
			RF, 53 (53)	47		0			

CRC colorectal cancer, *RC* rectal cancer, *SCRLM* synchronous colorectal liver metastasis, *NR* not reported, *NS* not significant, *DFS* disease free survival, *OS* overall survival, *SR* simultaneous resection approach, *RF* rectum-first approach, *LF* liver-first approach

[a] Study included both synchronous and metachronous metastatic disease and no separate analysis of synchronous disease was performed. This study was not focused on surgical outcomes

[b]Morbidity related to rectal resections (R) and liver resections (L) reported separately

Table 20.2 Studies comparing DFS and OS of surgical approaches for CRC with SCRLM

Author (year)	N (RC with SCRLM)	Follow-up (months)	Approach, N (RC with SCRLM)	DFS (% 5-year *or* months)	P value	OS (% 5-year *or* months)	P value	RC cases analyzed separately (Y/N)	Quality of Evidence
Weber (2003) [31]	97 (34)	30	SR, 35 (10)	NR	–	21 %	0.967	N	Low
			RF, 62 (24)	NR		22 %			
Chua (2004) [32]	96 (45)	NR	SR, 64 (32)	9 %	0.53	29 %	0.52	N	Low
			RF, 32 (13)	14 %		43 %			
Minagawa (2006) [57]	160 (76)	49	SR, 142 (72)	NR	–	37 months	0.95	N	Low
			RF, 18 (4)	NR		31 month			
Thelen (2007) [35]	219 (78)	70	SR, 40 (6),	NR	–	53 %	0.983	N	Low
			RF, 179 (72)	NR		39 %			
Turrini (2007) [36]	119 (44)	66	SR, 57 (24)	19 months	0.04	32 %	0.06	N	Low
			RF, 62 (20)	14 months		25 %			
Yan (2007) [37]	103 (42)	24	SR, 73 (27)	14 %	NS	36 %	0.9	N	Low
			RF, 30 (15)	14 %		37 %			
Assumpcao (2008) [38]	141 (57)	31	SR, 21 (21)	33 %	–	34 %	–	Y (all RC)	Low
			RF, 36 (36)						
Yoshidome (2008) [58]	137 (59)	NR	SR, 116 (49)	52 %[a]	0.003	NR	–	Y	Low
			RF, 21 (10)	87 %					
Moug (2009) [40]	64 (24)	NR	SR, 32 (12)	10 month	0.487	21 %	0.838	N	Low
			RF, 32 (12)	14 months		24 %			
Slupski (2009) [41]	89 (24)	NR	SR, 28 (10)	NR	–	45 %	0.006	N	Low
			RF, 61 (14)	NR		38 %			

(continued)

Table 20.2 (continued)

Author (year)	N (RC with SCRLM)	Follow-up (months)	Approach, N (RC with SCRLM)	DFS (% 5-year *or* months)	P value	OS (% 5-year *or* months)	P value	RC cases analyzed separately (Y/N)	Quality of Evidence
Brouquet (2010) [42]	156 (81)	25	SR, 43 (18)	11 month	NS	55 %	0.389	N	Low
			RF, 72 (35)	11 month		48 %			
			LF, 27 (19)	11 month		39 %			
Cellini (2010) [43]	74 (74)	23	SR, 30 (30)	NR	–	54 months	0.1	Y (all RC)	Low
			RF, 13 (13)	NR		50 month			
De Haas (2010) [44]	228 (41)	41	SR, 55 (12)	8 %[b]	0.005	74 %[b]	0.871	N	Low
			RF, 173 (29)	26 %		70 %			
van der Pool (2010) [46]	57 (57)	34	SR, 8 (8)	15 months	–	73 %	NR	Y (all RC)	Low
		40	RF, 29 (29)			28 %			
		28	LF, 20 (20)			67 %			
Vigano (2011) [47]	36 (36)	39	SR, 32 (32)	40 %	–	59 %	–	Y (all low/ mid RC)	Very low
			RF, 4 (4)						
Abbott (2012) [48]	144 (87)	36	SR, 60 (34)	18 months	0.95	66 months	0.62	N	Low
			RF, 84 (53)	18 months		66 months			
Andres (2012) [59]	787 (202)	NR	RF, 729 (169)	26 %	0.992	46 %	0.965	N	Low
			LF, 58 (33)	30 %		48 %			
Dexiang (2012) [49]	1061 (357)	19	SR, NR	NR	–	44 %	NS	N	Low
			RF, NR	NR		49 %			
Mayo (2013) [50]	1004 (276)	34	SR, 329 (91)	NR	–	42 %	0.526	N	Low
			RF, 647 (170)	NR		44 %			
			LF, 28 (15)	NR					

Author (year)	N (RC with SCRLM)	Follow-up (months)	Approach, N (RC with SCRLM)	DFS (% 5-year *or* months)	P value	OS (% 5-year *or* months)	P value	RC cases analyzed separately (Y/N)	Quality of Evidence
Slesser (2013) [51]	112 (49)	NR	SR, 36 (19)	33 %[b]	0.837	75 %[b]	0.379	N	Low
			RF, 76 (30)	32 %		64 %			
van Dijk (2013) [52]	50 (50)	32	SR, 26 (26)	36%[c]	–	80 % [c]	–	Y (all RC)	Low
			RF, 12 (12)						
			LF, 7 (7)						
Fukami (2015) [53]	63 (28)	NR	SR, 41 (16)	NR	–	66 %[b]	0.054	N	Low
			RF, 22 (12)	NR		67 %			
Sabbagh (2015) [54]	52 (52)	42	SR, 15 (15)	32 months	0.1	48 months	0.4	Y (all low/ mid RC)	Low
			RF, 27 (27)	31 month		60 month			
			LF, 10 (10)	8 months		38 months			
She (2015) [55]	116 (32)	23	SR, 28 (13)	28 %[b]	0.089	0	0.003	N	Low
		28	RF, 88 (19)	11 %		33 %			

CRC colorectal cancer, *RC* rectal cancer, *SCRLM* synchronous colorectal liver metastasis, *NR* not reported, *NS* not significant, *DFS* disease free survival, *OS* overall survival, *SR* simultaneous resection approach, *RF* rectum-first approach, *LF* liver-first approach

[a]Tweleve-month hepatic disease free survival reported

[b]Three-year survival rates reported

[c]Two-year survival rates reported

Table 20.3 Case series reporting outcomes of surgical approaches for CRC with SCRLM

Author (year)	Approach	N (RC)	Follow-up (months)	Morbidity (%)	Mortality (%)	DFS (% 5-year *or* months)	OS (% 5-year *or* months)	RC cases analyzed separately (Y/N)	Quality of Evidence
de Santibanes (2002) [60]	SR	71 (41)	29	21	0	9 %	38 %	N	Very low
Tsai (2007) [61]	SR	97 (21)	29	8	0	10 %	34 %	N	Very low
Huh (2010) [62]	SR	91 (50)	28	37	1.1	NR	27 %	N	Very low
van der Pool (2010) [63]	BF	105 (33)	26	17	2	25 %	34 %	N	Very low
Boostrom (2011) [64]	SR	45 (45)	60	57	0	28 %	32 %	Y (all RC)	Very low
An (2012) [65]	SR	108 (108)	48	NR	NR	18 months	62 months	Y (all RC)	Very low
Nakajima (2012) [66]	SR	86 (38)	73	64	0	NR	45 %	N	Very low
Roxburgh (2012) [67]	SR	46 (24)	37	33	0	NR	NR	Y	Very low
Ayez (2013) [68]	LF	42 (42)	31	24 L, 31R[a]	NR	40 %	67 %	Y (all RC)	Very low
De Rosa (2013) [69]	LF	37 (25)	NR	40 L, 25R[a]	0 L, 4.2R[a]	NR	30 %[b]	N	Very low
Hatwell (2013) [70]	SR	51 (20)	NR	55	0	NR	NR	Y	Very low
Yoshioka (2013) [71]	SR	127 (49)	45	61	0	17 %	65 %	N	Very low

Author (year)	Approach	N (RC)	Follow-up (months)	Morbidity (%)	Mortality (%)	DFS (% 5-year *or* months)	OS (% 5-year *or* months)	RC cases analyzed separately (Y/N)	Quality of Evidence
Gall (2014) [72]	BF	53 (53)	30	32[c]	NR	19 %	39 %	Y (all RC)	Very low
Lin (2014) [73]	SR	154 (47)	36	29.9	NR	35 %	46 %	N	Very low
Buchs (2015) [74]	LF	34 (34)	36	27	0	NR	53 %	Y (all RC)	Very low
Ferretti (2015) [75]	SR	142 (58)	29	31	2.1	63 %	72 %	N	Very low

CRC colorectal cancer, *RC* rectal cancer, *SCRLM* synchronous colorectal liver metastasis, *NR* not reported, *NS* not significant, *DFS* disease free survival, *OS* overall survival, *SR* simultaneous resection approach, *BF* bowel-first approach, *LF* liver-first approach

[a]Morbidity and mortality related to rectal resections (R) and liver resections (L) reported separately

[b]Three-year survival rates reported

[c]Morbidity only related to liver resection reported

2 months [93]. Some studies have demonstrated no survival advantage to using preoperative vs postoperative chemotherapy [94, 95]. Nevertheless, patients with rectal cancer and SCRLM are more likely to have a locally advanced primary tumor [38, 96], and strong consideration should be given to neoadjuvant therapy.

Targeted chemotherapy with agents such as Cetuximab, Panitumumab, and Bevacizumab has demonstrated improvements in response and resection rates [97–108]. Hepatic arterial infusion chemotherapy may improve resectability or reduce recurrence in experienced centers [109–113].

Combined modality treatment including FU-based chemotherapy plus pelvic radiation is well established for nonmetastatic locally advanced rectal cancer as it has been shown to reduce local recurrence. However, the precise role, necessity and timing of radiation has not been established in the setting of locally advanced rectal cancer in the setting of SCRLM. Of 185 patients who underwent complete resection of rectal cancer and SCRLM by Butte et al., only 4 % developed isolated pelvic recurrence. The majority of recurrences were distant and concomitant radiation therapy was not associated with a reduction in pelvic recurrences [114]. Others have reported similar results [65, 115]. Lee et al. showed that radiation reduced local recurrence only in patients with T4 tumors [116].

FU-based chemotherapy alone, as commonly used as a sensitizer during the administration of pelvic radiation, is probably suboptimal treatment for the synchronous liver disease [117], and more intensive chemotherapy is likely required [29, 118, 119]. Indeed, there is early evidence to suggest that chemotherapy alone without radiation may result in adequate local control. Schrag et al. showed that of 30 patients who completed 6 cycles of FOLFOX with bevicizumab without RT, all had tumor regression and underwent total mesorectal excision with a 25 % complete pathologic response and a 0 % 4-year LR rate [120]. This concept shows promise for patients with rectal cancer and SCRLM.

Classic Staged Resection: Rectum- First Approach The classic staged bowel-first approach addresses the primary tumor prior to liver resection. As such, local symptoms which may interrupt subsequent treatment can be avoided. Additionally, aggressive disease may reveal itself between the staged resections to avoid unnecessary hepatectomy. Gall and colleagues reported on 53 patients with rectal cancer and SCRLM who underwent the rectum-first approach. Chemotherapy followed by combined modality chemoradiation were administered based on locoregional staging of the primary tumor. Proctectomy was performed, followed by hepatectomy 6 weeks later with additional chemotherapy. No patients had progression of liver disease prior to second stage surgery, and all proceeded without a delay caused by complications from the proctectomy. Two patients had unresectable disease at the time of hepatectomy. Five-year DFS and OS were 19 % and 39 % respectively [72].

Yoshidome et al. noticed that 43 % of patients who underwent the staged bowel-first approach for colorectal cancer and SCRLM developed new liver lesions prior to hepatectomy, which changed the initial surgical plan. None developed extrahepatic disease and all were ultimately resectable. The majority of new lesions occurred elsewhere in the liver, suggesting the presence of occult micrometastasis undetect-

able at initial evaluation. Further, hepatic disease free survival was improved when delayed hepatectomy was performed as opposed to simultaneous resection [58]. Disease progression to unresectability between stages is usually related to the identification of new liver or extrahepatic metastases rather than growth of the preexisting liver lesions. This may spare 36 % of patients a nontherapeutic hepatectomy without affecting survival [121].

Staged Resection: Liver-First Approach In the liver-first approach to rectal cancer with SCRLM, 2–6 cycles of neoadjuvant chemotherapy are typically administered prior to liver resection. Chemoradiation followed by proctectomy is then performed [74, 122]. An advantage of the liver first approach is that it avoids the period of at least 3 months required to treat the primary tumor with neoadjuvant chemoradiation and proctectomy prior to addressing the SCRLM, which is the prognostic determinant [122, 123]. Postoperative complications after proctectomy delay timely treatment in up to 50 % of cases [124]. In fact, less than 30 % of patients undergoing bowel-first surgery proceed to the initially planned hepatectomy due to disease progression, whereas up to 80 % undergo liver resection with the liver first approach [59, 125]. Further, resection of the primary tumor as an initial step may result in a loss of inhibition, and progression of metastatic disease [126–130].

A liver first approach with preliminary chemotherapy allows for some responders with initially unresectable SCRLM to be resected. For those whose liver disease remains unresectable for cure, a nontherapeutic proctectomy may be avoided [131]. Complications related to the primary tumor are uncommon during chemotherapy [132–139], and symptoms of bleeding, pain, and mild obstruction at presentation usually resolve after 1–2 cycles of chemotherapy [140].

Mentha et al. first described the liver first approach [122]. They subsequently reported their experience of 33 patients with rectal cancer demonstrating a 5-year overall survival of 61 %, with 15 % developing a pelvic recurrence. Complications related to the primary tumor requiring emergency intervention occurred in two patients (6 %), both of which had R1 rectal resections and ultimately developed recurrences [74].

In the largest reported experience of 42 patients with locally advanced rectal cancer and SCRLM, 74 % of patients completed the entire protocol including resection of the rectal primary. The remaining patients developed metastatic disease prior to addressing the primary tumor, of which 91 % were spared needless rectal surgery. Notably, five patients received a diverting stoma at some point during the protocol to prevent obstruction. Five-year disease free and overall survival were 40 % and 67 % respectively [68]. de Jong et al. reported the option of “watchful waiting” of the primary tumor with this approach should there be a complete clinical response [141].

Simultaneous Resections With advances in perioperative care, anesthesia, surgical technique, and outcomes after liver surgery [4–6, 142, 143], this approach allows resection of both the primary tumor and SCRLM in one operation, but is not recommended during emergent surgery for complications secondary to the rectal tumor

[144]. There are reports of laparoscopic simultaneous resections performed safely [70, 75, 145–152]. Advantages of this approach include shorter cumulative hospital stay, as well as patient convenience of a single operation with less interruption of chemotherapy. The majority of reports describing this approach combines colon and rectal resections, and have significant selection bias towards less extensive SCRLM and liver resections [153].

Boostrom et al. reported the Mayo Clinic experience with 45 patients who underwent synchronous resection for rectal cancer with SCRLM. There were no mortalities and 16 % suffered severe complications, which did not differ amongst patients undergoing abdominoperineal resection or major liver resection (three or more segments). Five-year disease free and overall survival were 28 % and 32 % respectively [64]. Vigano et al. described combined resection for 34 patients with locally advanced mid or low rectal cancer and SCRLM after neoadjuvant chemotherapy, chemoradiation, or both. There was one mortality and a 36 % morbidity rate. Five-year disease free and overall survival were 40 % and 59 % respectively. Five patients had major liver resections [47].

Ferretti et al. studied 142 patients from 14 centers internationally who underwent laparoscopic synchronous resections of SCRLM, 41 % of whom had rectal primaries; only 12 % involved major liver resection. Overall morbidity was 31 % with a 5.6 % anastomotic leak rate, and a mortality rate of 2.1 %. The independent predictors of morbidity were ASA score more than or equal to three and operative time. Rectal primary and major liver resections were not predictors [75].

Utilizing the synchronous approach, there have been successful reports of two-stage hepatectomy for bilobar or advanced SCRLM. This approach allows for proctectomy with the less extensive first stage hepatectomy, followed by major second stage hepatectomy with diverting stoma reversal. Bilobar advanced SCRLM can be addressed while minimizing the number of operations and optimizing timing of chemotherapy delivery [154, 155].

There are reports of increased mortality when extensive liver resections are combined with colorectal resections [34, 156]. Factors shown to increase morbidity of this approach include the presence of a diverting stoma, a rectal primary, duration of surgery, blood loss, and transfusion need [66, 157], indicating that more extensive surgery may be associated with increased morbidity. Others have demonstrated preoperative patient fitness to be the significant predictor as represented by age, ASA grade, and POSSUM score [67]. Outcomes from some reports suggest that this approach may not be appropriate for elderly patients [35, 158], those with locally advanced rectal cancer [144], or those requiring major resections [34, 35]. These data suggest that patient selection is critical to the safety of this approach.

Comparison of Surgical Approaches There are no prospective randomized trials comparing surgical approaches, and most studies combine colon and rectal cancer without analyzing results pertaining to rectal cancer specifically. Comparison of approaches is difficult given the selection bias of staging more extensive SCRLM resections, and difficulty determining cumulative resection rates and morbidity from staged procedures [159, 160].

There are only two small retrospective studies comparing all three approaches for rectal cancer with SCRLM [46, 54]. Sabbagh et al. showed similar complete resection rates, overall complications, mortality, DFS, and OS between all three groups [54]. van der Pool et al. also showed similar morbidity and mortality between the groups. The simultaneous approach was associated with shorter hospital stay, but was applied to patients with early stage primaries and limited liver disease [46].

Silberhumer et al. compared 43 patients who underwent staged rectal first resection with 145 who underwent synchronous resections. The staged group included a larger number of major liver resections for larger liver lesions, and patients undergoing abdominoperineal resection. Morbidity and mortality rates were similar, even in a subgroup analysis of those undergoing major hepatectomy. Hospital stay was significantly shorter in the simultaneous group [56].

Mayo et al. performed the largest multi-institutional retrospective comparison of all 3 approaches including 1004 patients with colorectal cancer and SCRLM, of which 276 had rectal cancer. The liver first group was more likely to have a rectal primary, bilobar disease, and more hepatic lesions treated during liver surgery. Patients in the simultaneous group were less likely to undergo major hepatectomy. Morbidity and mortality rates were similar between groups, even in those undergoing major hepatectomy, although there was a nonsignificant trend towards increased mortality in patients undergoing extended hepatectomy in the simultaneous group. Five-year overall survival was similar among all three groups. Notably, a rectal primary was independently associated with worse survival [50]. Brouquet et al. reviewed the MD Anderson experience of 156 patients with colorectal cancer and SCRLM, 52 % of whom had rectal cancer. Morbidity, mortality, R0 resection rates, DFS, and OS were similar between all 3 approaches. Interestingly, 5 % of patients undergoing the liver first approach developed symptoms related to the primary tumor requiring colostomy, both of whom had nontraversable tumors on initial colonoscopy [42]. Similarly, a meta-analysis comparing all three approaches for CRC showed no difference in morbidity, mortality, or survival despite the tendency of patients with a larger burden of SCRLM to undergo a liver first approach. This suggests that the liver first approach may be appropriate for this group of patients [161].

Recommendations Based on the Data

Evaluation of the Rectal Cancer Patient with Synchronous Hepatic Metastasis

In addition to standard imaging for staging, contrast-enhanced MRI of the abdomen increases detection and further characterizes SCRLM, particularly after neoadjuvant chemotherapy (evidence moderate; weak recommendation). FDG-PET can detect extrahepatic disease prior to surgery; however sensitivity after chemotherapy is reduced (evidence moderate; weak recommendation).

Treatment Options: Multimodality Treatment

Patients with rectal cancer and SCRLM should receive perioperative chemotherapy (evidence high; strong recommendation), however there is no consensus on timing. Neoadjuvant chemotherapy can be recommended, particularly for patients with initially borderline resectable or unresectable SCRLM. Reassessment at 2–4 months from onset of therapy is recommended to minimize liver damage prior to hepatectomy (evidence low; weak recommendation). Radiation therapy may have a benefit in preventing morbid local complications in patients at high risk for pelvic recurrence (evidence low; weak recommendation). Priority should be given towards addressing more common and prognostically more significant distant disease. Isolated local recurrence is uncommon.

Treatment Options: Surgical Approach

All three approaches (rectum first, liver first and synchronous resection) are equivalent regarding safety and oncologic outcome. Patient selection and local expertise are important considerations (evidence low; weak recommendation). Fit patients undergoing surgery with low anticipated blood loss and operative time can safely undergo synchronous resection (evidence low; weak recommendation). Initially diverted, asymptomatic, or mildly symptomatic patients with a locally advanced primary tumor and/or advanced bilobar SCRLM are suitable for the liver first approach (evidence low; weak recommendation). Resectional surgery can be avoided in cases of disease progression. Non-diverted patients with significant symptoms secondary to the primary tumor who may not tolerate the simultaneous approach are well-suited for the rectum first approach (evidence low; weak recommendation.)

A Personal View of the Data

The summarized evidence regarding management of rectal cancer metastatic to the liver is heterogeneous. An individualized approach based on patient characteristics, disease factors, and degree of symptomatology is proposed in Fig. 20.1. In the absence of severe symptoms related to the primary tumor, the authors' approach is to initiate systemic chemotherapy in patients who are potentially resectable. Patients with diffuse bilobar metastatic disease or additional extrahepatic lesions can be palliated based on extent of disease, functional status, and degree of symptoms. Potentially resectable patients should be reassessed following systemic chemotherapy to select out nonresponders who can be palliated non-surgically. Patients who are resectable following chemotherapy can undergo synchronous resection if medically fit, R0 rectal resection is possible, and anticipated morbidity from liver

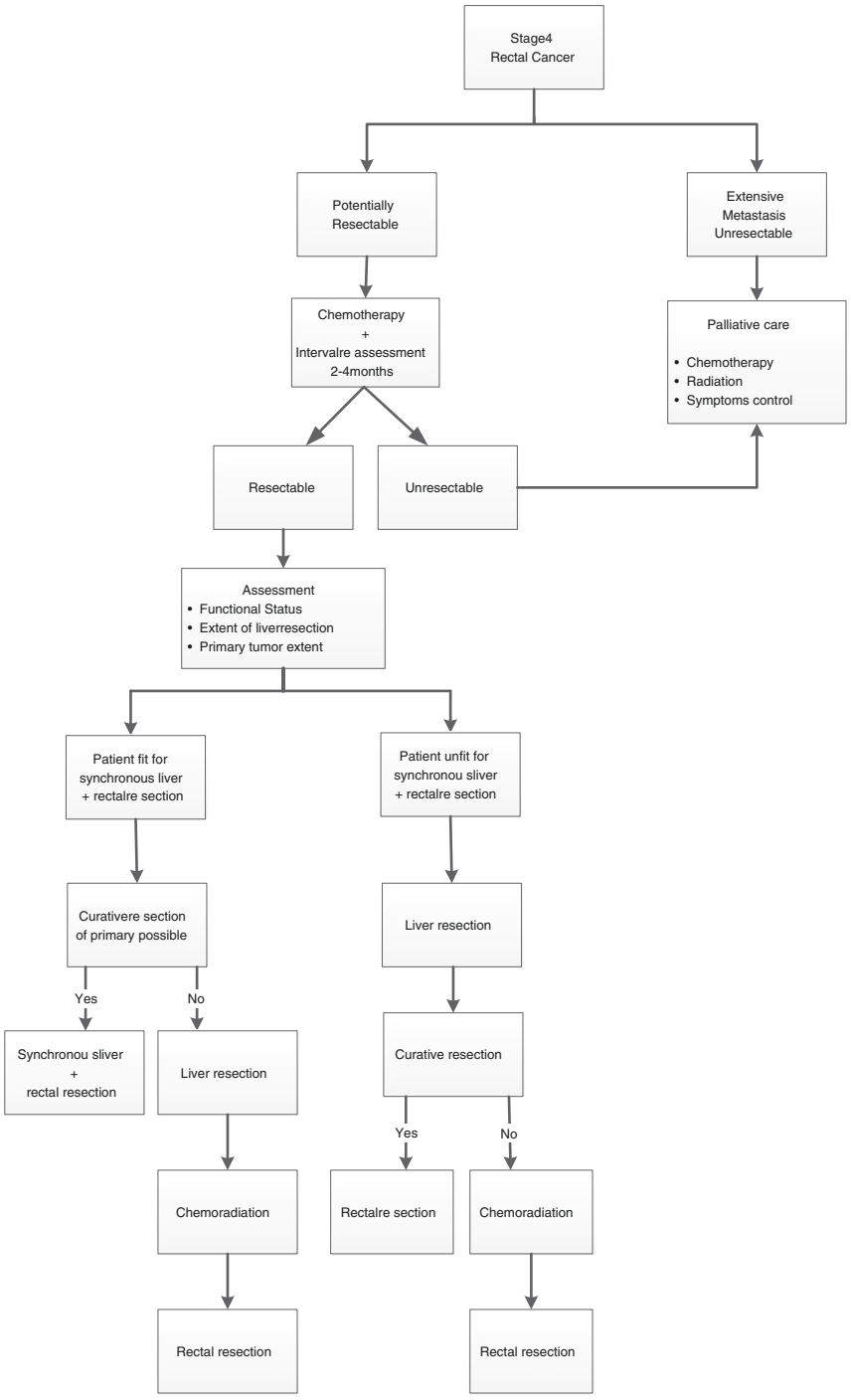

Fig. 20.1 Suggested algorithm for approach of patients with RC and SCRLM

resection based on extent of disease is minimal. Otherwise, a staged liver first approach is advisable, as systemic disease determines disease free and overall survival. Furthermore, complications of rectal resection may further delay treatment if the rectal tumor is resected first.

Following liver resection, proctectomy is performed if curative resection is possible. If radial and/or distal margins are threatened with a higher risk of pelvic recurrence, then chemoradiation precedes rectal resection. Not reflected in the provided algorithm is one additional variation. In healthy patients with extensive SCRLM requiring two-stage hepatectomy, the first stage (minor left-sided resection) is performed with rectal surgery. The second major hepatectomy can be performed with ileostomy reversal in diverted cases. Finally, these recommendations do not apply to patients who present with acute obstruction or profuse rectal bleeding. The former subgroup can be addressed by fecal diversion or in select cases endoluminal stenting, while the latter can benefit from resection of the primary tumor, endoluminal fulguration, or external beam radiation therapy.

Summary of Recommendations

1. In addition to standard imaging for staging, contrast-enhanced MRI of the abdomen increases detection and further characterizes SCRLM, particularly after NCT (evidence moderate; weak recommendation).
2. FDG-PET can detect extrahepatic disease prior to surgery, however sensitivity after chemotherapy is reduced (evidence moderate; weak recommendation).
3. Patients with rectal and SCRLM should receive perioperative chemotherapy (evidence high; strong recommendation), however there is no consensus on timing.
4. Neoadjuvant chemotherapy can be recommended, particularly for patients with initially borderline resectable or unresectable SCRLM. Reassessment at 2–4 month intervals is recommended to minimize liver damage prior to hepatectomy (evidence low; weak recommendation).
5. Radiation therapy may have a benefit in preventing morbid local recurrence in patients at high risk for local recurrence (evidence low; weak recommendation).
6. All three surgical approaches are equivalent regarding safety and oncologic outcome. Patient selection and local expertise are important considerations (evidence low; weak recommendation).
7. Fit patients undergoing surgery with low anticipated blood loss and operative time can safely undergo synchronous resection (evidence low; weak recommendation).
8. Initially diverted, asymptomatic, or mildly symptomatic patients with a locally advanced primary tumor and/or advanced bilobar SCRLM are suitable for the liver first approach (evidence low; weak recommendation).
9. Non-diverted patients with significant symptoms secondary to the primary tumor who may not tolerate the simultaneous approach are well-suited for the rectum first approach (evidence low; weak recommendation).

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Chapter 21
Who Needs a Loop Ileostomy After Low Anterior Resection for Rectal Cancer?

Walker Julliard and Gregory Kennedy

Pt population	Intervention	Comparator	Outcomes studied
Pts after LAR	Proximal diversion	No diversion	Leak rate, consequences

Introduction

The standard of care for rectal cancers has evolved over recent years to be restorative anterior proctectomy. The most feared complication after low anterior resection (LAR) is anastomotic leak. Overall risk of anastomotic leak varies between 3 and 21 % [1]. Anastomotic leak has a reported mortality of 2.1–22 % and requires intervention with methods ranging from interventional radiologic drainage to reoperation [2]. Furthermore, colonic conduit function after anastomotic leak is significantly worse than in patients without leakage [2]. Other complications from anastomotic leak include increased rate of local recurrence and decreased disease-free and overall survival [3, 4]. This increase in cancer recurrence may be due to a

W. Julliard (✉)
Department of Surgery, University of Wisconsin School of Medicine and Public Health, 600 Highland Drive, Madison, WI, USA
e-mail: wjulliard@uwhealth.org

G. Kennedy
Division of Gastrointestinal Surgery, Department of Surgery, University of Alabama at Birmingham, KB 430, 1720 2nd Ave S, Birmingham, AL 35294-0016, USA
e-mail: gkennedy@uabmc.edu

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delay or abandonment of the necessary adjuvant chemoradiotherapy [4]. Because of the serious morbidity associated with anastomotic leak, measures to minimize leak rates and the morbidity from such leaks has been implemented, the most ubiquitous of these being temporary fecal diversion. However, in recent years, the dogma of mandatory fecal diversion after LAR has been called into question.

Methods

A detailed search of the Embase-Medline databases was conducted for medical literature. The following search terms were employed to identify relevant articles: ("rectal" OR "colon" OR "colorectal") AND ("resection" OR "low anterior resection" OR "proctectomy") AND ("ileostomy" OR "ostomy" OR "colostomy" OR "diversion" OR "fecal diversion"). The title and abstracts of English-language articles were assessed for relevance

Why Not Divert?

When deciding if a patient should undergo fecal diversion, it is essential to fully understand the consequences of the procedure. Despite the widespread use of fecal diversion, it is not without complications. These complications include both short- and long-term problems and range from minor, requiring only local care, to major complications requiring reoperation and prolonged hospitalization [5, 6]. The most common complication after stoma construction is peristomal skin irritation [7]. While not necessarily defined by most members of the surgical community as a "major" complication, this can have major implications for a patient's quality of life [8].

A recent retrospective review using ACS NSQIP data identified multiple complications that were increased in patients undergoing low anterior resection with fecal diversion [6]. Patients who underwent diversion were found to have a higher rate of progressive renal insufficiency (2.1 % vs. 0.8 %) without an increased risk of acute renal failure (1.3 % vs. 0.7 %). Using a risk adjusted model, this increased rate of renal insufficiency was 2.37 times more likely to occur in patients undergoing fecal diversion. Furthermore, patients with fecal diversion had a significantly higher rate of deep surgical site infections (7.5 % vs 5.3 %) and a higher rate of 30-day readmission (20.3 % vs 11 %). Although not specifically discussed in this study, the findings of renal insufficiency and readmission are not surprising following stoma creation, as one of the most commonly encountered problems with diverting ileostomy is dehydration from high ostomy output. This complication has a reported incidence of 1–16 %, is most common 4–8 days postoperatively as bowel edema is resolving, and leads to electrolyte abnormalities, hypovolemia, and readmission [9]. Further out from the index operation, parastomal hernia occurs at a rate of 15–40 % [10]. Once identified, most hernias will require operative repair, which traditionally has overall poor results.

Finally, by definition, all temporary diverting ostomies require reversal; while this is technically not a difficult procedure, it is not without risk. In a study from Pokorny et al. in 2006, 243 patients who underwent loop ileostomy closure were retrospectively reviewed for complications [5]. An overall complication rate of 19 % was identified; 3 % had anastomotic leak, 6 % developed significant postoperative ileus, 1 % had bleeding complications, and 9 % had wound infections. In total, 4 % of patients undergoing ileostomy closure required reoperation for their complication.

Does Fecal Diversion Decrease Anastomotic Leak Rate?

The key question when considering fecal diversion following low anterior resection of the rectum is whether diversion changes the rate of anastomotic leak. There have been numerous retrospective studies over the years that have reported mixed results. While the number of large retrospective studies is quite high, all of these studies are inherently biased, as surgeons concerned about a particular anastomosis will favor temporary diversion. Given the fact that there are numerous studies on both sides of the issue of fecal diversion, it is difficult to draw sound conclusions from this retrospective data. Therefore, although limited in number and patients enrolled, randomized controlled trials comparing fecal diversion to anastomosis without diversion provide more reliable data with significantly less bias.

Graffner et al. were the first to design such a trial in 1983 and randomized 50 patients to fecal diversion versus no diversion [11]. 25 patients were in each group and there was a low overall leakage rate (4 % in the stoma group versus 12 % in the no stoma group). The next study was performed in 1997 by Pakkastie et al. In this study of 134 patients, there was a clinically detected 16 % leak rate in the stoma group versus a 32 % leak rate in the no stoma group. Importantly, there was also a lower re-operation rate in the stoma group, as only one of three leaks required re-operation compared to all six leaks requiring return to the OR in the no stoma group [12].

The next major study to address this issue was published in 2007 by Matthiessen et al. [13]. Importantly, this was a large multicenter trial, which enrolled a total of 234 patients for randomization, 116 in the stoma group and 118 in the no stoma group. Postoperatively, patients were monitored clinically for signs of anastomotic leak. There was a significantly higher leak rate in patients without a stoma (28.2 %) compared to those with a stoma (10.3 %; $p < 0.001$). Furthermore, there was a significantly higher rate of reoperation in the no stoma group with overall 25.4 % of patients requiring any reoperation versus 8.6 % in the stoma group. The largest of such studies, published in 2008 by Chude et al., included 256 patients, 120 without diversion and 136 with diversion [14]. Postoperatively, 12 of the 120 patients without diversion developed anastomotic leak (10 %) versus only 3 patients in the diverted group (2.2 %). Furthermore, two of the non-diverted patients required return to the OR for their anastomotic leak whilst none of the diverted patients required reoperation.

Another small study was performed by Ulrich et al. and reported in 2009 [15]. This study was much smaller than the other two published around the same time, with only 34 patients randomized. Again, there was a significantly higher rate of clinically detected anastomotic leaks in the no stoma group (37.5 %) compared to the stoma group (5.5 %, p = 0.02). All patients who developed a leak in the no stoma group required reoperation while none of the stoma patients with a leak returned to the OR. The differences in the study were in fact so dramatic that the study was halted after 34 patients were accrued due to clear superiority in the diverted group.

All of the above randomized trials were analyzed in a meta-analysis performed by the Cochrane Database and reported in 2010 [16]. When the results from these individual studies were combined, there was found to be a dramatic reduction in anastomotic leakage using fecal diversion (RR 0.33; 95 % CI [0.21, 0.53]). Furthermore, diverted patients had a decreased rate of urgent reoperation (RR 0.23; 95 % CI [0.12, 0.42]). Despite these differences, there was no significant decrease in terms of overall mortality (RR 0.58; 95 % CI [0.14, 2.33]). The conclusion of the review was that fecal diversion is an effective method in reducing the rates of anastomotic leak in patients undergoing low anterior resection and therefore the procedure can be offered routinely. This review did note significant limitations in all of the above studies and found that the methodology was overall poor; it was also observed that there was a lack of reporting of long-term mortality and quality of life.

Since the Cochrane Review was completed, at least one further study has been performed in a prospective, randomized fashion [17]. Thoker et al. reported in 2014 on 78 patients undergoing LAR randomized to stoma versus no stoma. In their study, they demonstrated a lower leak rate in the diverted group at 6 % compared to a rate of 11 % in the non-diverted group. Of note, they also followed patients for stoma related complications and found a higher rate of electrolyte imbalance in the postoperative period, as well as significant stomal complication rate of 25.4 %. Finally, they demonstrated that stoma closure was associated with an overall complication rate of 67.7 %.

Taken together, these data demonstrate that fecal diversion offers a clear benefit in LAR in lowering anastomotic leak rate and need for reoperation. While early retrospective studies arrived at varying conclusions, prospective randomized trials have all demonstrated a clear benefit to fecal diversion. Therefore, at this point, it is clear that at a population level, fecal diversion should be the default operation in combination with LAR. However, what these studies fail to address is which patients are at decreased risk of anastomotic leak and therefore could avoid defunctioning stoma placement.

Who Is at Highest Risk for Developing a Leak?

There are multiple risk factors for development of anastomotic leak, some which are associated with wound healing in general, and some which are specific to rectal cancer. Patient factors that increase the risk of developing an anastomotic leak are

risk factors that are associated with poor wound healing in general. Patients that have malnutrition, preoperative weight loss, preoperative steroids, and obesity are at higher risk for developing an anastomotic leak [18]. In a retrospective analysis from 2010 which reviewed 1495 consecutive patients who underwent LAR, an overall leak rate of 11 % was observed [19]. In reviewing specific patient factors associated with anastomotic leak, distance from anal verge was found to have the strongest association with leak rate (OR = 2.0 for anastomosis 10 cm from anal verge, OR = 3.6 for anastomosis 7 cm from anal verge, and OR = 5.4 for anastomosis 5 cm from anal verge). This finding that anastomoses close to the anal verge were at high risk for anastomotic leak was also observed by Rullier et al. [20]. Their study examined outcomes in 272 consecutive patients undergoing LAR and found by multivariate analysis that anastomoses within 5 cm of the anal verge were six times more likely to develop an anastomotic leak. Further operative factors related to anastomotic leak include male gender (OR = 2.36), and intraoperative blood loss (OR = 1.05).

Finally, intraoperative assessment of the anastomosis may play an important role in reducing the leak rate and in deciding on the need for proximal diversion. Common methods of evaluating a colorectal anastomosis include air leak testing, saline leak, methylene blue leak tests and endoscopic assessment. Two randomized trials have evaluated the validity of performing an intraoperative leak test and have found that the risk of leak in those tested was significantly lower than the untested controls (5.8 % versus 16 %, $p < 0.05$) [21, 22]. Therefore, intraoperative leak testing should be performed and patients found to have concerning findings on exam should undergo repair, revision, or anastomotic resection.

One area of continued controversy is the role of neoadjuvant radiotherapy in promoting anastomotic leak. The largest study which compared preoperative radiotherapy to selective postoperative chemoradiotherapy was published in 2009 by Sebag-Montefiore et al. [23]. In this multicenter randomized trial, 1350 patients with rectal cancer were randomized to neoadjuvant radiotherapy versus adjuvant chemoradiotherapy. While the purpose of the study was to identify best timing of treatment in relation to overall and disease-free survival, one of the data points collected was the rate of anastomotic leak. After low anterior resection with fecal diversion, 9 % of patients treated with neoadjuvant therapy developed an anastomotic leak compared to 7 % in the adjuvant group, which was not statistically significant. However, the application of these findings is limited by the fact that both groups underwent fecal diversion and only clinically significant leaks were reported; therefore leaks which may have been clinically significant if not diverted were not detected.

In a retrospective study published in 2012 by Nisar et al., 1862 patients who underwent resection between 1980 and 2010 were stratified into two groups based on preoperative radiotherapy and assessed for anastomotic leak [24]. An overall leak rate of 6.3 % was identified with no difference between the two groups (8 % neoadjuvant group versus 5.7 % in the no radiotherapy group, $p = 0.06$). On multivariate analysis, neoadjuvant therapy was not found to be associated with increased leak rate (OR = 1.44; CI 0.85, 2.46; $p = 0.18$). However, there were significant preoperative differences between the groups, including a rate of defunctioning ostomy

of 87 % in the neoadjuvant group versus 44 % in the no radiotherapy group. These differences make interpretation of the data difficult.

To further evaluate this issue, a recent meta-analysis was performed by Qin et al. and included seven randomized controlled trials comparing preoperative radiotherapy to no preoperative therapy [25]. Pooling these studies, a total of 1660 patients formed the preoperative radiotherapy group while 1715 patients formed the control group. In this analysis, rates of anastomotic leak were not increased in the preoperative radiotherapy group (OR = 1.02; CI 0.80, 1.30; p = 0.88). This study, however, is once again limited by the use of clinically detected anastomotic leaks in the individual trials making up the analysis, which may underreport anastomotic leaks that would be clinically significant if no defunctioning stoma were in place. Because of the lack of studies which truly examine the rate of all leaks, not only clinically significant leaks in the presence of a defunctioning stoma, making strong recommendations in patients who received preoperative radiotherapy remains difficult.

What Type of Diverting Ostomy Should We Use?

When considering fecal diversion, there are two common options; loop ileostomy or loop colostomy. Four randomized trials have compared these two options to each other, with two studies favoring the use of loop colostomy [26, 27] and two favoring loop ileostomy [28, 29]. In 2007, a Cochrane review was conducted which found five randomized studies involving 334 patients: 168 in the loop Ileostomy group and 166 in the loop colostomy group [30]. There was a very large difference in rates of stomal prolapse, with a rate of only 2 % in the ileostomy group versus 19 % in the colostomy group ($p < 0.01$), however, there were no other differences noted. Given the large difference in rates of prolapse, current recommendations are to create a loop ileostomy when possible.

Personal View of the Data

While it is clear that proximal diversion is not without risks, the consequences of an anastomotic leak are such that the benefits often outweigh the risks. Therefore, proximal fecal diversion following anterior resection for rectal cancer should be considered standard practice in all but a select few patients. This group of patients should include those at the lowest risk for developing an anastomotic leak such as non-smoking women with high rectal lesions who have not had preoperative radiation therapy. After creation, all colorectal anastomoses should be tested for the presence of an anastomotic leak. A positive test may necessitate a revision of the anastomosis followed by proximal diversion.

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Chapter 22
Selection Factors for Reoperative Surgery for Local Recurrent Rectal Cancer

Scott R. Kelley and David W. Larson

Introduction

In the modern era of total mesorectal excision combined with neoadjuvant or adjuvant therapy, local recurrence following curative resection for rectal cancer has decreased from approximately 30 to around 10 % or less [1–4]. Recurrence treated with chemoradiation alone affords a median survival of 12–15 months compared to the alternative of no therapy (3–8 months) [2, 3]. However, up to 40–50 % of patients with local recurrence are candidates for re-resection. With multimodal therapy, 5-year overall survival can be as high as 55 % after a microscopically negative resection (R0) [2, 4–9]. With preoperative chemoradiation, radical/extended radical R0 resection, and intraoperative radiotherapy when appropriate, patients are offered the best chance for cure.

A multitude of variables need to be taken into consideration prior to pursuing surgery including the patient's physical condition, the presence of metastatic disease, local extent of the recurrence, and purpose of surgery (palliative or curative). Reoperative surgery for locally recurrent rectal cancer is technically challenging with morbidity rates ranging from 20 to 80 % and mortality up to 8 % [5, 6, 8]. In light of the potential for major complications, a multidisciplinary approach is imperative for surgical evaluation, planning, and execution [10, 11]. These high-risk surgeries should be performed in dedicated referral centers capable of managing these complex patients [13–15].

Herein we review the literature and discuss selection factors for reoperative surgery in the setting of locally recurrent rectal cancer.

S.R. Kelley, MD, FACS, FASCRS • D.W. Larson, MD, MBA, FACS, FASCRS (✉)
Division of Colon and Rectal Surgery, Mayo Clinic, 200 First Street SW,
Rochester, MN 55905, USA
e-mail: larson.david2@mayo.edu

N. Hyman, K. Umanskiy (eds.), *Difficult Decisions in Colorectal Surgery*,
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Search Strategy

Utilizing PubMed and Google Scholar a systematic review of the English literature was conducted using the terms recurrent rectal cancer, locally recurrent rectal cancer, unresectable, multimodal therapy, sacrectomy, and intraoperative radiotherapy. We limited our search timeline to the last 10 (2015–2005) years. Original studies evaluating outcomes of patients treated for local recurrence of rectal cancer were included and manuscript reference lists were searched for additional articles. Studies from the same institution/author were excluded if previously reported. A total of 102 studies were chosen for review.

Patients	Intervention	Comparator	Outcomes
Locally recurrent rectal cancer	Reoperation	Non-operative Palliation	Cure Survival Morbidity Mortality Quality of life

Results

Suspicion of recurrence should prompt evaluation with imaging to assess anatomy, extent of localized and/or disseminated disease, and to determine resectability. Differentiating between tumor and inflammatory changes can be difficult and a complement of imaging modalities is often necessary [16]. Computed tomography (CT) of the chest, abdomen, and pelvis should be obtained to assess for extrapelvic metastasis and the extent of local involvement. Since CT is less discerning for predicting local tumor infiltration and adjacent organ involvement, magnetic resonance imaging (MRI) of the pelvis should typically be performed to evaluate for invasion of surrounding structures [17, 18]. High resolution MRI has been shown to have a negative predictive value of 93–100 % for identification of local invasion, however is also limited in its ability to distinguish recurrence from diffuse fibrosis [19–21]. Despite lower accuracy for anterior recurrence close to the bladder and mucinous tumors, PET – CT has a sensitivity and specificity of nearly 100 and 96 %, respectively, for diagnosing local recurrence [22–28].

For any patient with a suspicion for recurrence, histologic proof should be vigorously sought prior to proceeding with surgery, though at times can be difficult to definitively obtain. If unable to confirm histologically, other factors should be taken into consideration such as an increase in the dimensions of the area of interest over time, invasion of surrounding structures, a rising carcinoembryonic antigen (CEA), the development of symptoms (e.g. pain from neural or osseous involvement, urinary, fecal, or neurologic complications, bleeding), and overall multidisciplinary assessment [29].

Different classification systems to assess tumor resectability and provide prognostic information are based on the anatomic location of pelvic recurrence, degree

and site(s) of fixation, and symptoms. None can unfailingly predict resectability prior to surgery since new findings may be discovered intraoperatively. The system utilized at the Mayo Clinic classifies recurrence based on pain (S0 – asymptomatic, S1 – symptomatic without pain, S2 – symptomatic with pain) and fixation to surrounding structures (F0 – not fixed, F1 – fixed to 1 site, F2 – fixed to 2 sites, F3 – fixed to ≥3 sites). Fixation is defined anatomically as anterior, posterior, and lateral [30, 31]. Wanebo developed a system identifying five stages of invasion. (TR1) limited muscularis propria invasion, (TR2) full thickness muscularis propria involvement, (TR3) anastomotic recurrence into perirectal soft tissue, (TR4) adjacent organ invasion/not fixed, and (TR5) invasion of sidewalls or bony ligaments [32]. A system proposed by the Leeds group classifies recurrence as central (confined to pelvic organs without osseous involvement), sidewall (involving lateral sidewall), sacral (abutting or invading sacrum), or composite (sacral and sidewall involvement) [33]. Yamada and colleagues devised a system evaluating the pattern of pelvic fixation as localized (adjacent organs or tissue), sacral (lower sacrum – S3/S4/S5, coccyx, periosteum), and lateral (sciatic nerve, greater sciatic foramen, lateral sidewall, upper sacrum – S1/S2) [34]. Memorial Sloan Kettering utilizes a system based on involvement of surrounding structures and anatomic location; axial (anastomotic recurrence, perineal and perirectal invasion), anterior (urogenital involvement), posterior (presacral fascia or sacral invasion), and lateral (sidewall and bony pelvis involvement) [35]. The Royal Marsden Hospital system evaluates the extent of tumor invasion in seven different pelvic compartments based on MRI; (C) central, (P) posterior, (I) inferior, (L) lateral, (PR) peritoneal reflection, (AA-PR) anterior above and (AB-PR) anterior below the peritoneal reflection [36].

Hruby and colleagues evaluated sites of pelvic recurrence in 269 patients with rectal cancer untreated with radiotherapy and found nearly 90 % in the posterior or central pelvis, with 20 % at the level of the anastomosis [32]. The Mayo system found worse outcomes in those presenting with pain and increased points of fixation [30, 31]. Yamada found a 5 year survival rate of 38 % for localized disease, 10 % for sacral involvement, and 0 % for lateral invasion [34]. The Memorial Sloan Kettering group documented the likelihood of a R0 resection for axial only recurrence as 90 %, versus 36 % for lateral involvement [24]. Based on findings from the Royal Marsden Hospital, survival is decreased when MRI reveals involvement of more than two compartments, or when the lateral or posterior planes are involved [36].

Surgery, chemotherapy, and radiation alone result in high rates of local and distant failure; but when combined in a multimodal fashion have been shown to improve local control, survival, rates of salvage surgery, and resection with R0 margins [7, 31, 38–44]. Radiotherapy naïve patients should receive a full course (5040 cGy/50.4 Gy) of external beam radiotherapy (EBRT) administered concurrently with sensitizing 5-floururacil (5-FU) based chemotherapy The addition of other cytotoxic (oxaliplatin, irinotecan) and biologic (cetuximab, bevacizumab) agents along with 5-FU has not shown benefit to date [45]. For those previously irradiated, a hyperfractionated course of 2000–3000 cGy EBRT along with 5-FU can be completed prior to surgery. Although safe and effective, there is a lack of high quality data to support this approach [39, 42, 46, 47]. Intensity modulated

radiotherapy reduces the dose of radiation to surrounding structures, though supporting evidence is limited regarding a benefit over conventional radiotherapy [48]. To maximize tumor response, surgery is planned for 6–8 weeks following completion of radiation [49].

As part of a multimodal treatment approach, intraoperative radiotherapy (IORT) has been shown to increase survival by 15 % or more and improve local control in selected patients [50, 51]. Intraoperative radiotherapy overcomes the dose restriction of EBRT by limiting exposure to surrounding unaffected structures. The total dose administered is dependent on preceding amounts of preoperative radiotherapy delivered. The Mayo Clinic has a dedicated operating room with a linear accelerator to provide electron beam radiotherapy, and a dose of 1000 cGy is given for minimal residual disease (margin microscopically involved or clear by <5 mm), 1500 cGy for unresectable gross disease less than 2 cm, and 2000 cGy for more than 2 cm [52]. Other means of administering locally directed radiation include high dose intraoperative brachytherapy (HDR-IORT), perioperative brachytherapy, and photon radiosurgery [53, 54]. Multiple institutions have shown improved disease free and overall survival, as well as local control, following R0 and microscopically positive (R1) resections when IORT is incorporated into a multimodal treatment regimen, regardless of the IORT approach chosen [50, 51, 55–62]. Others have not been able to document a benefit [42, 63–65]. The largest series evaluating 304 patients with locally recurrent rectal cancer was reported by the Mayo Clinic in 2003. Of those, 138 underwent a R0 resection, 27 a R1, and 139 had gross (R2) residual disease. The 5 year survival rates were greatest for R0 versus the R1 and R2 resections (37 versus 16 %, $p<0.001$). Survival after extended procedures (sacrectomy, pelvic exenteration, cystectomy with ileal conduit) was comparable to more limited resections (28 versus 21 %, $p=0.11$) [31]. Overall, results from specialized centers support an oncologic advantage for IORT in select patients. However, there is a significant amount of heterogeneity between centers, making broad consensus statements challenging.

A R0 resection provides the highest rate of local control as well as cancer specific and overall survival. The presence of microscopically or grossly positive (R2) margins decreases survival [66]. Resection is based on defining invasion into adjacent structures, as well as the presence of metastatic disease. Factors typically associated with the inability to pursue a curative (R0) resection include poor performance status, encasement of external iliac vessels, presence of venous or lymphatic obstruction, distant metastasis, fixation to two or more sites (F2 or F3 involvement), predicted R1/R2 resection, sacral invasion above S2, extension though the greater sciatic notch, circumferential or multiple sites of pelvic sidewall involvement, bilateral ureteral obstruction outside the bladder trigone, and S1/S2 nerve root involvement [35, 67–70].

Upwards of 50 % of patients with local recurrence will have a metastatic lesion noted during initial evaluation. If resectable, surgical intervention can be pursued in a synchronous or staged approach, and in highly selected patients outcomes are favorable [71, 72]. En bloc resection of involved ureteral or iliac vessels is possible and is associated with an increased R0 resection rate [6, 35, 69, 73–75]. Extended resections to achieve negative margins, including a high sacrectomy, improve local

control and survival [6, 8, 68, 73, 76–84], though can result in significant life altering morbidity. Complications are higher for fixed tumors, and reduced tumor free resection margins and survival has been demonstrated in those with symptomatic pain and fixation to more than one area [30, 31]. Other factors noted to decrease R0 resections are male sex, increased age, previous abdominoperineal resection, higher stage of primary tumor, and elevated CEA level [35]. If the morbidity of an extended resection to obtain a R0 margin outweighs the potential benefit, an R1 resection with IORT should be pursued.

Following radiation, surgery, and IORT, complications occur in upwards of 65 % of patients owing to the heavily irradiated field [31, 46]. The most common complications include pelvic abscesses (6.6 %), bowel obstruction (5.3 %), enteric fistulas (4.3 %), and wound complications (4.6 %). Those with extended resections and more than two sites of fixed recurrence, experience the highest rates of postoperative complications [31]. Nelson and colleagues from the Mayo Clinic reported reduced wound complications and length of hospital stay when flap repairs were utilized in comparison to primary closure. Other studies have corroborated the benefit of perineal defect closure/reconstruction with techniques including omentoplasty combined with biologic implants, vertical rectus or myocutaneous oblique abdominis muscle flaps, gluteal rotation flaps, gracilis flaps, and free flaps [85–91].

If cure is not possible (R2 resection would be required), then palliation of symptoms may be sought with a combination of modalities (chemoradiotherapy, urinary and colonic stents, nephrostomy tubes, endoscopic laser ablation, targeted surgery), all of which have been shown to improve quality of life, though rarely halt disease progression [92–96]. External beam radiation, therapy (EBRT) including reirradiation when necessary, has been noted to control pain in 50–90 % of patients [97, 98]. The addition of chemotherapy to EBRT also improves symptoms, but not 5 year survival [41, 99, 100]. Improvement in symptoms and quality of life has been shown to be superior following surgery compared to non-surgical approaches, even for selective cases with distant metastasis, although less so for extended resections [25, 101, 102].

Recommendations Based on the Data

The available evidence regarding the management of locally recurrent rectal cancer consists primarily of single institution case control and retrospective studies. Few multicenter studies exist and there are no randomized trials.

High resolution MRI is the preferred imaging modality to evaluate for pelvic recurrence. Computed tomography of the chest, abdomen, and pelvis should be obtained to assess for extrapelvic metastasis. Questionable findings can be further investigated with PET – CT (evidence moderate, strong recommendation).

A classification system to assess for tumor resectablilty and prognostic information should be incorporated into the preoperative workup and evaluation (evidence moderate, strong recommendation).

Neoadjuvant chemoradiotherapy should be administered to radiotherapy naïve patients (evidence moderate; strong recommendation) and re-irradiation prior to surgery can be administered in those previously irradiated (evidence low, weak recommendation).

Re-staging should be performed 4–6 weeks prior to surgery (evidence low, strong recommendation) and surgery should be planned 6–8 weeks after completing neoadjuvant therapy (evidence moderate, strong recommendation). IORT, when indicated, should be part of the multimodal treatment regimen (evidence moderate, strong recommendation). To decrease issues with postoperative pelvic wound complications, flap reconstruction should be pursued for large defects (evidence moderate, strong recommendation).

The best chance for survival is a R0 resection, which may require an extended radical resection (evidence moderate, strong recommendation). If morbidity outweighs the benefit of an extended resection to achieve a R0 margin, an R1 resection with IORT should be pursued, which has better outcomes than R1 without IORT (evidence moderate, strong recommendation). Surgery does not offer adequate survival or local tumor control following a R2 resection and should be avoided (evidence moderate, strong recommendation).

If curative resection is not possible, palliation of symptoms should be sought with a combination of modalities to improve quality of life (evidence moderate, strong recommendation).

A Personal View of the Data

Based on our experience at the Mayo Clinic, as well as the literature, we perform a high resolution CT of the chest, abdomen, and pelvis to evaluate for metastases. A high resolution musculoskeletal pelvic MRI that includes axial, sagittal, and coronal/oblique views is the imaging modality of choice when evaluating for local recurrence. Questionable findings are further investigated with PET – CT. A classification system to assess for tumor resectablilty and provide prognostic information should be incorporated into the preoperative workup and evaluation. Tumor location and local extent of involvement are two of the most important factors in determining resectability. For those cases with a high probability of an R0 resection, the collaboration of an experienced multidisciplinary team (colorectal surgery, urology, gynecology, plastic reconstructive, vascular, neurosurgery, orthopedics, radiation oncology) should be pursued.

Although the literature is controversial regarding the benefit of reirradiating previously irradiated patients, we have found it to be beneficial in our patient population. A short course boost is often followed by surgery within a week. Unless contraindicated, all radiotherapy naïve patients should receive neoadjuvant chemoradiation. Multimodal therapy with IORT improves local control and survival and offers the best possibility of cure, though is does not compensate for inadequate or incomplete resections (R2). IORT reaches its peak effect if delivered within 8 weeks following

EBRT. Imaging should be repeated 4 weeks after completion of CRT and if no progression or metastasis is found, surgery should be pursued within the next 4 weeks.

It has become widely accepted that the surgical management of locally recurrent rectal cancer offers the potential for cure and improved quality of life in patients who are candidates for re-resection. A planned R2 resection should be avoided since outcomes are no different than non-operative measures. These high-risk surgeries should be performed in dedicated referral centers capable of managing such complex patients.

Abstracted Recommendations

High resolution MRI is the preferred imaging modality to evaluate for pelvic recurrence. Computed tomography of the chest, abdomen, and pelvis should be obtained to assess for extrapelvic metastasis. Questionable findings can be further investigated with FGD\PET – CT (evidence moderate, strong recommendation).

Histologic confirmation of recurrence should be ascertained whenever possible (evidence moderate; strong recommendation).

Neoadjuvant chemoradiotherapy should be administered in radiotherapy naïve patients (evidence moderate; strong recommendation).

Re-irradiation prior to surgery can be administered in those previously irradiated (evidence low, weak recommendation).

Re-staging should be performed 4–6 weeks prior to surgery (evidence low, strong recommendation).

Surgery should be planned for 6–8 weeks after completing neoadjuvant therapy (evidence moderate, strong recommendation).

IORT, when indicated, should be part of the multimodal treatment regimen (evidence moderate, strong recommendation).

To decrease postoperative pelvic wound complications closure/reconstruction should be pursued for large defects (evidence moderate, strong recommendation).

The best chance for cure is a R0 resection, which may require an extended radical (involvement of surrounding organs/structures) resection (evidence moderate, strong recommendation).

If morbidity outweighs the benefit of an extended resection to achieve a R0 margin a R1 resection with IORT should be pursued, which has better outcomes than R1 without IORT (evidence moderate, strong recommendation).

Surgery does not offer adequate survival or local tumor control following a R2 resection and should be avoided (evidence moderate, strong recommendation).

If the potential for cure is not possible palliation of symptoms should be sought with a combination of modalities to improve quality of life (evidence moderate, strong recommendation).

Patients with local recurrence of rectal cancer, or suspicion of, should be referred to dedicated centers for care (evidence low, strong recommendation).

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Part IV
Anal Dysplasia/Cancer

Chapter 23
Anal Dysplasia/Cancer: Management of Patients with AIN 3

Amy L. Lightner and Mark L. Welton

Pt population	Intervention	Comparator	Outcome studied
Pts with AIN 3	HRA	Clinical followup	Cancer prevention, cost

Introduction

Anal squamous cell carcinoma (ASCC) is an uncommon malignancy caused by infection with oncogenic strains of *Human papilloma virus* (HPV). The precursor lesion, anal intraepithelial neoplasia III(AIN III) or high-grade squamous intraepithelial lesion (HSIL), has a similar causal association with HPV [1–3]. Although HPV infections are extremely common, peaking in the third decade of life, they are usually transient with evidence of infection absent by the end of that decade. This tends not to be true in high-risk groups – those who practice anoreceptive intercourse and those immunocompromised from drugs or disease. The frequency of progression of HSIL to anal squamous cell cancer is uncertain, but has an estimated risk in the range of 8.5–13 % [2–4].

Despite the known association of HSIL and anal squamous cell carcinoma, many patients go undiagnosed, or potentially worse yet, diagnosed and not treated. Many factors contribute to the lack of treatment. Historically, poor adoption of preventative techniques resulted from a lack of standardized definitions and treatment patterns, leaving treating physicians confused regarding evidence-based practice. In addition, a lack of clear screening guidelines for low risk patients (eg heterosexual females who do not practice receptive anal intercourse) resulted in affected patients

A.L. Lightner
Mayo Clinic, Division of Colon and Rectal Surgery,
200 1st St SW, Rochester, MN 55901, USA

M.L. Welton (✉)
Department of Surgery, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA, USA
e-mail: MWelton@stanfordhealthcare.org

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being missed owing to the misconception that this was a disease limited to men who have sex with other men (MSM) and/or men and women who are HIV positive.

There has been relatively limited adoption of high-resolution anoscopy (HRA) likely owing to unfamiliarity with the equipment and poor physician reimbursement. Further, there continues to be a lively ongoing debate regarding the necessity and cost effectiveness of this treatment modality when compared to simple observation and clinical followup. The argument is that the relatively small subset of patients who do progress from HSIL to anal carcinoma can be identified early and treated successfully, without exposing the entire cohort to serial HRA. However, the 5-year survival for Stage I and Stage IV anal cell cancer remains at 80 % and 30 % respectively [5]. Thus, withholding treatment until a patient has developed anal squamous cell cancer, even in the setting of stage I disease,, may result in avoidable mortality from the disease not to mention the morbidity of chemoradiation therapy.

For the trained clinician, whether it is an advanced practice provider or physician, the screening tools (anal cytology and HRA) are relatively simple and cost effective [6]. However, no RCTs have shown that such screening programs are efficacious at reducing anal cancer incidence and mortality. Many believe that this is because the procurement techniques for anal cytology and the performance of HRA are highly variable and non-standardized. Fortunately, trials are currently underway in order to evaluate the efficacy of cancer prevention with screening and treatment. Further, national guidelines published by the National Comprehensive Cancer Network (NCCN) and American College of Colon and Rectal Surgeons (ASCRS) are now able to make recommendations based on higher quality of evidence [7, 8].

Search Strategy

An electronic search of the PubMed database was performed to obtain key literature in the field of anal cancer published between January 1 2000 and July 1 2015, using the following search terms: (anal cancer) OR (anal squamous cell carcinoma) OR (high-grade squamous intraepithelial lesion). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer reviewed biomedical literature, and is used by the NCCN when formulating updated guidelines. The search results were narrowed by selecting studies in humans published in English with full-length text. Results were then confined to the following article types: clinical trial, Phase II; Clinical trial, Phase III; Clinical Trial, Phase IV; practice guidelines, randomized controlled trial, meta analysis, systematic reviews, and validation studies. The PubMed search resulted in 17,299 citations and their potential relevance was examined. When ‘and treatment’ was added to the search terms, 15,227 items were resulted. These were sorted by relevance to improve detection of relevant studies.

The National Comprehensive Cancer Network (NCCN) and American College of Colon and Rectal Surgeons (ASCRS) were then searched for additional relevant studies for inclusion. This did not result in any further inclusion that was not found in the PubMed search.

Results

Prevention

Prior to discussing treatment of AIN, brief mention will be made of prevention. A quadrivalent HPV vaccine is currently available, and has been proven effective in preventing high-grade cervical intraepithelial neoplasia related to HPV strains 6, 11, 16 or 18 in women, and genital lesions associated with the same HPV strains in men [9–11]. Thus, a study was prompted to look at the efficacy of the vaccine for prevention of HSIL and ASCC in MSM [12]. Although none of the 602 healthy men aged 16 to 26 developed ASCC within the 3-year follow-up period, there were 5 cases of grade HSIL in the vaccine arm and 24 cases in the placebo arm. This amounted to an observed efficacy of 77.5 % for prevention of HSIL, suggesting the quadrivalent HPV vaccine may reduce the risk of ASCC in this patient population.

Recently, the quadrivalent HPV vaccine has been tested in HIV positive children, a group at high risk for HPV, and subsequent associated cervical and anal cancer. A randomized clinical trial found the vaccine to be safe and immunogenic in 126 HIV positive aged 7–12 years. Initially, antibody titers were lower for HPV 6 and 18 compared with historic age-matched immunocompetent controls [13], but this difference was lost after the fourth dose of vaccine [14]. The success of vaccines could lead to a significant decrease or near elimination of ASCC if used early and universally. Thus, their clinical importance cannot be underscored enough.

Patients with condyloma acuminatum or low-grade squamous intraepithelial lesion (LSIL) have very low potential for malignancy [15]. It is not clear that LSIL actually directly progresses to HSIL or ASCC. Rather, LSIL may be a marker in certain at risk groups for the presence of virus. Those patients that are symptomatic may wish to have the lesions excised or destroyed and this can be done with cautery, IRC or chemical agents. Follow up of these patients depends heavily on age, risk factors, underlying disease states and behavior patterns.

Treatment

The goal of treating HSIL is the prevention of ASCC while maintaining anal function, including continence of stool and gas. Several therapies are available for the treatment of HSIL including surgical excision, electrocautery, topical imiquimod, trichloracetic acid and topical fluorouracil (5-FU). Limited studies, largely in the form of case series, have addressed the relative efficacy of the potential treatment options.

In 2000, a survey of 663 members of the ASCRS found that 87 % of respondents chose surgical excision with clear margins as the optimal treatment for HSIL [16]. However, a number of subsequent studies have suggested that surgery may not be the best treatment approach. Brown reported 34 patients with HSIL treated

surgically in the UK. Within 41 months, 14 of 34 patients had macroscopic recurrences and 25% of patients had anal function deficits postoperatively [17]. Scholefield reported on 35 patients who underwent limited excision for HSIL and were followed for 63 months. Three of 35 (9%) had progression to ASCC [2]. Watson reported their experience with 72 patients treated surgically, of whom nine developed incontinence; four of these required a colostomy. Despite their aggressive surgical approach, 8 patients (11%) progressed to invasive ASCC [3]. These studies have suggested surgical excision is not an ideal treatment due to incomplete excisions, frequent recurrences, and complications including stenosis and incontinence. They argued further that because chemoradiation for small invasive anal carcinoma is effective, a less radical approach may be warranted, because early surgical intervention with the associated complications may compromise later definitive treatment.

Other investigators suggest that rather than using an excisional approach, the use of HRA allows targeted destruction of suspicious lesions with the lowest reported rates of progression to cancer and preservation of anorectal function. HRA is used to identify dysplastic epithelium under the magnification of a standard colposcope or operating microscope. The technical application of HRA itself is discussed in more detail in the section regarding our treatment approach; but, briefly, HRA can be used with either targeted infrared coagulation (IRC) or electrocautery (EC). Both procedures are outpatient with only enemas given in preparation. IRC can be used with facility for lesions above the dentate line although local anesthesia is often necessary because the heat generated by the instrument causes pain. It coagulates lesions using 1.6 s pulses until the entire surface and an approximately 3 mm surrounding border are coagulated. The coagulated tissue is then scraped off with a small cotton Q-tip or forceps. This is repeated until the submucosal vessels are identified and coagulated. HRA directed EC, unlike IRC, uses bipolar cautery creating a smoke plume that requires a smoke evacuator to prevent transmission of HPV. Across the four listed studies (Table 23.1) regarding HRA targeted IRC for HSIL, there was no reported anal function compromise, 10–38% had recurrence of HSIL, and none had progression to ASCC [18–21]. Similarly, in the two listed studies regarding HRA targeted EC, there was no reported anal function compromise, 17–31% had recurrence of HSIL, and 0.4% had progression to anal squamous cell carcinoma [22, 23]. Of note, recurrence of HSIL was higher in HIV patients and patients with higher burden of disease.

The use of topical medical treatments has recently become more widespread. Topical fluorouracil (5-FU) and imiquimod have the advantages of treating AIN by the patient themselves without compromising anorectal function. However, topical treatments have the disadvantage of extended treatment courses and significant side effects including perianal pain and irritation that may result in non-compliance. Treatment with 5-FU is not standardized. The amount and frequency are variable. Despite several treatment interruptions due to side effects and variable protocols administered, there has been very little progression to ASCC. Only one patient among the three studies listed in Table 23.1 had progression to ASCC [24].

Table 23.1 Treatment practices for HSIL

Study ID	Patients	Anal function compromised (%)	HSIL at last f/u (%)	Developed ASCC (%)	Grade of evidence (GRADE system)
Surgery					
Excision					
Watson et al. [3]	10/62 immunocompromised	13	Not reported	11	Moderate
Scholefield et al. [2]	6/35 immunocompromised	0	Not reported	9	Moderate
Devaraj and Cosman [4]	40 HIV + MSM	3	Not reported	8	Moderate
Brown et al. [17]	34 M and F	15	Not reported	0	Moderate
Marchesa et al. [36]	16 M, 31 F	0	38 %	6	Moderate
HRA-targeted IRC					
Goldstone et al. [19]	52 HIV-MSM/44 HIV + MSM	0	HIV + 18 %; HIV-10 %	0	High
Weis et al. [21]	99 M/25 F all HIV+	0	Treated 13 %; untreated 93 %	0	Moderate
Stier et al. [37]	16 M/2 F all HIV+	0	38 %	0	Moderate
Cranston et al. [18]	68 HIV + MSM	0	36 %	0	Moderate
HRA-targeted EC					
Marks and Goldstone [22]	132 HIV + MSM; 100 HIV-MSM	0	HIV + 31 % HIV-17 %	0.4	High
HRA-targeted EC f/u IRC or TCA					
Pineda et al. [33]	194/246 immunocompromised	0.8	22 %	1.2	High
Topical medical therapy					
5-FU					
Snyder et al. [29]	11 HIV + MSM	0	72 %	0	Moderate
Richel et al. [28]	46 HIV + MSM	0	30 %	0	Moderate
Graham et al. [24]	1/9 HIV+	0	13 %	13 (n = 1)	Low

(continued)

Table 23.1 (continued)

Study ID	Patients	Anal function compromised (%)	HSIL at last f/u (%)	Developed ASCC (%)	Grade of evidence (GRADE system)
Imiquimod					
Wieland et al. [30]	28 HIV + MSM	0	9 %	0	Moderate
Kreuter et al. [27]	10 HIV + MSM	0	Not reported	0	Low
Fox et al. [25]	64 HIV + MSM	0	39 %	3	High
Van der Snoek et al. [38]	44 HIV + MSM	Not reported	34 %	Not reported	Low
TCA					
Singh et al. [39]	54 MSM; 35 HIV+	0	39 %	0	Moderate
Cranston et al. [18]	72 HIV+ MSM	Not reported	20 %	Not reported	Moderate
RCT					
Richel O et al. [26]	246 HIV + MSM	0	At 72 weeks: 71 % imiquimod; 58 % 5-FU; 68 % EC	1.2 % (n = 3)	High

Similarly the use of topical imiquimod 5 % cream applied three times weekly has been associated with very little progression to ASCC, with only one series reporting 2 patients with progression (3 %) [25]. Importantly, with topical medical treatments, significant education of patients is required. Namely, patients should be told that symptoms of itching, burning, and pain are evidence that imiquimod is working and is not a sign that treatment should be discontinued. Additionally, imiquimod can actually cause transient flu like symptoms the day following treatment. If patients do not develop signs of erythema or erosions, the imiquimod frequency can be increased throughout the treatment course. Unfortunately, the adherence rate of topical imiquimod is low due to these side effects, and therefore make this treatment strategy less effective.

Recently, RCTs are beginning to compare the aforementioned treatment approaches. A recent RCT looking at 246 HIV-positive MSM found that electrocautery had significantly increased rates of complete resolution compared to both topical imiquimod and topical fluorouracil, and concluded that EC was the superior treatment option [26]. Recurrence rates of HSIL were high in all treatment groups underscoring the need for frequent surveillance and follow up. At week 24, 48 and 72, 22 %, 46 %, and 67 % of patients had recurrence respectively. Specifically, recurrence at 72 weeks was found in 71 % (n = 10/14) of patients treated with imiquimod,

58 % (n = 7/12) of patients treated with 5-FU, and 68 % (n = 13/19) of patients treated with EC. Treatment side-effects, most commonly pain, bleeding and itching were significantly more common in the imiquimod and 5-FU group at 43 % and 27 % respectively, as compared to 18 % in the electrocautery group.

Expectant Management

It has been suggested by many that expectant management may be an appropriate, cost effective approach for HSIL rather than treatment, as there are no associated treatment costs or side effects. A trial addressing this approach was conducted at a university and VA practice. Forty 40 HIV infected patients were followed for a mean of 32 months [4]. Patients had a clinical exam every 6 months, and biopsies of new macroscopic or symptomatic disease. Of the 40 patients, 23 had HSIL. Three of the 28 patients developed ASCC at 10, 16 and 84 months, all of whom had a cancer less than 2.5 cm in diameter. This trial suggested that very few patients progress to cancer, and, if so, were diagnosed at an early stage. To better understand this question, a large ongoing randomized phase III trial comparing topical or ablative treatment with active monitoring in HIV-positive patients with HSIL is currently ongoing. The primary measure is time to anal cancer. The study is estimated to be completed in 2022 (clinicaltrials.gov NCT02135419) and may provide additional answers regarding active monitoring versus treatment in a high-risk group with HSIL. No trials are currently underway for low risk patient cohort with HSIL, likely because there are so few patients, and even fewer who progress to ASCC.

Recommendations Based on the Data

Several limitations exist when interpreting the aforementioned data. Studies of HSIL screening and treatment practices are largely comprised of only immunosuppressed patients. And the single RCT to date includes only high risk HIV+ MSM, limiting the applicability of the results to other patient cohorts. Treatments reported for HSIL are not standardized, and reports of treatment outcome are mainly in the form of case series and open-label studies, with only the one aforementioned RCT.

Despite these limitations, there is strong evidence that HSIL, left untreated, can and does progress to ASCC [1]. Once diagnosed, these patients then require chemotherapy with radiation, and possible surgical intervention, all with associated morbidity. Several studies, albeit small in patient number, have demonstrated nearly zero progression to malignancy with both electrocautery and topical medical therapy [22, 27–30]. A RCT has suggested electrocautery is the superior ablative modality [26]. This suggests patients with HSIL should be actively treated with EC in order to prevent progression to ASCC.

Given that women have largely been left out of the discussion but develop anal cancer at a higher rate than men, consensus guidelines developed by an international panel of experts are available to guide the approach to a given patient based on their specific risk factors [31].

Personal View of the Data

There is no controversy that colonic polyps should be removed to prevent progression to colon and rectal cancer. However, there seems to be controversy regarding the definition, prognosis, method of diagnosis, surveillance, and treatment for AIN/HSIL. Part of the challenge lies in the fact that the disease prevalence is low, making RCTs difficult to perform based on a primary outcome measure of progression to cancer. Additionally, potential prevention practices with HRA have low reimbursement rates and serve as a barrier to implementation..

However, therapy with HRA targeted EC may be performed as an office based procedure without the need for anorectal preparation or narcotics upon dismissal if the lesions are above the dentate line or limited in extent. Alternatively, for extensive disease below the dentate line involving anal mucosa and or perianal skin, the patients may be treated on an outpatient basis and discharged with instructions for sitz baths, topical analgesics (5 % Lidocaine Cream – Recticare (Ferndale labs) preferred), and either Ultram, Tylenol with codeine, NSAIDS or Tylenol. HRA targeted destruction is technically straightforward and can be performed by colorectal surgeons, family practitioners, gynecologists and advanced practice providers, to name a few. The obstacles to performing HRA targeted destruction of lesions may be cost, reimbursement, clinical practice and the training required to visualize lesions via either a microscope, the colposcope or even surgical loupes. Training is readily available through the ASCCP (www.asccp.org) and may be efficiently built into one's office based practice.

As is well recognized by our readers, many patients referred for colorectal evaluation with a diverse array of symptoms and findings often come with a chief complaint of "hemorrhoids." We perform a history to document risk factors for anal dysplasia including HPV infection (anal-genital warts), history of receptive anal intercourse or sexually transmitted disease, a history of cervical vulvar or vaginal cancer, immunosuppression after solid organ transplant or HIV infection, hematologic malignancies, certain autoimmune disorders including Crohn's disease [32] and smoking. Physical exam includes perianal inspection, digital rectal exam, and anoscopy as indicated.

We prefer the operating room for the initial examination and treatment of patients with HSIL, and for needed re-treatment of extensive disease or disease complicated by synchronous anal pathology (eg overlying hermorrhoidal tissue or complicating fistulous disease). HRA in the operating room is preferred for our initial evaluation and treatment because we feel we get the best exposure with the sphincters completely relaxed with an anal block which allows for flattening of the hemorrhoidal

complexes and clear visualization of the tissues that might otherwise hide at the base of a large complex when visualized with a plastic anoscope in the office.

In the operating room, the patient is positioned prone jack knife with the buttocks taped apart. Anesthesia with MAC local with 0.25 % Marcaine in the subcutaneous tissues and 0.5 % Marcaine with 1:200,000 epinephrine in the sphincters for the anal block are administered. A thorough examination looking for hyperpigmentation, erythema, elevation, or scaling is performed. The distal rectal mucosa, anal mucosa, and perianal skin is then treated with 3 % acetic acid by placing one acetic acid soaked Ray-Tec in the anal canal and distal rectum, and one over the anus/perianal skin. We use an operating microscope for magnification. We look for a distinct vascular pattern within the acetowhitened rectal and anal mucosa or perianal skin that is characteristic of HSIL. Any concerning lesions are biopsied and then treated with needle tip cautery [23]. A deep burn is avoided by quickly moving superficially across the surface of the tissue, sparing the surrounding normal mucosa. Our experience is that we can limit the depth of injury to less than that observed with excision, which may contribute significantly to our low observed rate of complications [33]. This is safe and effective in both HIV (+) and HIV (−) men and women [34].

We inform patients with condyloma acuminatum (low-grade intraepithelial neoplasia LSIL, AIN-1) that they have a very low potential for malignancy [15]. We therefore offer treatment to symptomatic patients or those who simply want to have the lesions removed (the vast majority). In high risk groups, LSIL can be a marker for the presence of HSIL, especially in immunosuppressed populations; annual surveillance including digital anal rectal examination, anal cytology, and HRA for early detection of HSIL may be beneficial. Recently some have suggested that the rate of anal cancer is extremely low before age 30 so that close surveillance might begin after age 30 even in the high risk patients. How to follow "low-risk" patients with LSIL remains unclear. This is where routine typing of HPV may be beneficial in stratifying follow up. For patients who have been treated for HSIL, we perform a 1 and 6 month follow up examination with anoscopy.

If the patient is not involved in high risk behavior, we recommend annual surveillance, again with digital anal examination and anal cytology. If involved in high risk behavior, HRA is added to this algorithm on an annual basis. If immunosuppressed, or if the patient has "high risk disease", this interval may be shortened to 3–6 months on a case by case basis. If a recurrence is found, we treat them in the office with trichloracetic acid, IRC or hyfrecation unless the disease is complex as noted above. We, and others, have experienced excellent control of HSIL and minimal progression to cancer using this approach [19, 23, 33, 35]. We cannot comment on topical treatments as we have no personal experience with their use. However, we are referred patients who have been on them with recurrence. There may be benefit in combination with electrocautery to prevent recurrence, but this has yet to be studied.

Ultimately, the goals of treating patients with HSIL is preventing morbidity associated with the treatment of anal cancer without causing disturbances of anal function. We have low cost, outpatient tools to do this and evidence from RCT supporting

its use. We do not feel annual surveillance, in isolation, provides adequate care of our patients.

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Chapter 24
Management of the Abnormal Pap Smear in HIV Positive Patients

Brad Champagne and Andrew J. Russ

Introduction

Condylomaacuminata, anal intraepithelial neoplasia and anal cancer are diseases that commonly afflict men who have sex with men (MSM). The disease process may often be complicated by a coexisting infection with the Human Immunodeficiency Virus (HIV). Other than patients with HIV and MSM populations, transplant recipients on immunosuppression or other immunosuppressed states, and women with a history of genital cancers are at increased risk [1, 2] High risk populations have been encouraged to undergo screening with anal pap smear with increasing frequency and intensity over recent years. However, the appropriate follow-up, diagnostic work-up and treatment modality for patients with a positive smear remains nebulous.

Although anal squamous cell carcinoma (ASCC) represents only approximately 2 % of all GI cancers, its incidence has steadily risen over the past decade [1, 3, 4]. This increase is particularly remarkable in specific populations, such as individuals infected with HIV, and even more so among men who have sex with men (MSM), which makes this patient group a primary focus for screening [5]. It has long been recognized that, much like cervical cancer, there is a strong, causal relationship

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B. Champagne (✉)
Lerner College of Medicine, Cleveland Clinic, Cleveland, OH, USA

Cleveland Clinic, Fairview Hospital, Cleveland, OH, USA
e-mail: brad.champagne@uhhospitals.org

A.J. Russ, MD FACS FASCRS
University of Tennessee, Department of Surgery, Knoxville, TN 37920, USA

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between anal cancer and human papilloma virus (HPV) infection [6, 7]. Anal intraepithelial neoplasia (AIN), HPV-related dysplastic changes in the cells at the anal transition zone, is the presumed precursor lesion for ASCC [1, 8]. Anal intraepithelial neoplasia is classified into three grades, corresponding to low-grade (AIN I), moderate grade (AIN II), and high-grade dysplasia (AIN III). The terms low-grade (LGAIN) and high grade (HGAIN) have been used to refer to AIN I/II and AIN III, respectively [1]. The epithelium in both the cervix and anus may contain atypical squamous cells of undetermined significance, low grade squamous intraepithelial lesions, and high grade squamous intraepithelial lesions. It is fairly well established that high grade squamous intraepithelial lesions represent the precursor to cervical SCC [9]. Given the similarities between cervical and anal intraepithelial lesions and the association with anogenital HPV, this precursor pathway is similarly applied to concepts of progression to anal SCC [10]. Therefore, recognizing its effectiveness in relation to cervical cancer, anal Pap smear cytology has been adapted as one of the first steps in screening for AIN [2, 11]. There is little debate that the destruction of AIN is paramount in the prevention of progression to ASCC [1–3].

However, once AIN has been identified, there is considerable debate on the optimal protocol for management and surveillance of these lesions, specifically in high risk populations [12]. This controversy is largely centered on recommendations of routine high-resolution Anoscopy (HRA) in all patients with suspected AIN versus clinical follow-up with expectant management (EM). High resolution anoscopy (HRA) is similar to colposcopy, wherein the anal canal and transition zone are inspected under a high resolution microscope with the addition of acetic acid and/or Lugol's iodine solution to identify areas of dysplasia, which are then biopsied [13–17]. Expectant management includes regular office-based examination, operative fulguration of larger lesions, and treatment of dysplasia with imiquimod [18]. With this debate in mind, we set out to analyze the literature in an effort to answer the question regarding optimal follow up of HIV patients with an abnormal anal Pap smear.

Methods

Our search strategy involved a Pubmed search with the following keywords: High Resolution Anoscopy (HRA), Anal Intraepithelial Neoplasia (AIN), Papanicolaou (pap) smear, cost, and screening. We limited our search from the year 1995 to present. The evidence is analyzed, described, and placed in tabular form.

Patient population (P)	Intervention (I)	Comparator (C)	Outcome studied (O)
HIV pts with abnormal pap smear	High resolution anoscopy (HRA)	Clinical follow-up	Cancer prevention, cost

Results

Screening HIV-infected MSM with annual anal cytology has been shown to be cost-effective, with an incremental cost-effectiveness ratio compared to no screening of $16,600 per quality –adjusted life year (QALY) saved, which is similar to other accepted screening test such as colorectal cancer screening [10].

Currently, there are no randomized controlled trials comparing the efficacy of HRA versus clinical follow-up with regards to ASCC prevention. We are thus left with observational studies and retrospective reviews. A meta-analysis of published studies suggests that the pooled prevalence of histological high grade AIN in MSM with HIV was 29.1 % [7], with incidences of 8.5 % and 15.4 % per year respectively in two estimates [19, 20]. The pooled anal cancer incidence was 45.9 per 100,000 men [7]. This number is corroborated by a pilot study which found that high grade AIN (AIN II and III) was found on histological analysis after HRA in approximately 32 % of asymptomatic MSM living with HIV. In this population of 368 asymptomatic MSM, 1.4 % developed invasive anal cancer at a median follow up of 4.2 years after HRA. All patients had high grade AIN at initial HRA screening. Additionally, during this study, the cumulative risk of anal cancer following HSIL diagnosis was 0.6 % at 5 years [14]. It is clear from this and other studies that AIN II-III represents a significant risk factor for development of ASCC.

However, does the incidence of ASCC support the widespread usage of HRA, and does the cost outweigh the benefit? A recent large retrospective review addresses the utility of routinely performing HRA. Crawshaw et al performed a single institution retrospective analysis of 424 patients from 2007 to 2013 comparing HRA to clinical follow-up. Surgeons in the group differed in their views on this controversy and their use of HRA, creating a natural experiment of sorts. 220 patients underwent HRA after abnormal pap smear, and 204 patients underwent clinical follow-up. The authors found no significant difference in progression to ASCC among the two groups [12]. It is important to note, however, that the surgeons in the clinical follow-up group performed mapping biopsies, ablated all visible lesions, and readily used imiquimod. Therefore, the only real difference between the groups was the use of HRA. HRA was not associated with prevention of ASCC when compared to the non HRA arm.

A recent Markov model analysis suggests that surveillance strategies after treatment for HGAIN that included HRA at 6 and 12 month intervals, with or without anal cytology testing, were more effective than using HRA only for confirmatory testing of abnormal anal cytology testing. However, a combined strategy of HRA and anal cytology extended life expectancy and quality-adjusted life expectancy (QALE) while remaining below the commonly-cited threshold of 100,000/QALY gained [21]. Similarly, Lam et al built a decision analytic model, and found that of 18 screening strategies, the direct use of HRA was the most cost-effective approach for the detection of high grade AIN [22]. However, neither of these analyses compare HRA to that of clinical follow-up.

Proponents of clinical management without HRA cite the increased morbidity as well as the additional cost incurred with repeated procedures often seen with HRA, as well as the low rate of disease progression to ASCC in compliant patients [1]. However, whilst HRA has been shown to be more effective in the detection of AIN than standard anoscopy with biopsies, this has failed to translate into lower rates of disease progression to ASCC [14, 16, 17]. The purpose of cancer screening is to reduce cancer-related mortality; there is a paucity of high quality evidence to make clear recommendations regarding the true benefit of HRA.

Recommendations Based on the Data

MSM with HIV are consistently more affected by HPV and HPV related abnormalities than are HIV-negative MSM. Furthermore, longitudinal data suggests a very high annual incidence of high grade AIN in HIV-positive men. Therefore, we strongly recommend based on high and moderate quality evidence that HIV positive MSM undergo screening with anal pap. In regards to treatment, the absence of data from randomized and longitudinal trials showing that treatment of high-grade AIN reduces the incidence of anal cancer and the morbidity associated with treatment needs to be considered. Therefore, the recommendation that approaches to cervical cancer prevention and treatment can be extrapolated to anal cancer are weak and based on very low quality evidence.

High-resolution anoscopy is costly, time consuming and technically demanding when compared to colposcopy for cervical cancer or to clinical follow-up with mapping biopsies in patients with a positive pap. The recommendation that HRA is superior to clinical follow-up or expectant management is weak with very low quality evidence. In addition, the low progression rates of high grade AIN to anal cancer also question the real value of repeated surgical treatments in this patient population. Therefore, the recommendation that aggressive and repeated treatments are warranted in patients with AIN to prevent anal cancer is weak and based on very low quality evidence. Lastly, the argument that the cost of HRA is nominal when compared to the cost savings achieved with cancer progression is not substantiated by high quality data. Therefore, the recommendation that HRA is cost-effective when applied to HIV positive MSM is weak with low quality data.

A Personal View of the Data

There is little debate that the destruction of AIN is paramount in the prevention of progression to ASCC. Thus, identification of, and surveillance for the presence of AIN is a key step in any screening protocol. While HRA has been shown to be more effective in the detection of AIN than standard anoscopy with biopsies, there has not been definitive proof that its utilization results in lower progression to ASCC than

more traditional expectant management. Recent studies at our institution, as outlined above, showed that there was no progression to ASCC in patients regardless of their treatment protocol (HRA vs EM), if they were compliant with therapy.

The majority of our patients now follow the expectant management (EM) algorithm.

All patients are initially evaluated in the office with DRE and anoscopy. If they had a positive anal pap smear or visible condyloma they are brought to the operating room for evaluation. During surgery, all visible abnormal areas are both biopsied and ablated. Furthermore, representative biopsies are performed from every quadrant in the anal canal and the anal margin in areas with no identifiable lesions. Postoperatively, patients with anal intraepithelial neoplasia are treated with imiquimod and followed. Recurrent lesions amendable to office-based therapy with acetic acid and or podophyllin are not brought back to the operating room for ablation unless the disease persists for 3 months after treatment.

. Overall, in our recently published data, we found that patients with anal intraepithelial neoplasia rarely progress to squamous cell cancer after ablation when followed with expectant management or high-resolution anoscopy. Our results support the concept that physicians treating these diseases should utilize the technique that they are most comfortable with. The cost, morbidity and value of high-resolution anoscopy should be further critically evaluated before it is regarded as the gold standard in anal cancer screening.

Specific Recommendations

1. HIV positive men who have sex with men (MSM) should undergo routine screening with anal pap (Grade: High. Recommendation: Strong)
2. Approaches to cervical cancer prevention and treatment can be extrapolated to anal cancer. (Grade: Low. Recommendation Weak)
3. HRA is superior to clinical follow-up or expectant management for AIN. (Grade: Low. Recommendation: Weak)
4. Aggressive and repeated treatments with HRA are warranted in patients with AIN to prevent anal cancer. (Grade: Low. Recommendation: Weak.)
5. HRA is a cost-effective strategy to prevent anal cancer in HIV positive MSM. (Grade: Low. Recommendation: Weak).

Questions Utility/sens/spec of abnormal pap smears, cost of HRA, sens/spec of HRA, increased incidence with HIV positivity, cost of pap smears

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Part V
Benign Colon Disease

Chapter 25
Indications for Surgery in Patients with Severe Clostridium Difficile Colitis

Vikram Reddy and Walter Longo

Introduction

Clostridium difficile colitis (CDC) is the leading cause of nosocomial diarrhea in the United States, with a broad spectrum of symptoms ranging from mild diarrhea to fulminant colitis which can lead to multisystem organ failure and death. For the majority of cases, surgical therapy is unnecessary as CDC responds to antibiotic therapy. Medically refractory colitis carries a high morbidity and mortality, and often necessitates surgical intervention which may also be associated with poor outcomes. The timing of surgery in the setting of CDC is critical; surgical intervention early in the course of disease may lead to an unnecessary colectomy with ileostomy when medical therapy may have been sufficient, but delaying surgical therapy in fulminant colitis commonly leads to a fatal outcome.

Recommendations for intervention requires is based on the severity of disease. Mild disease is characterized by diarrhea without any systemic symptoms. Endoscopic findings in mild disease show non-specific diffuse or patchy erythematous colitis, and pseudomembranes are usually not found. Imaging shows no evidence of colitis. Moderate disease is associated with more severe diarrhea, and mild systemic signs such as fever, leukocytosis, nausea and general malaise. Pseudomembranes, though not specific for CDC, are likely to be noted on endoscopy. Severe disease is progressively worsening CDC with hypoalbuminema (<3 g/dL) in the setting of worsening leukocytosis (>15,000 cells/mm^3) or abdominal tenderness. Fulminant colitis is a rare but life-threatening progression of severe CDC characterized by segmental or total colonic distention with signs of systemic toxicity (fever,

V. Reddy, MD, PhD • W. Longo, MD, MBA (✉)
Department of Surgery, Yale University School of Medicine, New Haven, CT 06510, USA
e-mail: walter.longo@yale.edu

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leukocytosis, distention, tenderness, hemodynamic instability, and organ dysfunction) and clinical deterioration with peritonitis and sepsis. Unfortunately, a clear algorithmic approach to surgical management is difficult as the ability to categorize the severity of the disease is challenging. Most of the studies addressing indications for surgery are limited by small sample sizes, retrospective analysis, and inconsistent criteria in distinguishing severe from fulminant colitis.

Non-surgical options include treatment with antibiotics, fecal microbiota transplant (FMT) and intravenous immunoglobulin (IVIG) transfers. Antibiotic therapy includes single agent therapy with oral metronidazole or vancomycin for mild to moderate disease, and dual coverage with metronidazole and vancomycin for severe disease. Nitazoxanide and fidaxomicin have also been used, but their utility in severe CDC needs to be more fully addressed. FMT is the transfer of stool from a heathy donor to a patient with CDC to remedy the decreased colonic diversity that is thought to drive CDC [1]. Instillation can be done by colonoscopy, upper endoscopy, per nasogastric tube, or by retention enemas. Lower GI tract instillations are associated with better outcomes.

Surgical options for the management of fulminant colitis include segmental colectomy, total or subtotal abdominal colectomy (TAC) with a stoma, or a diverting stoma with lavage of the distal bowel [2]. Of these, TAC with end ileostomy is the gold standard [3] which eliminates the diseased colon while avoiding the added morbidity of a pelvic dissection. Diverting stoma and lavage of the distal bowel markedly decreases the magnitude of the surgical procedure and diminishes the likelihood of a permanent ileostomy.

Search Strategy

The MEDLINE database was searched using the following MeSH headings: “Clostridium difficile”, “surgery”, and “outcome.” The time interval of the retreived articles was limited to 2005–2015. Non-english language publications were excluded. Information obtained was graded according to published GRADE guidelines. In general, the strength of the evidence is moderate to low, as it has been difficult to initiate large randomized controlled trials to evaluate the role of surgery in severe Clostridium difficile colitis. Meta-analyses, case reports, and reviews not containing original data were also excluded (Table 25.1).

Table 25.1 PICO table

P (patient population)	I (intervention)	C (comparator)	O (key outcomes)
Patients with severe Clostridium difficile colitis	Surgery	No surgery	Morbidity, mortality, quality of life

Results

The overall quality of the evidence is very low. Of the articles which met the search criteria, there were no randomized controlled trials, and only one was a prospective study (Table 25.2). Note that the data in the table shows some studies which included all patients with CDC while others show patients who underwent an intervention for CDC.

The mortality for surgical intervention was 19–67 % in the included studies (Table 25.2). Koss et al. showed that 80 % of those undergoing a segmental colectomy died, while mortality was significantly lower in those undergoing total abdominal colectomy; 6 of the 9 patients who underwent a TAC eventually had re-establishment of continuity [4]. Kenneally et al. studied CDC patients in the intensive care setting (ICU) [5]. The overall 30-day mortality was 36.7 % and the surgical mortality was 33.3 %. This study is limited by the selection of the population: patients in the ICU setting who were more likely to have other co-morbidities and likely at a greater risk of hospital mortality. Lamontagne et al. studied CDC in the ICU setting and noted that patients undergoing surgery had fewer co-morbidities, higher leukocytosis and increased probability of sepsis, but lower mortality [6]. Ali et al. studied factors associated with survival after colectomy and noted higher mortality with delaying surgical intervention, worsening leukocytosis, multisystem organ failure and the preoperative use of pressors [7].

Byrn et al. showed increased mortality with mental status changes, vasopressor requirement and delayed surgical therapy [8]. Hall et al. reported a lower mortality after colectomy in the absence of preoperative vasopressor requirement and ventilator support [9]. Hermensen et al. reported that in patients considered candidates for surgery, mortality was 46 %, while all patients who declined surgery died [10]. Pepin et al. showed that mortality after surgery increased with age, preoperative lactic acidosis, leukocytosis and hypoalbuminemia [12]. Sailhamer et al. studied patients with fulminant CDC and noted a decreased mortality with surgical intervention [13]. Age greater that 70 years, severe leukocytosis, leukopenia or bandemia, and cardiopulmonary failure were associated increased mortality (57 % when all three were noted, but 0 % in the absence of all three factors). Care on the surgical service was associated with higher operative intervention and better survival. Seder et al. also noted increasing age, acute respiratory failure and acute renal failure to be associated with increased mortality [14]. Dudukgian et al. noted that among the patients with CDC who died, 12.2 % underwent surgery while 87.8 % did not. Non-survivors who were medically managed had a longer pre-CDC hospital stay and more co-morbidities. Halabi et al. reviewed the Nationwide Inpatient Sample and noted an inpatient mortality of 30.7 % in patients undergoing colectomy [20]. Delaying surgery was associated with worse outcomes.

In assessing overall mortality, there are few studies comparing surgical to medical therapy for severe disease [22]. Two studies show a decrease in mortality with surgical intervention in the setting of severe CDC [6, 13]. Lamontage et al. identified patients in the ICU with CDC and noted a significant decrease in mortality with surgical inter-

Table 25.2 Summary of studies

Year	Study	Design (quality)	Study size (N)	Surgery (N)			Mortality (%)		
				Total	TAC	Other	Overall	Surgical	Medical
2006	Koss et al. [4]	Retrospective (very low)	3472	14	9	5	–	36	–
2007	Kenneally et al. [5]	Retrospective (very low)	278	6	–	–	37	33	37
2007	Lamontagne et al. [6]	Retrospective (very low)	165	38	35	–	53	34	58
2008	Ali et al. [7]	Retrospective (very low)	36	36	28	8	–	47	–
2008	Byrn et al. [8]	Retrospective (very low)	5718	73	63	10	–	34	–
2008	Hall and Berger [9]	Retrospective (very low)	3237	36	34	2	–	36	–
2008	Hermsen et al. [10]	Retrospective (very low)	7588	13	13	–	–	46	–
2009	Chan et al. [11]	Retrospective (very low)	15	15	12	3	–	67	–
2009	Pepin et al. [12]	Retrospective (low)	130	130	124	6	–	37	–
2009	Sailhamer et al. [13]	Retrospective (low)	4796	75	69	6	35	24	45
2009	Seder et al. [14]	Retrospective (very low)	6841	69	68	1	–	42	–
2010	Al-Abed et al. [15]	Retrospective (very low)	528	20	17	3	–	40	–
2010	Dudukgian et al. [16]	Retrospective (very low)	398	14	11	3	–	36	–
2010	Gash et al. [17]	Retrospective (very low)	1398	17	16	1	–	53	–
2010	Perera et al. [18]	Retrospective (very low)	35	35	32	3	–	46	–
2011	Markelov et al. [19]	Retrospective (very low)	13	13	12	1	–	46	–
2011	Neal et al. [2]	Prospective (low)	42	42	–	42	–	19	–
2013	Halabi et al. [20]	Retrospective (low)	2,773,521	19,374	3900	–	–	31	–
2015	van der Wilden et al. [21]	Retrospective (very low)	100	100	100	–	–	25	–

vention [6]. Sailhamer et al. reviewed all patients with severe CDC at their institution, and noted a trend towards decreased mortality with surgery [13]. Care on the surgical service was associated with a significantly lower mortality rate (12.8 % vs 39.3 %).

When comparing TAC with a segmental resection, several studies show the inferiority of segmental resection, need for additional intervention and ultimately, the increased mortality [4, 8, 9, 12, 14–16, 18, 19]. Interestingly, segmental colectomy as the first intervention was associated with a slightly lower mortality as noted on two meta-analyses [3, 23]. However, when corrected for re-intervention and an eventual completion colectomy in patients undergoing a segmental resection, the relative risk of a TAC trended lower [23]. Of the patients who undergo a segmental colectomy, 15.9 % need an eventual re-operation to decrease the disease burden [3].

A less aggressive alternative to a subtotal colectomy was studied prospectively, and involved the creation of a loop ileostomy, washout of the colon with warm polyethylene glycol 3550, and postoperative antegrade colonic vancomycin flushes [2]. When compared to historical controls, a lower mortality (19 vs 50 %) was noted and preservation of the colon was achieved in 93 % of subjects. However, selection and management bias cannot be ruled out as this was a small study cohort with no randomization and retrospective comparison to historical controls.

Several studies show that delaying surgical intervention is associated with worse outcomes. Respiratory failure [4, 8, 9, 13, 14, 20], renal failure [4, 9, 14, 20], and vasopressor requirement due to hemodynamic instability [4, 7–10, 12–14, 18–20] were associated with increased mortality. Ali et al. showed that survivors had surgery at a mean of 3.2 days vs. 5.4 days [7]. Sailhamer et al. similarly showed that the mean time to surgery was lower for survivors at 1.9 days vs. 3.9 days [13]. Halabi et al. reviewed a large administrative database and noted that surgical intervention more than 3 days after admission for CDC was associated with poorer prognosis [20].

Antibiotic treatment of patients after TAC for CDC was addressed by van der Wilden et al. who noted that intravenous metronidazole or enteral vancomycin for no more than 7 days was sufficient [21]. Mortality did not improve with antibiotic usage more than 7 days. Studies on the long-term follow-up of patients after colectomy for CDC are limited. Though Koss et al. [4] showed a 67 % re-establishment of continuity in survivors after colectomy, Miller et al. noted that the 5-year survival rate after colectomy was 38 % and intestinal continuity was re-established in only 20 % of the patients [24].

Recommendations Based on the Data

Mortality rates attributable to CDC remain high and even with surgery are as high as 19–67 %. The judgement for surgical intervention is empirical, and no clear evidence exists due to the lack of prospective, randomized controlled studies. Compounding the decision to intervene surgically is the lack of data on the timing of the intervention. Overall, the quality of the data is low, but most patients and all clinicians would place a high value on the reduction in mortality; despite the adverse

effects of surgery (for example on quality of life), surgical intervention in complicated severe CDC warrants a strong recommendation.

Patients with complicated severe CDC benefit from early surgical intervention, as delaying definitive surgery will increase the morbidity and mortality. Intervention should be considered prior to the onset of cardiopulmonary collapse (need for ventilator assistance or the use vasopressors) and renal failure. Transfer to or admission to the surgical service may be prudent for closer monitoring and quicker intervention. Intervention within 3 days of medically refractory severe disease may be warranted to improve outcomes.

Of all the surgical options, TAC with ileostomy has the best outcome. Long-term prognosis of the patients who undergo colectomy for CDC is limited. A retrospective study of 61 patients from a single institution estimated a mean survival of 18.1 months [25]. The cause of death could not be distinguished between CDC, colectomy for CDC, or comorbid diseases.

A diverting loop ileostomy with colonic lavage is a more palatable approach and may enable both the medical and surgical teams to intervene more quickly as there is less fear of a permanent ileostomy and a major abdominal operation. However, the evidence supporting this approach is limited, and extreme caution is warranted when proceeding with diversion and lavage alone.

Personal View of the Data

Our approach to a patient with severe CDC has always been to assess the risk vs. benefit of the surgery, be aggressive about the approach, and if uncertain, proceed with surgical resection. Patients with severe CDC are transferred to our service in the ICU. Close hemodynamic monitoring, serial abdominal exams, laboratory evaluations and computed tomography (CT) imaging are obtained. Immunosuppressed patients or those in whom a reliable abdominal exam cannot be obtained are more likely to undergo TAC with ileostomy. Early signs of hemodynamic compromise such as fluid responsive hypotension, decreasing urine output, labored breathing or subtle mental status changes warrant surgery. Worsening leukocytosis, hypoalbuminemia, or lactic acidosis also decrease the threshold for surgery. Patients with severe comorbidities who may not survive a TAC with ileostomy are considered candidates for a diverting loop ileostomy and colonic lavage. Survivors after TAC will more than likely need disposition to long-term care facilities, and prolonged recuperation prior to consideration of ileosigmoid or ileorectal anastomoses.

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Chapter 26
Do We Need to Operate on Patients After Successful Percutaneous Drainage of a Diverticular Abscess?

Wolfgang B. Gaertner and Robert D. Madoff

Introduction

Sigmoid diverticular disease is a significant health problem, resulting in annual estimated costs of over 2.6 billion dollars and 312,000 hospital admissions in the USA [1, 2]. Most cases of diverticular abscess are managed non-operatively with intravenous antibiotics, and the addition of percutaneous drainage (PD) in selective cases [3–5].

The natural history of diverticular disease after PD of a diverticular abscess is not well defined. Clinical practice guidelines from the American Society of Colon and Rectal surgeons have evolved over the past 10 years from recommending elective colectomy after one episode of diverticular abscess treated non-operatively to an individualized approach for elective colectomy based on the severity of the disease and not on the number of recurrent episodes or attacks [6, 7].

Search Strategy

A comprehensive literature search of PubMed, MEDLINE, EMBASE, and the Cochrane Database of Collected Reviews was performed to identify all English language publications related to non-operative management and outcomes of diverticular abscesses from 1986 to 2015. Key search terms included the following: "management," "colon," "sigmoid," "diverticulitis," "abscess," "percutaneous drainage," "surgery," "colectomy," and "resection". Studies that focused on the

W.B. Gaertner • R.D. Madoff (✉)
Division of Colon & Rectal Surgery, Department of Surgery, University of Minnesota, 420 Delaware St SE, MMC 450, Minneapolis, MN 55455, USA
e-mail: madoff@umn.edu

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Table 26.1 PICO table

P (patients)	I (intervention)	C (comparator)	O (outcomes)
Patients status post percutaneous drainage of diverticular abscess	Colectomy	Expectant management	Recurrent diverticulitis

management of Hinchey 3/4 diverticulitis, surgical management of diverticular disease, antibiotic treatment alone for diverticular abscess, laparoscopic peritoneal lavage, case reports, letters, review articles, non-sigmoid diverticulitis, and duplicate articles were excluded. The reference lists from the included articles were manually reviewed, and additional studies were included when appropriate.

Patients undergoing elective colectomy after successful PD were compared with those followed by observation. The primary outcome reviewed for each study was the rate of recurrent diverticulitis after PD (Table 26.1). Secondary outcomes and parameters recorded included failure of PD, elective colectomy after successful PD, and postoperative morbidity after elective colectomy.

Results

The initial literature search retrieved 362 studies. After applying the exclusion criteria, 21 studies were included in the final review. There are no randomized clinical trials comparing outcomes of different management strategies for diverticular abscess. The majority of studies are retrospective series from single institutions reporting on different treatment strategies for diverticular abscess with short follow-up intervals (Table 26.2). The outcomes from these studies are heavily influenced by institutional policy and surgeon preference, and biased towards performing colectomy even after successful PD. Furthermore, patients who did not undergo colectomy after PD commonly followed a non-operative pathway because they were unfit for surgery, refused colectomy or lost to follow-up.

Failure of PD requiring urgent fecal diversion with or without colectomy was reported in 20 studies and was required in 9.4 (0–33) percent of cases with various definitions of failure (Table 26.3). Operative indications for failed PD largely depended on clinical parameters of infection and peritonitis, as well as surgeon preference. Elective colectomy after successful PD was performed in 64.3 (33–100) percent of cases with no clear operative criteria. Gaertner et al [23] reported the largest experience with interval colectomy (137 of 191 patients [72 %]) after successful PD but did not specify operative indications or the morbidity of interval colectomy after successful PD. The overall postoperative morbidity rate of elective colectomy after successful PD was 7 (0–28.6) percent in 7 of 21 studies. Severity of postoperative morbidity after interval colectomy and its association with operative approach (laparoscopic *vs.* open) was not described in detail in the reviewed studies.

Table 26.2 Descriptive data of the analyzed studies

Author (year)	Study type	Level of evidence	Patients managed with percutaneous drainage (%)	Average size of drained abscess (cm)	Immunosuppressed patients managed with percutaneous drainage alone (%)	Average follow-up (m)
Saini et al. (1986) [8]	PSI	4	8 (73)	NS	NS	NS
Mueller et al. (1987) [9]	PSI	4	21 (100)	NS	NS	10
Neff et al. (1987) [10]	PSI	4	16 (100)	NS	NS	12–29
Stabile et al. (1990) [11]	PNR	4	19 (100)	8.7	NS	17.4
Hachigian et al. (1992) [12]	PSI	4	4 (31)	NS	NS	NS
Ambrosetti et al. (1992) [13]	PSI	3b	1 (4.5)	NS	NS	24
Bahadursingh et al. (2003) [14]	R	4	6 (24)	NS	NS	NS
Macias et al. (2004) [15]	R	4	10 (36)	5.8	NS	NS
Ambrosetti et al. (2005) [16]	PSI	3b	19 (26)	6.7	NS	43[a]
Kaiser et al. (2005) [17]	R	4	16 (16)	7.1	NS	46.5
Siewert et al. (2006) [18]	R	4	4 (13)	5.9	NS	13.1[a]
Durmishi et al. (2006) [19]	R	4	34 (100)	6.0	NS	NS
Brandt et al. (2006) [5]	CC	3b	34 (52)	6.0	NS	NS
Singh et al. (2008) [20]	R	4	16 (100)	8.5	3 (19)	34.8
Dharmarajan (2011) [21]	R	4	38 (39)	>4.0	NS	19.7
Van de Wall (2013) [22]	R	4	54 (8.1)	>5.0	NS	27.5[a]
Gaertner et al. (2013) [23]	R	4	191 (100)	4.7	7 (21.8)	88.8
Felder et al. (2013) [24]	R	4	40 (100)	5.6 ± 2.0	5 (13)	46.8[a]
Subhas et al. (2014) [25]	R	4	42 (35.8)	6.3	NS	NS
Elagili et al. (2015) [26]	R	4	133 (100)	5.0	1/18 (5.5)	90[a]
Knapp et al. (2015)[b] [27]	R	4	29 (100)	NS	NS	NS

R retrospective series, *CC* case control study, *PSI* prospective single institution series, *PNR* prospective nonrandomized series, *NA* not applicable, *NS* not specified

[a]Median

[b]Meeting abstract

Table 26.3 Outcomes after percutaneous drainage of diverticular abscess

Author (year)	Colectomy or fecal diversion for failed percutaneous drainage (%)	Elective colectomy after successful percutaneous drainage (%)	Postoperative morbidity for elective colectomy after successful percutaneous drainage (%)	Overall symptomatic recurrence after percutaneous drainage alone (%)
Saini et al. (1986) [8]	0 (0)	7 (87.5)	0 (0)	NA
Mueller et al. (1987) [9]	0 (0)	17 (80.9)	NS	2/3 (66.6)
Neff et al. (1987) [10]	1 (6.2)	11 (68.7)	0 (0)	1/4 (25)
Stabile et al. (1990) [11]	3 (15.7)	14 (73.6)	0 (0)	3/3 (100)
Hachigian et al. (1992) [12]	0 (0)	4 (100)	NS	NA
Ambrosetti et al. (1992) [13]	0 (0)	1 (100)	NS	NA
Bahadursingh et al. (2003) [14]	0 (0)	NS	NS	NS
Macias et al. (2004) [15]	0 (0)	NS	NS	3/10 (30)
Ambrosetti et al. (2005) [16]	NS	NS	NS	NS
Kaiser et al. (2005) [17]	1 (6.2)	3 (18.7)	NS	5/16 (41.7)
Siewert et al. (2006) [18]	0 (0)	4 (100)	NS	1/4 (25)
Durmishi et al. (2006) [19]	10 (29.4)	12 (52.1)	0 (0)	2/11 (18.1)
Brandt et al. (2006) [5]	10 (29.4)	12 (52.1)	0 (0)	2/11 (18.1)
Singh et al. (2008) [20]	0 (0)	8 (50)	NS	2/8 (25)
Dharmarajan (2011) [21]	NS	NS	16 (21)	NS
Van de Wall (2013) [22]	0 (0)	22 (40.7)	NS	18/54 (33.4)
Gaertner et al. (2013) [23]	22 (11.5)	137 (71.7)	NS	10/32 (31.2)
Felder et al. (2013) [24]	13 (33)	20 (50)	NS	0/7 (0)
Subhas et al. (2014) [25]	13 (30.9)	14 (33.3)	NS	NS
Elagili et al. (2015) [26]	22 (16.5)	NS	NS	7/15 (46.6)
Knapp et al. (2015)** [27]	0 (0)	14 (49.7)	4 (28.6)	NS

NA not applicable, *NS* not specified

The definition of recurrent diverticulitis after successful PD varied amongst studies and included clinical recurrence of abdominal and infectious symptoms as well as computed tomography-proven diverticulitis or abscess. Persistent colo-cutaneous fistula as a result of PD was not specifically described as persistent or recurrent disease in any of the studies. Overall, recurrent diverticulitis after successful PD was reported in 13 of 21 studies and occurred in 35.4 % (0–100 %) of cases. Average follow-up of patients after PD was 41.0 (13.1–90) months. Van de Wall and colleagues [22] demonstrated that colectomy for recurrent diverticulitis after successful PD was most commonly performed in the first year after initial abscess presentation.

The presence of severe medical comorbidities and immunosuppression was inconsistently reported in patients who underwent PD alone. Four studies reported the number of immunosuppressed patients with an average rate of 14.8 %. Factors associated with recurrent diverticulitis and the need for colectomy included abscess size >5 cm [23], pelvic abscess [16], and >2 PD procedures [25]. Felder et al [24] identified immunosuppression and renal insufficiency as independent risk factors for failure of PD and need for emergent colectomy. No significant associations between failure of PD or recurrent diverticulitis and previous episodes of diverticulitis and patient age were identified [17, 23, 26].

Recommendations Based on the Data

Percutaneous drainage allows for the resolution of intra-abdominal sepsis for most cases of diverticular abscess, and has been associated with an increased rate of single-stage colectomy with primary colorectal anastomosis, as well as decreased perioperative morbidity and mortality when compared to urgent Hartmann's procedure [17, 28]. The majority of cases of successful PD for diverticular abscess reported in the literature underwent interval colectomy regardless of symptoms, with no clear operative criteria. Patients treated with PD alone are typically managed this way because of prohibitive operative risk, severe co-morbidities, or refusal of colectomy. Based on the current literature, patients with diverticular abscess who undergo successful PD alone have a 35 % rate of recurrent diverticulitis, while those who undergo interval colectomy have a 7 % postoperative morbidity rate and negligible recurrent diverticulitis.

- Elective colectomy should typically be considered in patients with appropriate operative risk, after an acute episode of diverticular abscess has resolved with PD. Grade of Recommendation: weak recommendation based on low-quality evidence, 2C.
- Percutaneous drainage of colonic diverticular abscess without subsequent colectomy appears to be a safe, low-risk, and reasonable management option in selective patients with prohibitive operative risk or in healthy patients who prefer to avoid surgery. Grade of Recommendation: weak recommendation based on low-quality evidence, 2C.

A Personal View of the Data

The need for colectomy after successful PD of a diverticular abscess has not been well studied. The majority of studies describing the use of PD of diverticular abscess did so to demonstrate its feasibility and safety with imaging guidance, as well as a temporizing measure to decrease the perioperative morbidity of interval colectomy. Many agree with the decision to not operate on patients with prohibitive operative risk after successful PD, but what about the otherwise healthy individual? The current literature would favor interval colectomy with low (7 %) morbidity as compared to the risk of recurrent diverticulitis (35 %). Although limited, the current literature would also support that recurrent diverticulitis after successful PD does not typically require an emergency operation nor is it associated with an increased risk of stoma with operative treatment. Recurrent or persistent disease after PD alone typically presents with abdominal symptoms, CT-evidence of diverticulitis without abscess or perforation, or a persistent colo-cutaneous fistula. Could patients be followed closely for recurrent symptoms and managed accordingly without the pre-emptive decision of performing interval colectomy? We believe that, ultimately, the decision of whether to undergo colectomy after successful PD also depends upon other factors including the number of episodes before abscess occurrence, disease-free intervals, ready access to health care, and patient preference.

Our current practice is to recommend interval elective colectomy after successful PD of a diverticular abscess in those patients with persistent abdominal symptoms or complications such as fistula, those with a pattern of recurrent symptomatic diverticulitis, and immunosuppressed patients who do not have prohibitive operative risk.

1. Elective colectomy should typically be considered in patients with appropriate operative risk, after an acute episode of diverticular abscess has resolved with PD. Grade of Recommendation: weak recommendation based on low-quality evidence, 2C.
2. Percutaneous drainage of colonic diverticular abscess without subsequent colectomy appears to be a safe, low-risk, and reasonable management option in selective patients with prohibitive operative risk or in healthy patients who prefer to avoid surgery. Grade of Recommendation: weak recommendation based on low-quality evidence, 2C.

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Chapter 27
The Role of Laparoscopic Peritoneal Lavage in the Operative Management of Hinchey III Diverticulitis

Lisa Marie Cannon

Introduction

The 2014 American Society of Colon and Rectal Surgeons practice parameters for the treatment of sigmoid diverticulitis recommend urgent sigmoid colectomy for patients presenting with diffuse peritonitis or for those in whose initial nonoperative management fails [1]. While open Hartmann's procedure has been long considered the 'gold standard' in these situations, primary anastomosis with proximal diversion is increasingly supported in recent literature [2, 3]. Laparoscopic sigmoidectomy in the emergency setting is safe, with decreased morbidity compared to open sigmoidectomy [4].

In the only recent randomized clinical trial (RCT)comparing primary anastomosis with diversion to Hartmann's procedure in the emergency setting, Oberkofler [3] reported similar outcomes with the initial colectomy, but superior overall results in the primary anastomosis group owing to the higher rate of stoma closure and relative safety/efficiency of ileostomy closure as opposed to Hartmann takedown. The trial has been criticized for the influence of surgeon discretion on the choice of technique, as well as calculation of the sample size [5, 6]. A similar RCT [7] was prematurely terminated due to slow accrual.

Stoma avoidance altogether in the emergency setting is also described in limited and somewhat dated series; intraoperative colonic lavage is often employed in these studies to prepare the colon for primary anastomosis, with acceptable morbidity and anastomotic leak rates [8, 9]. Two recent retrospective analysis also concluded that primary anastomosis without diversion is an appropriate option in the urgent setting,

L.M. Cannon, MD
Section of Colon and Rectal Surgery, Department of General Surgery, University of Chicago Medicine, 5841 S. Maryland Avenue, MC 5094, Chicago, IL 60637, USA
e-mail: lcannon@surgery.bsd.uchicago.edu

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including patients with Hinchey III (purulent) and Hinchey IV (feculent) peritonitis; careful patient selection is advised [10, 11].

The broad body of literature does not stratify outcomes based on intraoperative Hinchey classification, though authors recognize that patients with Hinchey IV disease are likely to have increased perioperative morbidity and mortality as compared to those with Hinchey III disease. Pending further meta-analysis or randomized trials, choice of operation in the emergency setting is still predicated on surgeon experience and preference.

Attempts at nonoperative management in patients presenting with complicated diverticulitis including extra-digestive air and free fluid is supported by single-institution series. In one series including 136 patients, ~88 % of patients with extra-digestive air >2 cm, non-loculated fluid, or abscess >4 cm were able to be successfully treated without surgery [12]. Another study reported similar results, with an 86 % success rate in 132 patients with nonoperative management in the absence of diffuse peritonitis or free pelvic fluid [13]. One study including 39 patients, ¾ of whom presented with signs of peritonitis, described a 92 % success rate with nonoperative management [14].

Elective sigmoidectomy after episodes of acute uncomplicated diverticulitis is an individualized, case by case decision based on patient specific factors. In contrast, patients with *complicated* diverticulitis who are successfully managed nonoperatively are still generally offered elective resection owing to high recurrence rates [1].

The technique of laparoscopic peritoneal lavage, first described and largely popularized in European centers [15], challenges both the notion that sigmoidectomy is necessary in patients requiring emergency operative intervention, and that elective resection is really required in patients that do successfully navigate an initial nonresectional approach. This chapter aims to examine the evidence for or against laparoscopic peritoneal lavage.

Search Strategy

Using the PICO format, laparoscopic peritoneal lavage (hereafter also referred to as simply 'lavage') was compared to any technique of sigmoidectomy—laparoscopic or open Hartmann's procedure or primary anastomosis with or without diversion—in patients presenting with Hinchey III diverticulitis requiring operative intervention due to generalized peritonitis or failure of medical management (Table 27.1). The outcomes evaluated were morbidity and mortality, non-resolution requiring reintervention and sigmoidectomy, rate of disease recurrence requiring sigmoidectomy,

Table 27.1 PICO table

P (patients)	I (intervention)	C (comparator)	O (outcomes)
Hinchey III diverticulitis	Sigmoidectomy (Hartmann's or primary resection and anastomosis with or without diversion)	Laparoscopic peritoneal lavage (washout)	Resolution recurrence

and the number of patients who are symptom free with no episodes of recurrence (definitive lavage), or those who were successfully able to undergo elective sigmoidectomy prior to a recurrent episode (lavage as a bridge to elective resection).

A systematic literature search was performed of MEDLINE and PubMed to identify English language publications related to utilization of laparoscopic peritoneal lavage in perforated diverticulitis, published from January 1990 through December 2015. Combinations of key words were constructed and applied to these databases. The search strategy used in MEDLINE included both MeSH subject headings when possible and/or keyword mapping alias operator commands for the terms 'diverticulitis' or 'diverticulum', AND 'laparoscopy' or 'laparoscopic', AND 'peritoneal lavage', 'lavage', or 'therapeutic irrigation'. Similar combinations were then applied to PubMed. The biographies of all the original articles were then explored for any additional germane publications. Studies that did not include more than one laparoscopic peritoneal lavage or therapeutic irrigation patient were excluded. Case reports, letters, systematic reviews, and duplicate articles were also excluded.

Results

Twenty-two English language studies were identified. Several studies represented extended series including previously reported patients [15–22]. One database analysis out of Ireland [23] may include the patients reported by Myers et al. [24].

Results of Low and Very-Low Quality Studies

Using the GRADE system approach to developing practice guidelines, 19 of 22 studies were rated either low or very low quality; reasons for this included small sample size, lack of institutional comparator, allocation concealment, surgeon bias, failure to adhere to the intention-to-treat principle, and lack of reporting on salient outcome metrics such as non-resolution or recurrence requiring resection. Most of the excluded studies had more than one of these limitations. These studies are summarized in Table 27.2.

There are a total of 946 patients represented by low or very low quality studies undergoing laparoscopic peritoneal lavage and at least 758 are presumed unique patients across a 22-year period (1991–2013). Of studies clearly reporting intraoperative Hinchey classification, 76 % of patients (311 of 416) had Hinchey III diverticulitis, defined as free purulent contamination of the peritoneal cavity. Some studies allowed patients who had failed an initial trial of medical management with or without percutaneous drainage of accessible abscess cavities; others only included patients determined to be urgent surgical candidates on presentation. Four studies included an intraoperative decision point to proceed with lavage, recognizing the inherent surgeon bias in this approach.

Table 27.2 Low and very low quality evidence on laparoscopic peritoneal lavage

Study	Study period	Unique lavage patients	H3	Lavage population	Morbidity (%)	Death (%)	Non-resolution requiring resection (%)	Recurrence requiring resection (%)	Elective resection without recurrence (%)	Symptom free, no resection (%)
O'Sullivan et al. [16]	'91–'94	8	8	CD and GP intra-op; (H3 only)	2 (25)	0	0	0	0	6 (75)
Faranda et al. [24]	'94-'98	18	16	CD and GP on presentation	3 (17)	0	0	NR	15 (83) ~4 m	NR
Mutter et al. [29]	'96–'03	10	10	CD, (−) PCD, intra-op with (−) GP, (−) visible perforation, (−) H4	0	0	1 (10)	0	6 (60) ~2–3 m	NR
Taylor et al. [20]	'02–'05	14	10	CD with perforation	0 (major)	0	3 (21)	0 2–15 m	8 (57) ~6w later	2 (14) 2–15 m
Bretagnol et al. [18]	'00–'04	24	18	CD and GP or FoMM or septic shock	2 (8)	0	0	0 ~4 m; 2–6 m	24 (100%) ~4 m; 2–6 m	0
Franklin et al. [22]	'91–'06	40	32	CD and GP	8 (20)	0	0	0 96 m; 1–168 m	24[a] (60)	16 (40) 96 m; 1–168 m
Myers et al. [26]	'00–'07	92	67	CD and GP; (+) free air, (−) H4	(4)	3 (3.2)	1 (2)	0 36 m; 12–84 m	0 36 m; 12–84 m	88 (96) 36 m; 12–84 m
Favuzza et al. [30]	NR	7	NR	CD and peritonitis; Imaging (+) fluid (−) discrete abscess	NR	0	1 (14)	1 (14) 3 m	5 (71)	0

Karoui et al. [23]	’94–‘06	35	35	CD and GP on presentation (H3 only)	9 (26)	0	1 (3)	0	25 (71) 4 m; 2–7	8 (23) 21 m; 7–48 m
White et al. [19]	’99–‘08	35	11	CD and GP, or (+) free air or 2QP (+) >3 cm collection with FoMM	19 (54)	0	8 (23)	8 (23) 6 m; 2–12 m	8 (23) 2–3 m later	11 (31) 20 m; 6–60 m
Liang et al. [21]	’91–‘10	47	36	CD and GP with (+) free air and (+) contrast extravasation	2 (4)	0	3 (6.4)	0	18[a] (38)	26 (55)
Rogers et al. [25]	’95–‘08	427	NR	NR	60 (14)	17 (4)	NR	NR	NR	NR
Edieken et al. [31]	’09–‘12	10	8	CD with FoMM or (+) free air; (+) HDS	NR	0	3 (30)	3 (30)	0	NR
Swank et al. [32]	’08–‘10	38	33	CD with perforation; (+) free air or H3	17 (45)	4 (11)	5 (13)	3 (8) 6–12 m	0	30 (79) 3 m
Gentile et al. [33]	’09–‘12	14	3	CD with perforation (H2-3 only)	3 (21)	1 (7)	NR	NR	NR	NR
Rade et al. [17]	’00–‘13	71	47	CD with GP; (−) shock (−) distention (−) previous surg (−) H4	20 (28)	4 (6)	11 (15)	NR	55 (77) 3 m; 1–9 m	NR

(continued)

Table 27.2 (continued)

Study	Study period	Unique lavage patients	H3	Lavage population	Morbidity (%)	Death (%)	Non-resolution requiring resection (%)	Recurrence requiring resection (%)	Elective resection without recurrence (%)	Symptom free, no resection (%)
Rossi et al. [34]	'06–'13	46	46	CD with GP; intra-op H3 only, (+) HDS	11 (24)	0	5 (11)	NR	NR	NR
Horesh et al. [35]	'07–'12	10	7	CD and peritonitis with (+) free air, or FoMM	3 (30%)	0	1 (10%)	2 (20%) ~9 m	NR	6 (60%)
Sorrentino et al. [36]	'01–'13	63	54	CD and intra-op; (−) fecal peritonitis >1 quadrant	9 (14)	1 (2)	6 (10)	4 (7) ~5y	0	53 (84) ~5y

Shaded studies are those whose patients are represented within more current studies in the table

CD complicated diverticulitis, *FoMM* failure of medical management, *GP* generalized or 4-quadrant peritonitis, *H* Hinchey, *HDS* Hemodynamic stability, *NR* Not recorded, *PCD* percutaneous drainage, *2QP* 2-quadrant peritonitis

[a]Value inferred from text

Lavage technique varied, including decision to disrupt inflammatory adhesions, use of pelvic drains, decision to patch, suture, or apply fibrin glue to visible perforations, volume of warm saline used, addition of agents to the irrigant (betadine or heparin) and duration of postoperative antibiotics. It is not known whether any one lavage technique positively or negatively influenced outcome.

Of unique studies reporting appropriate outcomes, the morbidity of lavage was ~19 %, with ~3 % mortality. Approximately 10 % of patients experienced non-resolution after lavage requiring return to the operating room and sigmoidectomy (~2/3 of studies reporting on this outcome); ~ 6 % of patients experienced a recurrence requiring sigmoid resection over a time frame ranging from 2 months to 14 years, ~28 % of patients underwent elective resection within 2–9 months after peritoneal lavage, and ~68 % of patients are symptom-free without any further intervention over an unknown time interval (~1/2 of studies reporting on the aforementioned three outcomes). The decision to proceed with elective resection was an institutional tenet defining lavage as a strategy to bridge patients through an emergency presentation so that they could undergo surgery in the elective setting. Other studies highlighted lavage as a potentially definitive procedure.

If we are to define success of peritoneal lavage as those patients who are either symptom-free with no recurrences or further intervention, or were able to undergo elective resection prior to any recurrent episode, then lavage was known to be successful in ~46 % of the total unique patient population represented by these studies, with approximately half of studies not reporting on these outcomes.

Several authors suggested criteria to identify those who are likely to fail lavage, including patients with elevated American Society of Anesthesia (ASA) classification, immune suppression, or advanced age [17], those with Hinchey IV diverticulitis (most series) or a visible perforation, and those with distention or obstruction limiting technical feasibility of lavage.

Results of Randomized-Controlled Trials

Of the 22 studies identified, 3 are recent randomized controlled multicenter trials, all rated high quality based on the GRADE system [37, 38, 39]. The results of these studies are summarized in Table 27.3. To allow for better comparison between trials, the author of this chapter utilized supplementary data from these trials to report on similar outcomes; that is 30–90 day morbidity beyond IIIb, and mortality, excluding Hinchey IV patients.

The DILALA Trial [37] included patients at 9 Swedish and Danish institutions from February 2010 to February 2014. All patients had extra-digestive fluid or gas on radiologic evaluation, were intraoperatively determined to have Hinchey III generalized purulent peritonitis, and were randomized to either lavage or open Hartmann's procedure. The primary end-point of the published study was short-term morbidity and mortality [37]; the primary endpoint of the trial will be the number of re-operations at 12-month follow-up with additional secondary endpoints [25].

Table 27.3 Randomized controlled trials on laparoscopic peritoneal lavage

Study	N	H3	Patients excluded after randomization	Morbidity (%)	Death (%)	Non-resolution requiring resection (%)	Recurrence requiring resection (%)	Elective resection w/o recurrence / Stoma reversal	Symptom free, no resection (%)	Conclusion
DILALA Angente et al. [37]	83	CD and (+) free fluid/air and intra-op H3								Lavage is feasible and safe in short-term analysis of patients. Long-term outcomes awaiting publication
Laparoscopic lavage	43	43	4 2 neoplasm 2 other	8 (21) ≥IIIb; 30d	3 (8) 90d	NR	0 3 m	0 3 m	NR	
Open Hartmann's	40	40	4 1 neoplasm 3 other	6 (17) ≥IIIb; 30d	4 (11) 90d			NR		
LOLA/LADIES Vennix et al. [38]	90	CD and GP with (+) free fluid/air and intra-op H3; (−) HDS, (−) high dose steroids								DSMB terminated LOLA arm early due to high short-term morbidity in the lavage group
Laparoscopic Lavage	47	47	1 protocol violation	20 (44) ≥IIIb; 90d	2 (4) 30d	9 (20)	6 (13) ~12 m	1[b] (2) ~12 m	24 (52) ~12 m	
Sigmoidectomy[a]	43	43	1 intra-op neoplasm	12 (29) ≥IIIb; 90d	1 (2) 30d			24/35 (71) <12 m		

SCANDIV Schultz et al. [39]	199	CD and GP; (−) obstruction, (−) pregnancy; intra-op (−) H4[c], (−) wrong diagnosis							Lavage led to worse outcomes; Findings do not support lavage in the treatment of diverticulitis
Lavage	101	69	27[c] 12 with no CD 15 with H4	19 (26) ≥IIIb[c]; 90d	6 (8) 90d[c]	NR	NR	NR	NR
Sigmoidectomy[a]	98	61	28[c] 13 with no CD 13 with H4 2 other	10 (14) ≥IIIb[c]; 90d	5 (7) 90d[c]			NR	

CD complicated diverticulitis, *NR* Not recorded, *H* Hinchey, *HDS* Hemodynamic stability, *GP* generalized peritonitis, *DSMB* Data & safety monitoring board

[a]Laparoscopic or open Hartmann's procedure, or primary resection and anastomosis +/− diversion at surgeon's discretion

[b]Four additional resections for cancer

[c]H4 included in primary outcome analysis in SCANDIV; shown are only H1-3 values to allow for better comparison between RCTs

The LOLA group of the LADIES trial [38] involved 42 hospitals in Belgium, Italy, and the Netherlands from July 2010 to February 2013. The LOLA group was designed to compare lavage to sigmoidectomy—Hartmann's or primary anastomosis with or without diversion—in Hinchey III diverticulitis. A separate subgroup analysis compared Hartmann's procedure vs. resection and primary anastomosis in both Hinchey III and IV diverticulitis and is not relevant to the aim of this chapter. Patients with generalized peritonitis and radiologic evidence of diffuse extradigestive fluid or gas were randomized during diagnostic laparoscopy; those with Hinchey III purulent peritonitis were then eligible for the LOLA group. Patients on high-dose steroids, dementia, advanced age, or hemodynamic instability were excluded. The primary end-point of the LOLA group was a composite including major morbidity and mortality within 12 months.

The SCANDIV Trial [39] included patients at 21 participating centers in Sweden and Norway from February 2010 to June 2014. Patients with diverticulitis and peritonitis were randomized to receive lavage or sigmoidectomy— Hartmann's or primary anastomosis with or without diversion— and then underwent diagnostic laparoscopy. Those with a non-diverticular pathology identified intraoperatively were then excluded from all but the primary analysis. Those with Hinchey IV feculent peritonitis were randomized but were included only in a modified intention-to-treat analysis, as they all underwent sigmoidectomy. Those with Hinchey I-III disease, and those with Hinchey IV disease, were analyzed separately in regard to secondary outcome measures. The primary outcome was severe postoperative complications within 90 days.

The short-term analysis of the DILALA trial concluded that lavage for Hinchey III diverticulitis, as compared to open Hartmann's procedure, is feasible and safe in the short term with no difference in30-day ≥ IIIb morbidity (21 % vs. 17 %, respectively) or 90-day mortality (7.7 % vs. 11.4 %, respectively), and resulted in shorter operating time and length of stay. This trial is awaiting final review and publication of its 12-month outcomes.

The other trials, LOLA/LADIES and SCANDIV, did not support use of lavage. The LOLA group of the LADIES trial was terminated early by the Data Safety & Monitoring Board (DSMB) due to increased event rate defined as in-hospital major morbidity or mortality in the laparoscopic lavage group, with 37 events in the lavage group and 10 events in the sigmoidectomy group ($p = 0.0005$), owing mainly to an increased rate of surgical re-intervention. The study was not sufficiently powered to make a statement on inferiority of lavage, but suggested that it is not superior. Twenty percentage of lavage patients required sigmoidectomy due to non-resolution of their inflammatory process. 52 % of lavage patients were symptom free with no recurrence at 12-month follow up. Four cancers were missed in the lavage group and later required resection.

The SCANDIV trial was carried to completion. While 90-day ≥ IIIb morbidity and mortality was no different, patients undergoing lavage had a significantly higher reoperation rate within 90 days (20.3 % vs. 5.7 % in the sigmoidectomy group, p 0.01) in patients with Hinchey I-III diverticulitis. Hospital stay was not significantly different. As with LOLA/LADIES, four cancers were missed in the lavage group and later required resection.

Recommendations Based on the Data

There are some outcome measures for which lavage is clearly superior. The significantly shorter operating time offered by lavage is widely supported by both low- and high quality literature. While this makes lavage a tempting strategy for the surgeon to deploy in the emergency setting, the clinical benefit of a 1-h lavage vs. a 2- or 3- h sigmoidectomy is questionable. Length of stay in the lavage group was not significantly different in the SCANDIV or LOLA/LADIES Trials; it was significantly shorter in the DILALA Trial (6 vs. 9 days; p 0.037) [37, 38, 39].

In order to make a recommendation on the role of laparoscopic peritoneal lavage in the management of Hinchey III diverticulitis, one must define what is an acceptable and unacceptable outcome. For whom is this intervention applicable, how should it be applied, and what are the outcomes of alternative techniques? Is laparoscopic peritoneal lavage a rescue procedure meant to bridge a patient to elective resection with the goal of stoma avoidance, or is lavage better defined as a definitive intervention?

The author defined unacceptable outcomes in utilization of the lavage technique as significantly increased morbidity and mortality, non-resolution requiring resection, and missed neoplasm.

In patients presenting with Hinchey III diverticulitis and peritonitis, there is no subset for which laparoscopic peritoneal lavage is clearly the preferred method, as compared to sigmoidectomy. **(Recommendation:** Conditional; **Quality of Evidence:** High)

In patients presenting with Hinchey III diverticulitis and generalized peritonitis or who are failing nonoperative management, there is no subset of patients for which laparoscopic peritoneal lavage is clearly the preferred method compared to sigmoidectomy. This is a conditional recommendation based on high quality evidence with limited long-term data and lack of reporting on some of the outcomes of interest. Two randomized trials demonstrated a significant rate of surgical reintervention in the lavage group, many of which were take-backs for sigmoidectomy. Thirty to ninety day major (≥IIIb) morbidity in the three RCTs ranged from 21–44 % in the lavage group and 17–29 % in the sigmoidectomy group. Thirty to ninety day mortality ranged from 4–8 % in the lavage group and 2–11 % in the sigmoidectomy group. The overall reported major morbidity and mortality in the sigmoidectomy group in these three RCTs is lower than historically reported for the emergency setting, which may not be entirely explained by increased use of laparoscopic resection or improved perioperative care. The rate of recurrent diverticulitis after laparoscopic peritoneal lavage, when reported, is markedly lower than is expected after an episode of complicated diverticulitis and suggests further research is needed.

Patients with high ASA class, advanced age, immune suppression, distention or obstruction, or feculent peritonitis (Hinchey IV) should not be offered laparoscopic peritoneal lavage. An intraoperative assessment prior to any decision to proceed with lavage is reasonable. **(Recommendation:** Conditional; **Quality of Evidence:** Low)

There is no defined group for which laparoscopic peritoneal lavage is clearly favored, but there are several patient subsets in whom lavage should not be considered. The majority of low and very-low quality studies do not recommend this approach in Hinchey IV feculent peritonitis [16–20, 23, 26, 31, 33, 35–37]. Obstruction and bowel distention, as with any laparoscopic technique, limits visibility and precludes lavage [19, 31]. Rade et al. were the only authors to analyze factors predicting failure of the approach; patients with ASA class >2, advanced age >80 years, and immunocompromised patients were significantly more likely to require re-intervention due to failure of lavage [17]. The recommendation to exclude patients with Hinchey IV peritonitis, obstruction, advanced age, immune suppression, and high ASA class is conditional based on low quality evidence. Recognizing that not all patients with Hinchey III purulent peritonitis are alike, fully embracing surgeon discretion with diagnostic laparoscopy and intraoperative assessment prior to the decision to proceed with lavage is reasonable if use of the technique is desired, pending further data which may better guide patient selection and risk stratification.

If laparoscopic peritoneal lavage is to be used as a definitive or bridging strategy, recent complete colonoscopy should be documented in order to avoid missed neoplasm. (**Recommendation:** Strong; **Quality of Evidence:** Low)

While most studies excluded patients in whom cancer was apparent during initial operation, this cannot always be known intraoperatively. In the case of neoplasm masquerading as perforated diverticulitis, the strategy of sigmoidectomy clearly results in a more immediate diagnosis and therapy. Resection according to oncologic principles should be considered if recent colonoscopy is not documented. Three observational studies [19, 26, 33] and two randomized controlled trials [38, 39] reported on a total of 12 cancers that were not noted during laparoscopic peritoneal lavage. How many patients need to benefit from successful lavage for a missed neoplasm to be acceptable? It is unclear whether the delay in diagnosis caused by utilization of lavage influenced recurrence or survival these patients. If laparoscopic peritoneal lavage is to be used as a definitive strategy or as a bridge to elective resection, complete colonoscopy should be performed in order to avoid missed neoplasm. This is a strong recommendation based on low quality evidence, with risk of harm clearly outweighing reported benefit.

Personal View of the Data

In the author's opinion, the current evidence forecasts a future of low applicability of the technique of laparoscopic peritoneal lavage. There is no clear patient population standing to benefit, and this approach is not used in practice at our institution.

Stoma formation is an undesirable consequence of emergency surgery for diverticulitis. Though the morbidity is lower than end colostomy takedown, diverting loop ileostomy reversal does carry risk [3]. The technique of primary anastomosis without diversion for diverticulitis in the emergency setting is described but limited to observational series [9–12]. Stoma avoidance was not factored in to the proposed

recommendations. This is because the small number of patients present in the lavage literature who underwent sigmoidectomy *without* stoma formation limits this author's ability to make an evidence-based recommendation. That said, the LOLA/LADIES Trial [38] and the SCANDIV Trial [39] both reported on quality of life in patients up to 6 months postoperatively, with no significant differences in the lavage and sigmoidectomy groups; 16–24 % vs. 69–83 % had a stoma, respectively. This suggests patients are capable of adapting reasonably well to temporary stoma formation in the setting of emergent surgery for diverticulitis.

Future randomized controlled trials as well as longer follow up of the current laparoscopic peritoneal lavage cohort are likely to influence the author's conclusion. After successful nonoperative management of acute complicated diverticulitis, recurrence rates range from 28 to >40 %, and elective resection is recommended [1, 26, 27]. Particularly for surgeons' whose attitude is in support of restorative resection and primary anastomosis *without* stoma formation—including in the setting of Hinchey III diverticulitis— laparoscopic lavage does not avoid a secondary major surgical intervention and attendant morbidity, making it an unappealing option. If the validity of laparoscopic primary resection and anastomosis as one-stage management of Hinchey III diverticulitis is demonstrated in larger prospective studies, this is likely to further weaken the case for lavage. We would no longer need to factor in the known morbidity of a temporary stoma and takedown in those undergoing emergent resection.

The high recurrence rates reported after nonoperative management has also led to reasonable speculation that in these instances of short-term "recurrence", the original episode has actually not resolved— so-called 'smoldering' diverticulitis. In contrast, after appropriate resection with colorectal anastomosis, recurrence is <3 % [28]. Follow up of the current lavage cohort indicates astonishingly lower recurrence rates then are historically expected for complicated diverticulitis; does this suggest that lavage may alter the natural history of Hinchey III diverticulitis in a way not previously described? If this is substantiated, the increased rate of intervention with lavage due to non-resolution may be acceptable if it means the greater cohort is able to avoid emergent stoma formation, need for elective resection, and future recurrence. One can easily envision a shift toward the strategy of laparoscopic peritoneal lavage in lower acuity patients, with greater applicability to Hinchey II patients, if long-term symptom-free resolution and these compellingly low recurrence rates are observed in prospective studies. As mentioned earlier, any nonresectional management approach should be limited to patients with recent complete colonoscopy, in order to avoid missed neoplasm.

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Chapter 28
Surgery for Acute Complicated Diverticulitis: Hartmann vs. Primary Anastomosis

Nitin Mishra and David A. Etzioni

Introduction

Acute diverticulitis is a significant and growing problem within the United States, accounting for over 160,000 hospitalizations per year and 875,000 days of inpatient care [1]. Rates of admission for acute diverticulitis are increasing, especially in the younger population [1, 2]. While the vast majority of cases can be managed without surgery, approximately 14 % require surgical intervention [1].

Historically, the most commonly performed operation performed for sigmoid diverticulitis is a Hartmann's procedure, in which the diseased segment of bowel is resected and an end colostomy formed [3]. As a surgical option, the Hartmann's procedure eliminates the risk of anastomotic complications at the time of initial surgery. By delaying anastomosis until there is complete resolution of pelvic inflammation, the risk of anastomotic leak is theoretically minimized. The risk of subsequent operation for restoration of bowel continuity is not without its own morbidity, however, with reported anastomotic leak rates of up to 30 %, and a reported mortality of up to 14.3 % [3–9]. As a result of the burden associated with colostomy reversal, a significant number of patients will never have the colostomy reversed, resulting in a permanent stoma [10, 11].

The natural alternative to a Hartmann's procedure is resection with primary anastomosis. The goal of this approach is to reduce the morbidity and mortality associated with the reversal of Hartmann's procedure, while maintaining an acceptable level of risk associated with anastomosis at the time of an urgent operation [6, 12]. With the intent of minimizing this risk, surgeons may choose to employ a defunctioning ostomy. Defunctioning ostomies (either loop ileostomy or loop colostomy)

N. Mishra, MD • D.A. Etzioni, MD, MSHS (✉)
Division of Colon and Rectum Surgery, Mayo Clinic Hospital, Phoenix, AZ, USA
e-mail: Etzioni.David@mayo.edu

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may serve to reduce rates of anastomotic leak while lowering the burden of the subsequent reoperation and restoration of gastrointestinal continuity.

The choice of which of these operations is controversial, and depends upon patient and surgeon factors. Current guidelines published by the American Society of Colon and Rectal Surgeons recommend immediate resection in the setting of purulent or fecal peritonitis (Hinchey III and IV), but do not offer any distinct guidance regarding the decision between Hartmann's procedure or primary anastomosis [13]. In this chapter, studies published over the last 20 years are evaluated to decide which operation (Hartmann's vs. primary anastomosis) should be preferred in treating acute diverticulitis. Options such as laparoscopic lavage have been intentionally excluded as the purpose of the chapter is to compare Hartmann's procedure to a primary anastomosis.

Methods/Search Strategy

To identify articles for inclusion in this review, we searched the MEDLINE database. The primary goal was to identify studies reporting outcomes of patients with acute diverticulitis who underwent surgical treatment with either Hartmann's procedure or primary anastomosis. Case reports, case series with 20 or fewer patients, case series with less than 10 patients in either of the intervention groups, and studies where no novel patient outcomes were reported (e.g. review articles) were excluded. Systematic reviews and meta-analyses were included, but considered separately.

We started our search by querying for diverticulitis, Hartmann and anastomosis as keywords, in the following orientation: ("diverticulitis" AND ["Hartmann" OR "anastomosis"]). The following limits were placed on the search: articles written in English, involving humans and published from January 1, 1995 to 2016. This initial search strategy yielded 295 articles. Abstracts of all articles were reviewed, as well as full text when a study potentially met the inclusion criteria. References from articles retrieved through this query were also examined for inclusion. A total of 24 articles were eligible for the final review.

Pt population	Intervention	Comparator	Outcome studies
Pts with complicated diverticulitis	Primary anastomosis (with or without diversion)	Hartmann's procedure	Morbidity, mortality

Results

The articles included in this review were individually analyzed for quality of evidence as per the GRADE criteria [14]. The results of the search are listed in Table 28.1.

A total of 24 articles (2 RCTs, 2 meta-analyses, 3 large database studies, 2 systematic reviews, 2 prospective cohort studies and 13 retrospective cohort studies) were reviewed. Analysis of the results based on study types and outcomes are summarized below:

Table 28.1 Summary of all studies included in this review

Author	Year	Study design/data source	Patients (HP)	Patients (PA)	Patients (PAD)	Author's conclusion	Evidence quality
Oberkofler [15]	2012	RCT	30	–	32	No difference in primary outcomes between HP and PA[a]	Low
Binda [16]	2012	RCT	34	56	–	No difference in primary outcomes between HP and PA[a]	NA
Jafferji [17]	2014	Retrospective Cohort Study	74	20	32	PA is underutilized	Very low
Hergoz [18]	2011	Retrospective Cohort Study	19	21	–	PA superior to HP with lower morbidity and mortality	Very low
Miccini [19]	2011	Retrospective Cohort Study	85	28	–	No difference in morbidity between PA and HP	Very low
Trenti [20]	2011	Retrospective Cohort Study	60	22	5	PA is safe with no difference in morbidity or mortality between PA and HP	Very low
Thornell [21]	2011	Retrospective Cohort Study	82	24	–	Randomized trial needed to accurately answer this question	Very low
Mueller [22]	2011	Retrospective Cohort Study	26	36	11	Decision to make anastomosis should be made on patients general condition, not local factors	Very low
Zingg [23]	2010	Retrospective Cohort Study	65	35	11	PA is not superior to HP. Diversion should be considered if PA is performed	Very low
Vermeulen [24]	2007	Retrospective Cohort Study	139	45	16	PA is not inferior to HP in carefully selected patients	Very low
Stumpf [25]	2007	Retrospective Cohort Study	30	36	–	PA is safe in selected patients	Very low
Zorcolo [26]	2003	Retrospective Cohort Study	86	29	–	PA is safe and comparable to HP	Very low
Blair [27]	2002	Retrospective Cohort Study	64	28	5	PA is safe	Very low
Gooszen [28]	2001	Retrospective Cohort Study	28	–	32	Both PA and HP equivalent	Very low
Wedell [29]	1997	Retrospective Cohort Study	15	10	4	PA superior to HP	Very low

(continued)

Table 28.1 (continued)

Author	Year	Study design/data source	Patients (HP)	Patients (PA)	Patients (PAD)	Author's conclusion	Evidence quality
Regenet [30]	2003	Prospective Cohort Study	33	27	–	PA has less morbidity than HP	Very low
Schilling [31]	2001	Prospective Cohort Study	42	13	–	PA has lower cost than HP	Very low
Tadlock [32]	2013	Retrospective Cohort Study NSQIP	991	285	38	PA and PAD are safe compared to HP	Low
Masoomi [33]	2012	Retrospective Cohort Study NIS	56,875	39,023	3361	PA with diversion is superior to HP	Low
Gawlick [34]	2012	Retrospective Cohort Study NSQIP	1678	340	–	No difference in morbidity and mortality between PA and HP	Low
Cirocchi [35]	2013	Systematic review plus meta-analysis	246	174	–	No conclusion could be drawn as evidence quality low	Low
Constantinides [36]	2006	Meta-analysis	416	547	–	Overall reduced mortality in PA group compared to HP	Low
Abbas [37]	2006	Systematic review	526	358	–	PA compares favorably to HP	Very low
Salem [38]	2004	Systematic review	1051	431	93	PA is a safe alternative to HP	Very low

HP Hartmann's procedure, *NIS* Nationwide Inpatient Sample, *NSQIP* National Surgical Quality Improvement Program, *PA* primary anastomosis, *PAD* primary anastomosis with diversion, *RCT* randomized controlled trial

[a]Trial prematurely terminated due to poor patient accrual

Randomized Control Trials (RCTs)

Two RCTs have been completed comparing outcomes between Hartmann's procedure and primary anastomosis in patients undergoing surgery for acute diverticulitis [15, 16]. These studies, however, fare poorly on the Cochrane Collaboration's tool for assessing risk of bias [39]. Additionally, both studies were terminated prematurely due to lack of accrual of patients.

Oberkofler et al. conducted a multicenter RCT in Switzerland to compare Hartmann's and primary anastomosis with loop ileostomy in patients with left-sided diverticulitis [15]. Their analytic approach considered the initial operation together with the subsequent ostomy reversal. Their power analysis included a very liberal estimate of expected differences in complication rates (40 % for primary anastomosis, 80 % for Hartmann's), and estimated that 68 patients should be enrolled. During the 3 years that the study was conducted, the researchers were only able to recruit a total of 62 patients (30 in Hartmann's and 32 in primary anastomosis + ileostomy group). In addition, 52 potential study patients were not assessed for eligibility because of the surgeons' choice not to enroll patients resulting in the potential for significant selection bias [15]. Their analysis revealed differences in several endpoints in favor of primary anastomosis with loop ileostomy. Only 15 of 26 (58 %) end colostomies (after Hartmann's procedure) were eventually reversed, whereas the stoma reversal rate after ileostomy was significantly higher at 90 % (26/29, $P < 0.012$). Diverting ileostomies were reversed much earlier than the end colostomies after Hartmann's procedure (median 3 months vs. 6 months, respectively). The rate of severe complications (20 % vs. 0 %, $P = 0.046$), as well as the total number of complications per patient (median 1 vs. median 0, $P < 0.001$), was significantly higher after reversal of Hartmann's procedure (colostomy) compared to ileostomy reversal. Anastomotic dehiscence, sepsis, and bleeding occurred only after reversal of the end colostomy. Furthermore, the duration of the operation (183 min vs. 73 min, $P < 0.001$) as well as the hospital stay (9 days vs. 6 days, $P = 0.016$) was significantly longer after reversal of Hartmann's procedure. Of note, all the advantages of primary anastomosis with diverting ileostomy relate to the reversal operation.

Binda et al. from Norway conducted a multicenter RCT, but terminated it prematurely as they could recruit only 15 % of the target sample size (300 patients in each group) in 9 years [16]. No conclusions could be drawn from this study.

Meta-analyses

Two meta-analyses have been performed that examined evidence regarding outcomes in patients undergoing Hartmann's procedure vs. primary anastomosis. The first of these, conducted by Constantinides et al. in 2006 included a total of 15 studies; 10 of these studies were published between 1984 and 1995 and 5 after 1995 – these 5 studies are a part of our review [36]. Results from this meta-analysis show lower mortality with primary anastomosis than with Hartmann's operation, (4.9 %

vs. 15.1 %). Another meta-analysis of 14 studies was performed by Cirocchi et al. in 2013, and also found lower mortality rates with primary anastomosis than Hartmann's procedure (9.8 % vs. 22.0 %) in the treatment of acute diverticulitis. The authors, however, found that the heterogeneity of the included studies was very high and recommended that their findings be interpreted with caution [35].

Despite the intuitive appeal of relying on meta-analyses as a quantitative synthesis of existing evidence, there is good reason to discount the findings from these two studies. First, the technique of meta-analysis does not apply well to small, non-randomized studies with heterogenous populations/interventions. This limitation was articulated nicely in the study performed by Cirocchi [35]. Second, these studies are ambiguous as to whether they are estimating the clinical burden of the initial operation or the initial operation plus any subsequent operations (to restore intestinal continuity).

Database Studies

Three studies have been conducted using secondary databases in order to compare outcomes of primary anastomosis vs. Hartmann's procedure for acute diverticulitis [32–34].

In 2012, Gawlick et al. published a study using patient data from the NSQIP database in 2005–2009 to analyze 2018 patients undergoing surgery for acute diverticulitis [34]. This study used wound classification (contaminated and dirty) as a surrogate marker for severity in patients who underwent emergent surgery with a diagnosis code of diverticulosis or diverticulitis. The study found no significant difference in the risk of infectious complications, return to the operating room, prolonged ventilator use, death, or hospital length of stay between Hartmann's procedure and primary anastomosis with diversion. In examining the subgroup of patients where the operation was classified as dirty/infected, however, the adjusted mortality rate was twice as high when primary anastomosis with diversion was performed compared to the Hartmann's procedure.

Also in 2012, Masoomi et al. published a study using discharge data from the NIS between 2002 and 2007 to analyze 99,259 patients undergoing primary anastomosis with diversion vs. Hartmann's procedure for acute diverticulitis [33]. This study found a lower complication rate in the primary anastomosis (plus diversion) group compared with the Hartmann's group (primary anastomosis: 39.06 % vs. Hartmann's: 40.84 %; $p = 0.04$). Mortality was lower in the primary anastomosis group (3.99 % vs. 4.82 %, $p = 0.03$). However, patients in the Hartmann's group had a shorter mean length of stay (12.5 vs. 14.4 days, $p < 0.001$) and lower mean hospital costs (USD 65,037 vs. USD 73,440, $p < 0.01$) compared with the primary anastomosis group. This study, while based on a very large cohort of patients, may suffer from issues regarding the granularity and accuracy of administrative coding. The International Classification of Disease (ICD) coding scheme is not a perfect system in terms of describing the type of operation performed, and there is the potential that

many of the patients in this study were mischaracterized in terms of the type of surgical care they received.

In 2013, Tadlock et al. published a study using patient data from the NSQIP database in 2005–2008 to analyze 1313 patients undergoing surgery for acute diverticulitis [32]. Three operative approaches were analyzed: Hartmann's procedure, primary anastomosis without diversion, and primary anastomosis with diversion. In this study, the 30-day mortality was 7.3 %, 4.6 %, and 1.6 %, respectively (P = 0.163), while surgical site infections occurred in 19.7 %, 17.9 %, and 13.2 % of patients (p = 0.59). In addition, the three groups did not have significant differences in surgical infectious complications, acute kidney injury, cardiovascular incidents, or venous thromboembolism after surgery. The authors of this study concluded that primary anastomosis in the acute setting is a safe alternative to a Hartmann's procedure, with no significant difference in mortality or postoperative surgical site infections.

As with meta-analyses, the results from large database studies should be interpreted with caution. Statistical differences in outcomes may not always be clinically significant due to the large sample sizes. This is illustrated by the small difference in complication rate between the primary anastomosis group (39.06 %) compared with the Hartmann's procedure group (40.84 %) in the NIS study above which was statistically significant (p = 0.04). More importantly, the translation of clinical phenomena into accurate representation in codes (ICD or otherwise) may lead to inaccuracy, bias, and confounding.

Retrospective/Prospective Cohort Studies

We reviewed 13 retrospective cohort studies and 2 prospective observational studies examining patient outcomes with Hartmann's vs. primary anastomosis [17–31, 40]. The quality and sample size vary widely, and taken together do not provide significant guidance regarding the central topic of this chapter.

Focus on Mortality

All studies, except two [19, 21] reported procedure-specific mortality. The mortality data from the studies included in this review are compiled in Table 28.2.

Most studies did not find a statistically significant difference in mortality between Hartmann's procedure and primary anastomosis. The three studies which showed a statistically significant difference in mortality were by Masoomi et al., Trenti et al. and Mueller et al. [20, 22, 33]. Masoomi's study analyzed a discharge database (NIS) and is not the best method for clinical assessment of cause specific mortality [33]. The study by Trenti et al. is a retrospective chart review with small patient numbers and an unusually high mortality rate (45 % mortality overall). Authors of

Table 28.2 Mortality data of studies included in this review

Author	Year	HP (n/N) (%)	PA (n/N) (%)	P	HP (n/N) (%)	PAD (n/N) (%)	P
Jafferji [17]	2014	1/74 (1.4 %)	0/20 (0 %)	NS	1/74 (1.4 %)	0/32 (0 %)	NS
Tadlock [32]	2013	72/991 (7.3 %)	13/285 (4.6 %)	0.465	72/991 (7.3 %)	1/38 (2.6 %)	0.479
Cirocchi [35]	2013	54/246 (22 %)	17/174 (9.8 %)	0.02	–	–	NA
Oberkofler [15]	2012	4/30 (13.3 %)	–	NA	4/30 (13.3 %)	3/32 (9.4 %)	NS
Binda [16]	2012	1/34 (2.9 %)	6/56 (10.7 %)	0.24	–	–	NA
Toro [41]	2012	139/800 (17.4 %)	38/1010 (3.8 %)	NA	139/800 (17.4 %)	11/153 (7.2 %)	NA
Masoomi [33]	2012	2741/56,875 (4.8 %)	NR	NA	2741/56,875 (4.8 %)	134/3361 (4 %)	0.03
Gawlick [34]	2012	89/1674 (5.2 %)	25/340 (7.4 %)	NS	–	–	NA
Hergoz [18]	2011	6/19 (31.6 %)	1/21 (4.8 %)	0.15	–	–	NA
Miccini *[19]	2011	–/85	–/28	NA	–	–	NA
Trenti [20]	2011	27/60 (45 %)	2/22 (9.1 %)	0.001	27/60 (45 %)	NR	NA
Mueller [22]	2011	7/26 (26.9 %)	2/36 (5.6 %)	0.008	7/26 (26.9 %)	0/11 (0 %)	NR
Zingg [23]	2010	19/65 (29.2 %)	8/35 (22.9 %)	0.156	19/65 (29.2 %)	0/11 (0 %)	NR
Vermeulen [24]	2007	47/139 (33.8 %)	6/45 (13.3 %)	<0.01	47/139 (33.8 %)	1/16 (6.3 %)	<0.01
Stumpf [25]	2007	5/30 (16.7 %)	0/36 (0 %)	0.025	–	–	NA
Constantinides [36]	2006	63/416 (15.1 %)	27/547 (4.9 %)	0.13	–	–	NA
Abbas [37]	2006	102/526 (19.4 %)	32/358 (8.9 %)	NA	–	–	NA
Salem [38]	2004	198/1051 (18.8 %)	56/569 (9.8 %)	NA	198/1051 (18.8 %)	9/93 (9.7 %)	NA
Regenet [30]	2003	4/33 (12.1 %)	3/27 (11.1 %)	0.9	–	–	NA
Zorcolo [26]	2003	19/86 (22.1 %)	3/29 (10.3 %)	0.3	–	–	NA
Blair [27]	2002	13/64 (20.31 %)	3/33 (9.1 %)	0.2	13/64 (20.31 %)	NR	NA
Gooszen [28]	2001	6/32 (18.8 %)	–	NS	6/32 (18.8 %)	5/28 (17.9 %)	NS
Schilling [31]	2001	4/42 (9.5 %)	1/13 (7.7 %)	0.9	–	–	NA
Wedell [29]	1997	4/15 (26.7 %)	0/10 (0 %)	NR	4/15 (26.7 %)	1/4 (25 %)	NR

HP Hartmann's procedure, *NS* not significant, *NR* not reported, *NA* not applicable, *PA* primary anastomosis, *PAD* primary anastomosis with diversion
*Procedure specific mortality not reported

this study attributed the high mortality to the fact that surgical quality was heterogeneous in their institution, with a disproportionate number of deaths being in the patients operated upon by general surgeons. This study is limited by selection bias and lack of generalizability. In addition, the groups were not matched and confounding factors were not accounted for. Thus, the results of this study are not reliable [20]. Mueller et al. found a statistically significant lower mortality with primary anastomosis compared with Hartmann's procedure. However, this was a retrospective chart review with a very small sample size. The number of deaths in the Hartmann's procedure group was 7/26 (27 %) and in the primary anastomosis group was 2/36 (6 %). However, it must be recalled that larger database studies show surgical mortality rates (both types of procedures combined) less than 5 % [1].

Focus on Anastomotic Leak

In the studies reviewed here, ten reported clinical anastomotic leak rate after primary anastomosis, with rates ranging from 3 to 28 % [18–20, 22–27, 30]. In one of the larger retrospective studies, the clinical anastomotic leak rate was 13/46 (28 %) in the primary anastomosis group [23]. During the same time period, the authors reported a 3 % anastomotic leak rate for their elective colon resections. This study highlights the increased risk for anastomotic leak in patients undergoing an urgent/emergent operation for acute diverticulitis compared with elective anastomoses.

Recommendations Based on Data

The procedures most reasonably performed in an urgent/emergent setting for acute diverticulitis are Hartmann's procedure, primary anastomosis without diversion, and primary anastomosis with diversion. Recent randomized trials have found increased rates of severe complications in patients undergoing laparoscopic lavage, and this *avant garde* approach is no longer widely considered appropriate [42, 43]. In analyzing the existing body of experiences for properly selected patients, each of these three procedures are equivalent in terms of morbidity and mortality from the index procedure. Some lessons can be taken however, to guide decision-making. Morbidity from anastomotic leak in patients with primary anastomosis is substantial, and higher than for elective resections. The likelihood of restoration of intestinal continuity is higher in patients who undergo primary anastomosis with loop ileostomy compared to those who undergo a Hartmann's resection. Finally, the morbidity and mortality from a Hartmann's reversal procedure is substantially higher than that of ileostomy reversal.

Thus, primary anastomosis with diverting loop ileostomy is recommended in stable patients undergoing surgery for acute diverticulitis. (Evidence quality: Low, Weak recommendation)

Personal View of Data

Each patient has a unique set of risk factors, and general/colorectal surgeons are well-acquainted with these. For the sake of discussion, these factors include sepsis/hemodynamic instability, age, functional status, immunosuppression, extent/duration of inflammation, and degree of involvement of regional tissues with the acute inflammatory process. For a patient who manifests with the most severe profile of disease (e.g. septic, feculent peritonitis), it would be foolhardy to challenge conventional surgical wisdom by constructing an anastomosis. The reverse may be true as well. A patient with refractory diverticulitis and localized disease may be best served with an anastomosis (with or without diversion), thereby minimizing the burden of subsequent reoperation.

The choice of surgery for acute diverticulitis, therefore, clearly depends on an individual surgeon's estimation of a patient's degree of risk, and a mechanism for translating this estimation into the selection of one of three competing options. In the authors' practice, primary anastomosis with diverting loop ileostomy (with or without colonic lavage) is preferred in patients who are stable and are not at an unduly high risk for anastomotic failure. The authors rarely perform primary anastomosis without diversion in patients undergoing urgent/emergent surgery for acute diverticulitis. For patients who are clinically unstable, the priority is to minimize the risk of mortality, and in these situations an anastomosis is an avoidable source of risk.

It is tempting to look to ongoing randomized studies, such as the Dutch LADIES trial [44] to give better guidance regarding the preferability of one approach over another. It is unlikely, however, that any trial will quantify the risk factors described above adequately, or allow for a translation of this quantification into standardized surgical decision-making. Given this, surgeons treating patients for acute diverticulitis will need to continue to exercise their best judgment, encompassing a broad spectrum of potential risks and challenges that face each patient.

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Chapter 29
Who Needs Elective Surgery for Recurrent Diverticulitis?

Janice Rafferty and Bobby Lynn Johnson III

Introduction

Diverticulitis a common condition encountered by the practicing surgeon. Currently, one of the more contentious topics in the management of diverticulitis is which patients with chronic or recurrent disease should be selected for elective sigmoid colectomy. Historic dogma dictated prophylactic colectomy after two episodes for uncomplicated diverticulitis, and after one episode in patients under 40, to reduce the risk of future emergency surgery with colostomy [1–5]. The use of CT scan to gauge severity of disease, construction of larger clinical databases, and the advent of less invasive techniques (percutaneous drainage, intraperitoneal lavage), has changed the way surgeons think and manage diverticulitis [6]. As a result, current guidelines recommend a more selective approach to sigmoid colectomy after an uncomplicated episode, and in the setting of chronic recurrent diverticulitis [7–9].

Despite these recommendations the frequency of elective colectomy appears to be increasing [10]. A prospective study by Simianu et al. [11], concluded that 31 % of patients failed to meet surgical indications of either complicated diverticulitis or three or more episodes prior to undergoing elective sigmoidectomy for diverticulitis [11]. To date, there are no published randomized controlled trials comparing outcomes for elective sigmoid colectomy to expectant management after an episode of diverticulitis. This chapter will attempt to provide the clinician with up to date graded evidence based recommendations regarding treatment.

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J. Rafferty, MD, FACS, FASCRS (✉)
Division of Colon & Rectal Surgery, UC Health,
2123 Auburn Avenue, Suite #524, Cincinnati, OH 45219, USA
e-mail: rafferjf@ucmail.uc.edu

B.L. Johnson III, MD
Department of Surgery, University of Cincinnati, Cincinnati, OH, USA

N. Hyman, K. Umanskiy (eds.), *Difficult Decisions in Colorectal Surgery*,
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Search Strategy

Patient population	Intervention	Comparator	Outcomes studied
Patients with recurrent diverticulitis	Resection	Expectant management	Risk of recurrence, morbidity, quality of life

We performed a systematic literature search with the aim of answering the following PICO (Patients, Intervention, Comparator, Outcome) question: "Who needs elective colon surgery for recurrent diverticulitis?" A targeted search of English language literature in MEDLINE, PubMed, EMBASE, and the Cochrane Database of Collected Reviews was performed. Key-word combinations using the Medical Subject Headings (MeSH) terms included "diverticulitis," "diverticular," "abscess," "fistula," "perforation," "complicated," "uncomplicated," "colectomy," "antibiotics," "resection," and "expectant management." Directed searches of the embedded references from the primary articles were also performed in selected circumstances. Review papers were also searched for cross-references. We decided to include exclusively those papers written in English language with a date of publication within the last 15 years in order to produce updated recommendations. The grade of both literature reviewed and final recommendation was performed by using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system [12, 13]. The search was carried out in November 2015.

Results

Uncomplicated Diverticulitis

Historically the recommendation was to proceed with elective resection after the second episode of uncomplicated diverticulitis, due to the presumed morbidity and mortality of subsequent attacks [1]. However close scrutiny of the evidence fails to support this practice; therefore the decision to proceed with surgery should take into account other factors. When recommending elective colectomy vs. expectant management for uncomplicated diverticulitis, the following should be considered: risk of recurrence, risk of developing complicated diverticulitis, patient comorbidities, possibility of emergency surgery, and quality of life.

Recurrence rates for uncomplicated diverticulitis treated nonoperatively vary from 8 to 48 % and are gathered from studies with varying lengths of follow up (Tables 29.1 and 29.2). The two largest series include ~181,000 [14] and ~179,000 [15] patients, and report recurrence rates of 8.7 and 16.3 %, respectively. Patients with uncomplicated disease were less likely to recur than their complicated counterparts [14, 16]. Of patients who recur, most recur within 12 months of the index admission [16, 17]. Patients who dorecur have a greater chance of yet another episode as well. Overall recurrence rates in patients with uncomplicated diverticulitis

Table 29.1 Diverticulitis outcomes

Study	N	Treatment	Results	Median F/U	QOE
Ho et al. [14] Retrospective multicenter	237,869 with diverticulitis (unspecified)	181,115/237,869 (76.1 %) treated non-surgically	8.7 % recurrence rate 23.2 % re-recurrence	Variable – NR	Moderate
Hall et al. [20] Retrospective	672 (index case of diverticulitis)	Non-surgical management	Overall recurrence 36 % Complicated recurrence 3.9 %	5 years	Low
Ambrosetti et al. [42] Prospective	542 patients with diverticulitis (unspecified)	405/542 (74.7 %) treated non-surgically	87/405 (21.2 %) had "bad outcome" (recurrence, abscess, stenosis, fistula) *Risk factors for bad outcome:* Age <50 Severity of disease as seen on CT	62 months	Low
Trenti et al. [16] Prospective	560 with diverticulitis (unspecified)	Non-surgical management	Recurrence observed in 14.8 %, Severe recurrence in 3.4 % *Risk factors for recurrence:* Chronic steroids Presence of abscess	67 months	Low
Rose et al. [15] Retrospective multicenter	210,268 with diverticulitis (unspecified)	179,569 (85 %) treated non-surgically	16.3 % recurrence rate 29.3 % rerecurrence *Risk factors for recurrence:* Complicated index episode Abscess Age <50	Variable – up to 15 years	Moderate
Anay and Elum [21] Retrospective multicenter	25,058 with acute diverticulitis (unspecified)	Non-surgical management = 20,136/25,058	19 % had recurrence 5.5 % required emergency operation at recurrence *Risk factor for recurrences:* Age <50 more likely to have recurrence (27 % vs 17 %)	Variable – NR	Moderate

(continued)

Table 29.1 (continued)

Study	N	Treatment	Results	Median F/U	QOE
Broderick-Villa et al. [18] Retrospective multicenter	3156 with acute diverticulitis (unspecified)	Non-surgical management = 2551/3156 (80.6 %)	Elective colectomy = 185/2551 Non-operative management = 2336/2551 13.3 % had recurrence *Risk factors for recurrence:* Younger patients Presence of comorbidities increased recurrence	8.9 years	Low
Klarenbeek et al. [40] Retrospective	291 patients	111 non op treatment 108 urgent/emergent surgery 72 elective surgery	Recurrence rate of 48 % in non op group *Risk of recurrence:* Complicated disease Immunosuppression Chronic renal failure Collagen vascular disease		Low
Holmer et al. [43] Prospective cohort	153 with acute diverticulitis (unspecified)	113 surgical resection 40 treated non-surgically	32 % of non surgically treated patients recurred 4 % of surgically treated patients recurred Risk factors for needing surgery: Perforated disease Recurrent episodes	32 months	Low
Li et al. [22] Retrospective multicenter	14,124 with acute diverticulitis (unspecified)	Non-operative management	9 % readmission for recurrence 1.9 % emergency surgery *Risk factors for readmission/ recurrence:* Patients with initial complicated disease Age <50 likely to be readmitted	3.9 years	Moderate

Chapman et al. [25] Retrospective	150 with prior episodes of diverticulitis Group A – Pts with 1–2 previous episodes Group B – Pts with >2 previous episodes	Non-operative and operative management	Perforation occurred more frequently in Group A Fecal Diversion occurred more frequently in Group A When needing surgery: no difference in operative morbidity/mortality	NR	Low
Eglinton et al. [17] Retrospective	502 with diverticulitis Uncomplicated = 337 Complicated = 165	Non surgical management: Uncomplicated = 320/337 Complicated = 62/165	Uncomplicated recurrence = 23.4 % Complicated recurrence = 24 % Complicated diverticulitis more likely to undergo surgical resection	101 months	Low
Lamb and Kaiser [38] Systematic review/ metanalysis	1051 patients – from 22 studies – diverticulitis with abscess formation	Urgent/emergent surgery (30 %) Elective surgery (36 %) Non-operative management (35 %)	Recurrence in patients waiting for elective resection = 39 % Recurrence in Non operative group = 18 % 28 % had no surgery and no recurrence	Variable	Moderate
Ambrosetti et al. [44] Prospective	73 patients with diverticular abscesses	Surgical and non-surgical management	22/45 (49 %) mesocolic abscesses & 8/28 (29 %) pelvic abscesses, successfully managed conservatively	43 months	Moderate
Kaiser et al. [45] Retrospective	511 patients with diverticulitis	Urgent, elective surgery Non-surgical management	Of 99 patients with abscess: 22 % required urgent operation 15 % underwent elective operation 41.2 % recurred after non operatively treatment	NR	Low

(continued)

Table 29.1 (continued)

Study	N	Treatment	Results	Median F/U	QOE
Chapman et al. [19] Retrospective	375 patients with complicated diverticulitis	Urgent, elective surgery Non surgical management	46 % had had previous episodes of diverticulitis 53 % was index episode of diverticulitis 6.5 % overall mortality rate *Risk of morbidity and mortality:* Older age Steroids/Immunodeficiency Diabetes Perforation on presentation	NR	Low
Nelson et al. [39] Retrospective	256 with complicated diverticulitis	99/256 (38.7 %) treated non-surgically	46/99 had recurrence 20/46 recurrences required sigmoid resection	14 years	Low
Gaertner et al. [41] Retrospective	218 patients treated with perc drain for complicated diverticulitis	32/218 (15 %) treated non-surgically	Recurrence rate was 42 % *Risk Factors associated with recurrence:* Abscess >5 cm	7.4 years	Low
Bridoux et al. [28] Retrospective	114 patients with Complicated diverticulitis	81/114 (71.1 %) treated non-surgically	7.4 % recurrence (median time of 12 months)	32 months	Low

Table 29.2 Quality of life

Study	N	Treatment	Results	Median F/U	QOE
Andeweg et al. [29] Systematic review/ metanalysis	1858 patients – from 21 studies – uncomplicated diverticulitis	Elective surgical vs non surgical treatment of recurrent diverticulitis	Higher QOL scores in laparoscopic surgical group Lower GI symptoms in surgical group Less chronic abdominal pain in surgical group	NR	Moderate
van de Wall et al. [30] Retrospective cohort	105 patients with diverticulitis (unspecified)	Elective surgical resection	Elective resection: Improved QOL Reduced chronic abdominal pain Decreased discomfort from defecation	1 year	Low
Forgione et al. [32] Prospective cohort	46 patients with diverticulitis (unspecified)	Elective surgical resection (laparoscopic)	36/46 patients significantly had increased GIQLI scores Patients with lowest GIQLI scores increased benefited the most from surgery	1 year	Low
Levack et al. [35] Retrospective	249 patients with diverticulitis (unspecified)	Laparoscopic and open sigmoidectomy	24.8 % reported relevant fecal incontinence 19.6 % reported fecal urgency 20.8 % reported incomplete emptying *Symptoms: risk factors* Fecal incontenence: pre-op abscess, female Urgency: divertiting ostomy, female Incomplete emptying : post-op sepsis, female	NR	Low
Pasternak et al. [31] Retrospective	130 patients with diverticulitis (unspecified)	Elective surgical resection (laparoscopic)	83 % of patients with GIQOL >100 after surgery vs before (43 %) Mean QOL score of 114 after surgery vs before (95)	40 months	Low

(continued)

Table 29.2 (continued)

Study	N	Treatment	Results	Median F/U	QOE
Scarpa et al. [33] Retrospective	71 patients with uncomplicated diverticulitis	25/71 underwent resection 46/71 non-surgical management	Cleveland global QOL: No difference in total score No difference in symptom frequency Current quality of health was lower in surgical group	47 months	Low
Egger et al. [36] Retrospective	124 patients	68 patients – elective colectomy	25 % suffered persistent symptoms: constipation, abdominal distention, abdominal cramps, diarrhea Complicated vs uncomplicated were unrelated to symptomatology Technique (open vs laparoscopic) were unrelated to symptomatology	33 months	Low

are approximately 4.7 % after the index episode, according to one study [17]. Two multicenter retrospective trials demonstrated re-recurrence risk of 23.2 and 29 % in patients who had had at least one previous recurrence [14, 18].

Most patients presenting with complicated diverticulitis do so at their index admission for diverticulitis; 89 % of patients who die of the disease have no prior history of diverticulitis [19]. These data suggest that in most cases, the first episode is the worst episode. That is not to say that patients with uncomplicated diverticulitis can't recur with a complicated form of the disease, and unequivocally will not require emergency surgery or a colostomy. However, rates of recurrent disease that is complicated range from 3 to 5 % in the literature [16, 17, 20]. Infact, most patients with a complicated or severe recurrence have had a previous episode of complicated/severe diverticulitis [16]. In addition, the risk of recurrent diverticulitis is positively associated with family history, length of colon involvement >5 cm [20], and presence of comorbidities [18]. Additionally risk of recurrence is associated with age <50 [14, 18, 21–23].

The risk of requiring an emergent colostomy after an initial episode of diverticulitis is strikingly low. A retrospective, multicenter study by Li et al. [22], described 14,124 patients treated nonoperatively, and found only 1.9 % of these patients subsequently had emergency surgery for perforation, with a median follow up of 3.9 years [22]. These findings are similar to another population-based study, which reviewed 25,058 patients where 20,136 patients were initially treated nonoperatively. While 19 % had a recurrence, only 5.5 % required a subsequent emergency colectomy [21]. The hazard ratio for emergency colectomy/colostomy was 2.2× higher in patients for each subsequent admission. According to this study, 18 patients would need to undergo elective colectomy to prevent one emergency surgery for recurrent diverticulitis [21].

After recovery from an initial episode of diverticulitis, the estimated risk of needing emergency Hartmann resection with stoma formation is 1 in 2000 patient-years of follow-up [24]. A study by Chapman et al. [25], grouped patients with diverticular recurrence in two categories: those with 1–2 previous episodes, and those with >2 previous episodes. Perforation and need for diversion occurred more in the group with only 1–2 previous episodes, and there were no differences in morbidity and mortality between groups. This suggests that patients with more than two episodes of diverticulitis are not at increased risk for poor outcomes [25]. To support this, a Markov model, developed by Salem et al. determined that performing colectomy after the fourth episode of diverticulitis rather than the second episode resulted in 0.5 % fewer deaths, 0.7 % fewer colostomies, and a reduction in cost per patient [26]. As practice patterns have shifted away from elective surgical management of diverticulitis, there has been an increase in the number of abscesses, but no increase in diverticular perforations requiring emergency surgery [27]. Because of this data, except in certain circumstances (see below), the current American Society of Colon and Rectal Surgeons (ASCRS) guideline states that patients with uncomplicated diverticulitis should not be counseled to undergo prophylactic elective colectomy as a means to prevent future emergency surgery and stoma creation [7].

Persistence of symptoms and quality of life is another factor to consider when recommending elective surgical resection for uncomplicated diverticulitis. In one

study of patients with uncomplicated diverticulitis treated nonoperatively, 68/81 (84%), remained asymptomatic, while 13/81 (16%) had recurrent abdominal pain at a mean follow up of 32 months [28].

Few studies are able to convincingly support elective resection for uncomplicated chronic diverticulitis. A single meta-analysis of 21 studies demonstrated higher QOL scores, fewer GI symptoms, and less chronic abdominal pain in those who had surgery for chronic and recurrent diverticulitis, compared to those who were managed nonoperatively [29]. Unfortunately none of the studies included in the meta-analysis were head-to-head comparisons of surgical vs. non-surgical management. A retrospective examination of 105 patients undergoing elective surgery for diverticulitis found that quality of life, abdominal pain, and discomfort with defecation were improved at 1 year after surgery [30]. This trend was seen in another retrospective review of 130 patients in which quality of life score was significantly improved after surgery [31]. A single prospective evaluation of 46 patients found improvement in QOL scores 3 months after surgery, which was maintained at 1 year. This study also demonstrated that improvement was most notable in patients with the lowest preoperative QOL score [32]. While these findings are worth noting, these studies only compare one subset of patients before and after surgery. In a study comparing colon resection (25/71) vs. non-surgical therapy (46/71) for uncomplicated diverticulitis, Scarpa M et al. [33], found no difference in total quality of life score or symptom frequency at median follow up of 47 months [33].

The surgeon must counsel the patient that sigmoid colectomy can negatively impact QOL as well. When compared with sigmoid colectomy for colon cancer, elective sigmoid colectomy for diverticular disease has relatively poor outcomes, and is associated with increased ostomy creation, postoperative infection, prolonged hospital stay, and increased cost [34]. A study by Levack et al. [35] found that in patients who underwent sigmoid colectomy, 24.8% reported clinically relevant fecal incontinence, 19.6% experienced fecal urgency, and 20.8% reported incomplete emptying [35]. Whether patients presented with complicated or uncomplicated disease did not seem to matter regarding persistent symptoms after elective sigmoid colectomy [36].

A Markov model simulating patients with two episodes of non-surgically managed diverticulitis found that after the third episode of diverticulitis, surgical or conservative or medical treatments provide similar quality of life adjusted years, but rates of abdominal symptoms are lower with the medical treatment strategy [37]. In the setting of uncomplicated diverticulitis, functional assessment and quality of life should be considered in deciding who would or would not benefit in elective resection surgery.

In agreement with the current ASCRS guidelines [7], the decision to recommend elective colectomy after recovery from uncomplicated acute diverticulitis should be approached on case-by-case basis [7]. The risk of recurrence, the persistence of symptoms, the patient's overall medical condition, lifestyle factors, and the quality of life should be considered against potential risks and benefits of surgery.

Complicated Diverticulitis

The decision to recommend elective surgery after resolution of an episode of complicated diverticulitis is a little more straightforward. Complicated diverticulitis includes free perforation, abscess, fistula, obstruction, or stricture. A large proportion of patients with complicated diverticulitis will ultimately undergo sigmoid resection [38] after successful medical management, where the goal is to convert an urgent or emergent operation with a high likelihood of stoma creation, into an elective procedure without an ostomy if possible.

Risk of recurrence is higher in patients with complicated diverticulitis, and has been reported as high as 46–48 % [39, 40]. If recurrence does occur, it is much more likely to be a complicated recurrence [38], and as many as 43 % who do recur will go on to require sigmoid resection [39]. A meta-analysis evaluating elective resection vs. non-operative management in the setting of diverticulitis with abscess, assessed 1051 patients across 22 studies. While 30 % of patients required urgent surgery, 35 % of patients went on to have elective surgery. Only 28 % of patients had no surgery and no recurrence [38]. In a series of 218 patients requiring percutaneous drainage for diverticular abscess, colectomy free survival was 0.17 at 7.4 years [41], meaning patients had a 17 % chance of having *no* colectomy (either emergent or elective) if they survived to 7.4 years after an episode of diverticulitis associated with abscess.

Many studies have evaluated risk factors for recurrence [22]. Risk factors include extra-luminal contrast on initial cross sectional imaging [42], abscess [38, 41, 42], extra-luminal perforation [42, 43], stenosis, and fistula [40]. One prospective study evaluated 73 patients with either mesocolicor pelvic abscesses with a mean follow up of 43 months, and found that 71 % of patients with pelvic abscess ultimately required surgery, but only 51 % of patients with mesocolic abscesses required surgery. The remaining patients were managed conservatively with success [44]. In fact presence of a pelvic abscess due to perforated diverticulitis is associated with recurrence rates up to 41 % [45].

Evaluation of subsequent morbidity and mortality due to complicated disease suggests that prior episodes of complicated disease were associated with increased risk for subsequent emergency surgery during recurrence [22]. In another large population based study, mortality for emergent resection during a second episode of diverticulitis was 4.6 % compared to an elective operative mortality of 0.3 %. Individual predictors of mortality with recurrence in this study were complicated initial presentation, age >50, and smoking [15]. These was echoed in another study where complicated diverticulitis and abscess were associated with recurrence, need for emergency surgery and increased mortality during recurrence [14].

Because of these findings including a higher risk of recurrence, and increased risk of morbidity and mortality after complicated diverticulitis, current recommendations are that elective colectomy should be strongly considered after recovery from an acute episode of complicated diverticulitis [7].

Special Populations

Historically, diverticulitis among younger patients has been associated with worse clinical outcomes, however careful review of the accumulated data does not entirely support this association. Age under 50 years does appear be associated with increased risk of recurrence [14, 18, 21–23]. However, despite a slightly higher risk of recurrence in patients <50 vs. >50 (27 % vs. 17 %) [21], younger age does not appear to predict worse outcomes [39, 46]. Specifically, risk of diverticular perforation and need for subsequent emergency colectomy in the young appears to be comparable to the risk in older age groups [23, 47]. Current recommendations are that younger patients should *not* routinely be counseled to undergo elective resection *based on age alone* [7].

While diverticulitis incidence may be similar in the immunosuppressed and the general population [48], the disease behavior is different in these groups. One systematic review [49] identified 11,966 post-transplant patients (kidney, liver, heart), across 17 different series, and evaluated the incidence of diverticulitis. It was estimated that 1.7 % of these patient experienced diverticulitis, and that approximately 40.1 % of these patients presented with complicated diverticulitis. This suggests that transplant patients are more prone to severe disease, rather than mild/moderate/uncomplicated diverticulitis [49]. Scotti et al. [50] looked at 717 kidney transplant patients, and found that while only 17 patients (2.3 %) developed diverticulitis, 9/17 (52.9 %) presented with perforated diverticulitis [50]. More severe presentation in this patient population is thought to be due, in part, to immunosuppressive medications masking early signs and symptoms of disease, and thus patients present later in the course of the disease.

Nonoperative management is more likely to fail in patients on chronic steroids or transplant medications, and a mortality rate as high as 56 % has been reported [51]. Not only are immunosuppressed patients more prone to a severe initial presentation, diverticular perforation in immunosuppressed patients is associated with higher morbidity and mortality (20–30 %) [52–56]. Other studies support the finding that immunosuppression leads to more severe bouts of diverticulitis and recurrence [16]. In a retrospective study, Chapman et al. [19], was able to show that steroid use, diabetes, and immunosuppression were associated with increased morbidity and mortality in patients presenting with complicated diverticulitis [19]. Another study demonstrated a five-fold risk of perforation during recurrent episodes for patients who were immunosuppressed, had chronic renal failure, or had collagen-vascular disease [40].

A recent study compared diverticulitis outcomes in immunocompetent vs. immunocompromised patients and found that immunocompromised patients presenting with a severe first episode of diverticulitis had significantly higher rates of recurrence and more severe episodes than their immunocompetent counterparts. Perioperative mortality in this study following emergency sigmoidectomy was 33.3 % in the immunocompromised group, vs. 15.9 % in the immunocompetent group [56]. This finding is consistent with another study [53] which demonstrated

that the morbidity and mortality for emergent/urgent surgery was increased in transplant patients compared to case-matched immunocompetent counterparts. In this same study, transplant patients undergoing *elective* surgery for diverticulitis had no difference in morbidity and mortality compared to case matched immunocompetent patients, although they did have a longer hospital stay [53].

Because of the high mortality of nonoperative management, high risk of complicated recurrence, and high mortality of emergent colectomy in immunocompromised and transplant patients, surgeons should consider "early" operative intervention in a semi-urgent/semi-elective manner during the first hospitalization for acute diverticulitis in these patients. Interestingly, this recommendation does not necessarily apply to patients receiving certain chemotherapies, who while more likely to recur with severe disease, also are much more likely to have post-operative complication (100 % vs. 9.1 %) and mortality compared to non-chemotherapy patients. These patients should be approached on a case-by-case basis [57].

While patients with end stage renal disease (ESRD) do have a much higher rate of recurrence of diverticulitis [40] than "healthy" counterparts, whether to pursue elective colectomy in this population remains controversial. A recent study by Mora-Atkin and colleagues [58], demonstrates that urgent/emergent surgery for patients with ESRD is associated with increased mortality, myocardial infarction, wound infection, length of stay and cost, compared with non-ESRD undergoing urgent/emergent colectomy. Surprisingly, these trends are similar to patients in this group undergoing elective colectomy as well [58]. Decreased risk of recurrence must be balanced against risk of surgery in patients with ESRD when recommending elective sigmoid colon resection.

Recommendations Based on the Data

1. Need for elective sigmoid colectomy following an episode of acute uncomplicated diverticulitis should be determined on a case-by-case basis, taking into account risk of recurrence, patient comorbidities, and patient lifestyle factors. (Moderate quality evidence; strong recommendation; 1B)
2. After recovery from an episode of acute complicated diverticulitis, elective colectomy should be considered, especially in settings of diverticulitis associated with pelvic abscess. (Moderate quality evidence; strong recommendation; 1B)
3. Recommending elective colon resection to patients under the age of 50 with uncomplicated diverticulitis should be individualized (low quality of evidence, moderate recommendation; 2C)
4. Immunosuppressed individuals should typically undergo elective colon resection either during or following an episode of acute uncomplicated diverticulitis, due to risk of more severe disease and higher morbidity and mortality (moderate quality evidence; strong recommendations; 1B)

Personal View of the Data

More and more patients are being referred to the surgeon for elective resection of diverticular disease, most likely due to the impression that laparoscopic surgery is easy and risk-free. While there may be less blood loss, shorter hospital stay, and lower rate of incisional hernia, the technique should not beget the procedure. The disease process has not changed, yet our understanding has evolved significantly. In the past we told patients that after two episodes it was safest to have surgery. Now we know their quality of life and complication rate is essentially no better after surgery in the setting of uncomplicated recurrent diverticulitis. I spend more time today talking patients out of surgery for uncomplicated disease than ever.

On the other hand, the evidence is compelling for resection after complication, including sizeable pelvic abscess, in select patients. If the patient is an acceptable risk for general anesthesia, I generally recommend it. That being said, I do try to minimize their risk for postoperative complication by insisting on smoking cessation and weight loss. I believe laparoscopic inspection for feasibility of minimally invasive resection should be done in the appropriate abdomen, if surgery is indicated. In other words, planning a laparoscopic resection for complicated diverticulitis is reasonable; if the induration or scarring is intense, a hand can be placed or the procedure can be converted to open, as long as this decision is made early in the course of the procedure.

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Chapter 30
Deciding on an IRA vs. IPAA for FAP

James Church

Setting the Stage

Familial adenomatous polyposis (FAP) is a dominantly inherited form of cancer predisposition due to a germline mutation in the colorectal cancer gateway gene, *APC*. The syndrome usually presents as colorectal adenomatous polyposis of varying severity, which, if untreated, will lead to colorectal cancer at a young age. While other organs are also affected by the cancer predisposition, by far the most serious threat to life and lifestyle comes from the large bowel. This is therefore the initial focus of treatment.

Patients with FAP are usually diagnosed on screening because dominant inheritance combined with 100 % penetrance makes the family history compelling. Genetic testing identifies affected family members, who begin colonoscopic surveillance at puberty. If genetic testing is not done or is uninformative, colonoscopic surveillance is the same, but is applied to every at risk relative. Patients diagnosed by screening are usually asymptomatic and the polyps are small. There is plenty of time to answer the next two important questions: what surgery and when?

About 25 % of patients with FAP do not have a family history, do not suspect the syndrome they have and the risks they carry, and ultimately present with symptoms due to relatively advanced disease [1]. These patients have a high risk of having a colorectal cancer at diagnosis, and in general have more severe disease that those diagnosed by screening. The same two questions apply however: what surgery, and when?

J. Church, MBChB, FRACS
Department of Colorectal Surgery, Sandford R. Weiss Center for Hereditary Colorectal Cancer, Cleveland Clinic Foundation, Cleveland, OH, USA
e-mail: CHURCHJ@ccf.org

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Aims of Surgery in Patients with FAP

Some studies addressing the issue of colorectal surgery in FAP seem to have lost sight of the true aims of the procedure [2, 3]. The focus tends to be exclusively on treating and preventing cancer (in particular, preventing death from cancer) while the secondary aim of lifestyle preservation is often disregarded. This leads to the preference of ileal pouch-anal anastomosis over ileorectal anastomosis for all or most patients with FAP, regardless of polyposis severity. However, when operating on young asymptomatic patients at a critical time in their social, sexual, academic, educational and psychological development, it is critical that prophylactic surgery does not cause harm. In fact, the two main surgical options are considerably different in their impact on lifestyle.

The Surgical Options

To absolutely prevent colorectal cancer, all of the colon and rectum must be removed. This leads to an end ileostomy, which is unacceptable to most patients, especially if they are young and asymptomatic. Before 1980, total colectomy and ileorectal anastomosis (IRA) was performed as a reasonable compromise, reducing the risk of cancer considerably but maintaining normal defecation. However, in patients with profuse polyposis, the risk of rectal cancer after IRA was high, as the surgery was too conservative [4]. The game changed in 1979 when the ileal pouch-anal anastomosis (IPAA) entered practice. It achieved near-complete removal of the colon and rectum while per anal defecation was preserved. Since then the IPAA has become an important option for the treatment of patients with FAP, and yet there is still debate over the indications for IRA and IPAA in patients with FAP. This chapter is devoted to a discussion of this choice and to providing guidance about making it.

How Are the Outcomes of Surgery to Be Judged?

Surgery is judged on the extent to which it achieves its aims. Prevention of cancer after surgery in patients with FAP is judged on the rate of metachronous cancer. However one of the advantages of an IRA is that the rectum can be removed at a second operation before cancer arises or before cancer has spread. In this circumstance, proctectomy can almost always be accomplished, and an IPAA can be constructed most of the time [5–7]. On the other hand patients with an IPAA are not free of cancer risk, either in the pouch- anal anastomosis, or the body of the pouch itself [8]. Anal transition zone (ATZ) cancer is more likely in patients with a stapled IPAA than a handsewn IPAA, arising from residual glandular epithelium [9, 10]. However

both types of anastomosis carry some type of risk [8, 9]. The literature is split in terms of the relative complication rates and function of stapled IPAA vs mucosectomy and hand-sewn IPAA [11–14]. However stapled IPAA is certainly easier to survey.

Quality of life, the second outcome to be considered, is difficult to measure or judge. There is often little correlation between bowel function and quality of life, as this measurement is always subjective and relative [15]. Under the best of circumstances, both IRA and IPAA can be followed by a nearly normal lifestyle. Under the worst of outcomes, life is miserable [16]. The quality of functional outcomes after IRA and IPAA depend largely on surgical skills and patient factors such as BMI, gender and compliance with follow-up. Adding to the complexity of evaluating these operations is the source of much of the information, specialty units, where there is broad experience and high skill. The relevance of these reports to the less experienced surgeon in usual practice can be debated.

Quality of Surgery

The "elephant in the room" when discussing surgery for patients with FAP is the quality of surgery, as this has a huge effect on quality of life. The stakes are high in this disease because many patients are young and are at critical developmental stages physically, emotionally, socially and academically. In addition, the majority are asymptomatic. To take a young, asymptomatic patient and leave them incontinent, impotent, or dealing with a permanent ileostomy may be considered a tragedy, especially when the operation that was so complicated was either unnecessary or too radical for the disease [16].

Both operations for FAP are technically challenging. An ileorectal anastomosis involves a difficult anastomosis between two ends of very different diameters. It is probably the most prone of intra-abdominal anastomoses to leak. An IPAA is also technically demanding, as there are multiple aspects of techniques that have to go well. There can be no tension on the small bowel mesentery. The bowel has to descend into the pelvis straight, without as much as a 90° twist to the side. The anastomosis should be at the level of the pelvic floor or below and the pelvic nerves and other organs must be protected. We have seen many poor outcomes due to suboptimal technique and have reported on some of them, including a 360 twist in the small bowel around its mesentery, an ultra-long efferent limb of small bowel from an S pouch to the anus, an IPAA 7 or 8 cm from the dentate line, incorporation of the vagina in an anastomotic staple line, and construction of a tiny pouch that holds very little stool [16]. Functional problems include passing up to 20 stools per day, severe fecal incontinence, disabling anal pain, and impotence. Surgeons should be very familiar with the technique of whichever operation they choose, or refer the patient to a high volume center. Bad outcomes have effects beyond the patient when relatives fail to be screened or to follow through on surgery out of fear of having a similar outcome.

What Do the Data Say?

A Medline and Pubmed search using the terms FAP, Familial adenomatous polyposis, surgery, ileal pouch anal anastomosis, ileo-anal anastomosis was conducted and then extended by searching by the names of those this author knew had written about the topic, going from 2015 back to 1946.

There are no randomized, prospective studies upon which to base surgical decisions in patients with FAP. Most are retrospective reviews of experience from large clinics, comparing cohorts of patients [17–22]. There is also one decision analysis [23] and one reasonable meta-analysis [24]. The decision analysis is flawed due to the weight given to the incidence of rectal cancer after IRA, many of which date back to the "pre pouch" era. Many studies of IPAA function include patients with ulcerative colitis and FAP, and should be excluded from consideration, as the diseases are so different. In addition there are few recent studies, most dating back at least 10 years. During this time surgery has changed considerably with minimally invasive techniques now almost routine [25].

Perhaps the most sensible datas on oncologic outcome of an IRA come from the Cleveland Clinic. They were the first to explain the high rates of rectal cancer after IRA as being due to the lack of surgical options prior to 1980, when IPAA entered practice [4]. When the only options are IRA or a permanent ileostomy, it is not surprising that most patients choose IRA, even those with severe polyposis. These are the patients who would go on to develop rectal cancer or advanced rectal polyposis. After 1980, patients with profuse polyposis had an IPAA and the incidence of rectal cancer after IRA dropped significantly.

The Cleveland group also set the criteria for either operation, based on rectal and colonic polyp counts at the preoperative colonoscopy [26]. Patients with <20 rectal polyps could safely have an IRA while those with >20 rectal polyps would be better served by an IPAA. These standards have stood the test of time and have resulted in an almost 50:50 ratio of IRA to IPAA in that institution [25].

While some institutions perform IPAA on every patient with FAP [2], most use criteria to select for IRA. Polyp count is the most powerful factor but others enter into the decision-making. Genotype has been suggested as a criterion for triaging patients according to the location of their mutation [27, 28]. However operating by genotype adds nothing to the use of polyp counts, as the correlation between profuse polyposis and genotype is close to absolute, and that between genotype and attenuated polyposis is also predictable. In young female patients an IRA may be selected to avoid the possibility of reduced fecundity after an IPAA. This sort of "staged" pouch (IRA first, knowing that proctectomy is likely to be needed later after childbirth) also avoids a stoma in the young, provides better bowel function during the key stages of a patient's life, and may well reduce the risk of desmoid disease [29]. It is a strategy that has become increasingly popular, especially as there is often a spontaneous decrease in rectal polyps for several years after IRA [30], and rectal polyposis can often be controlled

by aggressive endoscopy. Of course a rectum that is carpeted with adenomas, usually in a symptomatic patient, has to be removed and some patients must have an IPAA.

Studies measuring functional outcomes and quality of life after IRA and IPAA generally report similar themes: that bowel function is better after IRA than IPAA with less lifestyle restrictions and is stable over time [31–35]. IPAA function is very variable over a range of stool frequencies and continence scores. However, quality of life seems high. In many reports there is an important difference between a stapled IPAA and a handsewn IPAA with a mucosectomy. A stapled IPAA generally has better function with fewer complications than a handsewn IPAA, and is definitely easier to survey. It has twice the incidence of anastomotic and ATZ neoplasia however [9, 36]. This ATZ neoplasia can be difficult to deal with if the residual ATZ/rectal stump is over 2 cm long. A handsewn IPAA does not guarantee a neoplasia-free zone, and is trickier to survey during unsedated pouchoscopy. Some studies report good functional results with low complication rates after handsewn IPAA [2, 11–14]. If the technical ability of the surgeon can produce such results then a handsewn IPAA is a good choice. Some surgeons have better outcomes after a stapled IPAA, and this option offers the chance of an undiverted pouch. We would recommend that residual ATZ be less than 2 cm in length for easier management of neoplasia [36].

The role of surgical choice in stimulating desmoid disease is controversial. Data from the Cleveland Clinic suggest that IPAA doubles the risk of desmoid disease, and that laparoscopic IPAA is particularly desmoidogenic [29]. Others disagree and confirmatory data has not been reported to date [37, 38]. However there have been no other similar studies. It is plausible that the stretching of the small bowel mesentery that is part of an IPAA is the key factor in producing desmoid disease in the small bowel mesentery. When this is done in young women with a family history of desmoid disease, the perfect storm for desmoid formation occurs. Such patients should have an IRA.

Recommendation

Patients with <20 rectal and <1000 colonic adenomas are candidates for IRA. Patients with >20 rectal and >1000 colonic adenomas, or a curable rectal cancer on presentation, are better served with an IPAA. The IPAA can be stapled as long as the ATZ is free of adenomas and the length of the residual ATZ is minimized (<2 cm). Patients at high risk of desmoid disease should have an IRA.

Regardless of the procedure chosen, every patient should be surveyed endoscopically at least once a year.

Table 30.1 shows the advantages and disadvantages of IRA and IPAA, and the indications and contraindications for these procedures. Table 30.2 show the indications and contraindications for each operation.

Table 30.1 Indications and contraindications, advantages and disadvantages of ileorectal anastomosis and ileal pouch-anal anastomosis, in patients with familial adenomatous polyposis

	Ileorectal anastomosis (IRA)	Ileal pouch-anal anastomosis (IPAA), mucosectomy and handsewn anastomosis	Ileal pouch-anal anastomosis (IPAA), stapled anastomosis
Indications	<20 rectal adenomas Young patient High desmoid risk Woman	>20 rectal adenomas Older patient Low desmoid risk Adenomas in ATZ	>20 rectal adenomas Older patient Low desmoid risk ATZ clear of adenomas
Contraindication	Rectal cancer Uncontrollable rectal polyposis	Fecal incontinence Obese High desmoid risk	Fecal incontinence Obese High desmoid risk ATZ adenomas
Advantages	No ileostomy Low complications Good bowel function Low risk of desmoid disease	Minimal risk of rectal cancer Per anal defecation No urgency Low risk of ATZ neoplasia	Minimal risk of rectal cancer Per anal defecation No urgency Minimal seepage/incontinence
Disadvantages	Risk of rectal cancer	Temporary stoma Higher complication rate, both early and late Abnormal bowel function with seepage and incontinence High risk of desmoid disease Risk of ATZ polyps and cancer	High risk of ATZ neoplasia

Table 30.2 The outcomes of ileorectal anastomosis and ileal pouch-anal anastomosis: a literature review

Study	Variable	IRA	IPAA	P
Campos et al. (2009) N = 88 1977–2006	Complications Cancer	19.0 % 16.6 %	48.1 % 3.8 %	0.03
Gunter et al. (2003) N = 151 1970–2000				
Soravia et al. (1999) n = 131 1980–1997	Anastomotic leak Bowel obstruction Function	3 % 15 % Less nighttime stooling, better continence, less skin irritation	12 % 24 %	0.21 0.58
Bjork et al. (2001) n = 131 1984–1996	Complications Function	26 % Less night time stooling, better continence, less skin irritation	40 %	<0.05
Vasen et al. (2001)	Cancer	Risk of death from cancer 12.5 % by age 65	Increase in life expectancy by 1.8 years	
Koskenvuo et al. (2014)	Secondary proctectomy Anus preservation rate during secondary proctectomy Cancer rate	39/140 49 % 24 % at 30 years		
Niewenhuis et al. (2009)	Secondary proctectomy by genotype Attenuated Intermediate Severe	10 % 39 % 61 %		
Ko et al.	Bowel movements per day Leakage Pads usage Perianal skin problems Food avoidance Inability to distinguish gas	5.2 0 0 7 % 43 % 7 %	7.5 43 % 17 % 33 % 80 % 37 %	<0.05 0.01 <0.01 <0.01 <0.01 <0.01
Wuthrich	Soiling >6 bowel movements/24 h		25 % 67 %	

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Chapter 31
Rectal Prolapse: What Is the Best Approach for Repair?

Saleh Eftaiha and Anders Mellgren

Introduction

Rectal prolapse can be repaired through an abdominal or perineal approach. Choosing between these approaches has traditionally focused on patient age and comorbidities; younger, healthier patients undergo an abdominal procedure while elderly patients often receive a perineal procedure [1, 2]. In North America, abdominal repair is frequently carried out with laparoscopic posterior rectopexy, with or without resection, while perineal repair is performed with an Altemeier procedure. Meanwhile, in Europe, and laparoscopic ventral rectopexy takes precedence as the preferred abdominal repair and the Delorme procedure is utilized more frequently [2].

However, solely using a framework of abdominal vs. perineal approach infers an oversimplification of the principles and choices for the surgical correction of rectal prolapse. As we consider the available approaches, we inevitably encounter different operations associated with each approach: suture posterior rectopexy, with or without resection, vs. ventral rectopexy and the Altemeier procedure vs. the Delorme procedure. There is a paucity of high quality evidence regarding the optimal surgery for the treatment of rectal prolapse [3]. In our examination of the literature, we have included findings of two Cochrane reviews (2000 and 2008), two additional systematic reviews, two nonrandomized control trials (NRCT), seven randomized control trials (RCT), and a number of retrospective reviews.

The PROSPER trial, a multicenter RCT primarily based in the United Kingdom, represents the largest and most ambitious exploration in the choice of procedure for rectal prolapse. It included a power analysis and revealed a method of randomization. This trial, however, did not explicitly state whether the assessors were blinded

S. Eftaiha, MD • A. Mellgren, MD, PhD (✉)
Division of Colon & Rectal Surgery, University of Illinois Chicago, Chicago, IL, USA
e-mail: afmellgr@uic.edu

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and the trial was underpowered. The majority of the other reported RCT's were performed in a single center, often did not carry out a power analysis, usually included less than 50 patients, and frequently did not state method of randomization. One of them was limited to 6 months of follow-up [27]. With these methodological weaknesses in mind, the present assessment aimed to evaluate different types of rectal prolapse repair and review different types of outcomes including recurrence rates, function, quality of life and morbidity.

Search Strategy

The following broad PICO terms were used: patients with rectal prolapse, abdominal approach, and perineal approach, outcomes including recurrence of prolapse, functionality, quality of life, morbidity and mortality (Table 31.1).

Pubmed/Medline, Cochrane databases were searched for relevant articles including meta-analysis and systematic reviews. The following keywords and phrases were used in various combinations: 'rectal prolapse', 'procidentia', 'Altemeier', 'Delorme', 'open', 'laparoscopic', 'rectopexy', 'resection', and 'abdominal approach procidentia/prolapse', 'perineal approach procidentia/prolapse.' All articles identified within the initial search were screened for relevance and content, and their references were searched for additional relevant articles. Articles not written in English, retrospective series under 40 patients, and case reports were excluded.

Results

Abdominal Verses Perineal Approach

Recurrence Rates

Abdominal procedures usually considered to have a lower recurrence rate than perineal procedures, but this is not demonstrated in RCTs. There are two RCTs assessing the abdominal vs. perineal approach. The PROSPER trial [1] randomized 23

Table 31.1 PICO table utilized

Patient population	Intervention	Comparator	Outcomes
Patients' with rectal prolapse	Abdominal approach to correction of prolapse	Perineal approach to correction of prolapse	Recurrence of prolapse Functional outcomes
			Quality of life
			Morbidity
			Mortality

patients to abdominal procedures (suture posterior rectopexy and posterior rectopexy with resection) and 26 patients to perineal procedures (Altemeier and Delorme). The group allocation was controlled for age, ASA status and preoperative bowel function, with a median length of follow up of 36 months. Although underpowered, there was no statistical significance between abdominal (26%) and perineal (20%) operations regarding the incidence of recurrence (p=0.8). In addition, PROSPER performed a *non-randomized* comparison between abdominal and perineal procedures, with reported recurrence rates of 13/68 (19%) vs. 56/202 (28%) respectively (p=0.2). This is a higher abdominal recurrence rate (19-26%) than previously quoted in the literature (~10%). In another RCT, Deen et al. [4] allocated ten patients to each arm and median follow-up was 17 months. They reported no recurrence in the abdominal group and one recurrence in the perineal procedure group (NS). A third RCT from Germany comparing posterior rectopexy with resection and Delorme is ongoing and results are pending [5].

The University of Minnesota group reported their experience in one of the largest retrospective reviews in the literature [6]. They compared abdominal procedures (posterior rectopexy with and without resection) and perineal procedures (Altemeier or Delorme). Patients in the perineal group were significantly older and sicker (p=0.001) and had shorter recurrence free survival than the abdominal group (p=0.0001). The authors reported significantly lower recurrence rates after abdominal vs. perineal procedures (5% vs. 16%), despite longer follow up in the abdominal group (98 vs. 47 months respectively; p=0.002; Table 31.2). Recurrences were usually seen within 3 years, regardless of the type of procedure.

Lee et al. [7] reported similar results in a retrospective review of 104 patients, noting more recurrences after perineal (15%) than abdominal (6.3%) procedures (p=0.14). Yakut et al. [8] retrospectively looked at 94 patients and reported no recurrences after abdominal procedures (0/67) and four recurrences in 27 patients undergoing Delorme procedures (p<0.01; Table 31.2). A smaller 10 year retrospective review from Ochsner Clinic [9] reported a higher incidence of recurrences after perineal procedures (16%) compared to abdominal approach (8%). However, this was not significant, possibly because of the small sample size.

Table 31.2 Abdominal vs. perineal proctectomy recurrence rates

Study (year)	Type	Quality	Patients (N)	Abdominal (N)	Perineal (N)	Follow up (months)	P value
PROSPER (2013)	RCT	Moderate	49	5/19 (26%)	5/25 (20%)	36	0.8
PROSPER (2013)	Non-RCT	Moderate	270	13/68 (19%)	56/202 (28%)	36	0.2
Deen (1994)	RCT	Low	20	0/10	1/10 (10%)	17	NS
Kim (1999)	RR	Moderate	359	9/176 (5%)	29/183 (16%)	98, 47 (P)	0.002
Yakut (1998)	RR	Low	94	0/67	4/27 (15%)	36	<0.01
Hammond (2007)	RR	Low	75	1/13 (8%)	10/62 (16%)	39	0.7
Lee (2014)	RR	Low	104	4/64 (6.3%)	6/40 (15%)	60	0.14

RCT randomized control trial, *RR* retrospective review, *NS* not significant, *P* perineal

Function and Quality of Life

The PROSPER trial [1] reported significant improvements from baseline for incontinence (Vaizey score), bowel function and quality of life (EQ-5D) after abdominal and perineal procedures, without significant differences between the groups. However, it is noteworthy that patients with a recurrence of their prolapse had significantly worse quality of life (p = 0.0009). In the abdominal arm, patients reported significantly increased 'straining', possibly related with constipation.

Deen et al. [4] reported that the perineal group had greater residual fecal incontinence (OR 13.50) and significantly lower maximal resting and squeeze pressures on manometry (p = 0.003; Table 31.3).

Mirroring PROSPER's findings, Madoff and coworkers [6] large retrospective series noted improvement in continence, constipation, and overall satisfaction following both abdominal and perineal procedures, without significant differences between the two groups. However, Lee et al. [7] reported higher rates of persistent constipation following abdominal procedures (20.3 %) than after perineal procedures (15 %; p = 0.49), while perineal procedure patients struggled more often with persistent fecal incontinence (p = 0.054).

Yakut et al. [8] noted that both the abdominal (posterior rectopexy with and without resection) and perineal (Delorme) were effective treatments for rectal prolapse. They reported, however, a significant risk for sexual dysfunction in males (retrograde ejaculation and/or impotence) after posterior rectopexy, likely secondary to the pelvic dissection [8, 10].

Sexual dysfunction and persistent constipation may be more frequently encountered after abdominal procedures, while persistent incontinence may be more frequently encountered after perineal procedures.

Table 31.3 Abdominal vs. perineal functional outcome and morbidity comparison

Study	Type	Quality	Patients	Incontinence	Constipation	QOL[a]	Morbidity
Prosper (2013)	RCT	Moderate	49	Abd = Per (P = 0.5)	–	Abd = Per (P = 0.5)	–
Deen (1994)	RCT	Low	20	Abd < Per[b]	–	–	Abd > Per (P = NS)
Kim (1999)	RR	Low	359	Abd < Per (P = NS)	Abd > Per (P = NS)	Abd = Per[c] (P = NS)	Abd > Per (P = NS)
Lee (2014)	RR	Low	104	Abd < Per (P = 0.054)	Abd > Per (P = 0.49)	–	Abd > Per (P = 0.40)
Young (2015)	RR	Moderate	3,254				Abd > Per (P = 0.03)

Abd abdominal procedure, *Per* perineal procedure, *RCT* randomized control trial, *RR* retrospective review, *QOL* quality of life

[a]EQ-5D

[b]OR13.5; 95 % CI (1.2–152.2)

[c]Patient satisfaction, not validated QOL score

Morbidity and Mortality

There has been no significant difference in mortality in RCT or large retrospective reviews comparing abdominal and perineal procedures [1, 6, 7, 11, 12]. Morbidity is more frequent after abdominal procedures with longer length of stay, especially after open procedures. Morbidity reported in the PROSPER trial included four anastomotic leaks after Altemeier procedures, three of which were reported by one center. Deen et al. [4] reported prolonged ileus (n = 2), wound infection (n = 1), and anastomotic stricture (n = 1) following posterior rectopexy with resection [11]. Madoff and coworkers [6] reported bowel obstruction (n = 21) and anastomotic complications, such as leak, bleeding, and stricture (n = 7). Lee et al. [7] reported more frequent morbidity in the abdominal group, although not statistically significant, when compared to perineal resections (p = 0.40). Young et al. [12] evaluated 30 day NSQIP morbidity data after abdominal vs. perineal procedures in 3,254 patients of abdominal and found an increased morbidity after open posterior rectopexy with resection when compared to perineal procedures (OR: 1.89, p = 0.03; Table 31.3). Length of postoperative stay has been consistently shown to be significantly shorter after perineal procedure than after abdominal procedures [6, 7, 9, 11, 12].

Altemeier Verses Delorme's Procedure

Recurrence Rates

Recurrence rates after Altemeier and Delorme procedures range vastly in the literature. In retrospective reviews with at least 40 patients, the recurrence rates range between 3–18 % after Altemeier procedures and 6–26 % after Delorme procedures [6, 13–17]. Follow-up in different series varied, up to 60 months, and recurrence rates tended to be higher with longer follow-up.

The only RCT to compare recurrence rates between the two perineal approaches is the PROSPER trial [1]. With 36 month follow up data and controlling for age and ASA status, there were fewer recurrences after Altemeier procedures (24/102; 24 %) than after Delorme procedures (31/99; 31 %; p = 0.4; Table 31.4).

Elagali et al. [18] recently compared recurrence rates between these two procedures and reported a significantly higher recurrence rate after Delorme procedures (16 % vs. 9 %; p = 0.07) with 13 months of follow-up in a retrospective study. Agachan et al. [19] reported no significant difference in recurrence rates between Delorme procedures and Altemeier procedures without levatorplasty. Patients with a concurrent levatorplasty at time of Altemeier procedure had a lower recurrence rate (p < 0.05). Concurrent levatorplasty has been shown to improve continence as well. Chun et al. [20] supported this finding in a retrospective review, noting significantly reduced recurrence rates (p = 0.05) and improved continence (p = 0.002) with

Table 31.4 Altemeier vs. Delorme recurrence rate comparison

Study	Type	Quality of evidence	Pts (N)	Altemeier (N)	Delorme (N)	Follow-up (months)	P value
PROSPER (2013)	RCT	Moderate	201	24/102 (24%)	31/99 (31%)	36	P=0.4
Elagili (2015)	RR	Low	75	2/22 (9%)	9/53 (16%)	13	P=0.07
Agachan (1997)	RR	Low	61	5/53 (9%)	3/8 (38%)	27	P=NS

RCT randomized control trial, *RR* retrospective review, *NS* not significant

the addition of levatorplasty with perineal proctectomy, when compared to perineal proctectomy only. Of historic interest, Dr. Altemeier originally described a concurrent levator plication with the proctectomy [13], but this has not always been used after the procedure was 're-introduced' in the 1980s and 1990s by Gopal, Eftaiha et al. and Prasad et al. [21–23]. With respect to hand sewn vs. stapled anastomosis when performing the Altemeier technique, Boccasanta et al. [24], randomized 20 patients in each arm and found no significant difference in recurrence between the two techniques.

Function and Quality of Life

Quality of life after rectal prolapse surgery is important and is more frequently reported in the recent literature. The PROSPER trial [1] randomized Altemeier (n=102) and Delorme (n=99) cohorts. They found an overall improvement in quality of life (EQ-5D), overall bowel function and continence (Vaizey score) after 36 months of follow-up, without any statistical significance between both groups (Table 31.5). The only significance noted is an increased number of outpatient visits in the Delorme group (unknown reason) ($p<0.01$) [1]. Elagali et al. [18] retrospectively looked at QOL after both procedures without noticeable differences between the groups, or from baseline. Agachan et al. [25] reported resolution of postoperative constipation.

Morbidity and Mortality

Anastomotic complications are more frequently encountered after Altemeier than after Delorme procedures (Table 31.5). As previously mentioned, anastomotic leaks constituted the most severe morbidity with the Altemeier procedure in the PROSPER trial [1]. Agachan et al. [25] reported significantly higher complications in the Altemeier group when compared to Delorme, secondary to anastomotic leaks after perineal proctectomy ($p<0.05$). In a recent retrospective series, Elagali et al. [18] found significantly higher complication rates after Altemeier procedures when compared to Delorme procedures ($p=0.04$). They reported an 18% leak rate after Altemeier, but no mortality was recorded.

Posterior Rectopexy Without or With Resection

Recurrence Rates

Three RCTs have compared recurrence rates after posterior rectopexy with or without resesction [1, 26, 27]. In the PROSPER trial [1], posterior rectopexy with resection had fewer recurrences than posterior rectopexy without resection at 36 month follow up. However, this difference was not statistically significant (p = 0.2; Table 31.6). Mckee et al. [26] randomized nine patients each to posterior rectopexy with or without resection and they reported no recurrences in either group at 20 month follow-up. Luukkonen et al. [27] randomized 15 patients in each arm, comparing posterior rectopexy with resection vs. posterior rectopexy with mesh and found no recurrences in either group. Follow-up was limited to six months. Sayfan et al. [28] reported no recurrences in 29 patients in a non-randomized trial. Raftopoulos et al. [29] evaluated recurrence rates after abdominal procedures for prolapse in a 643 patient multicenter, systematic review. They concluded that surgical technique (posterior mobilization only, posterior rectopexy with and without resection), means of access (laparoscopy vs. open), and method of posterior rectopexy had no impact on

Table 31.5 Altemeier and Delorme procedure functional outcome and morbidity

Study	Type	Quality	Incontinence	Constipation	QOL	Morbidity
PROSPER (2013)	RCT	Moderate	Alt = Del (P = 0.8)	–	Alt = Del[a] (P = 0.6)	–
Elagili (2015)	RR	Low	Alt > Del (P = 0.72)	Alt > Del (P = 0.42)	Alt = Del[b] (P = 0.59)	Alt > Del (P = 0.04)
Agachan (1997)	RR	Low	Alt < Del (P = NS)	Alt = Del (P = NS)	–	Alt > Del[c] (P < 0.05)

Alt Altemeier procedure, *Del* Delorme procedure, *RCT* randomized control trial, *RR* retrospective review, *NS* not significant

[a]EQ-5D quality of life survey

[b]Cleveland Global Quality of Life survey

[c]Difference seen with leak & stricture rates, highest with perineal rectosigmoidectomy without levatorplasty

Table 31.6 Recurrence rates after posterior rectopexy without and with resection

	Type	Patients	Quality	Suture (N)	Resection (N)	Follow up (months)	P-value
PROSPER (2013)	RCT	39	Moderate	9/35 (26 %)	4/32 (13 %)	36	0.2
Luukkonen (1992)	RCT	30	Low	0/15	0/15	6	NS
McKee (1992)	RCT	18	Low	0/9	0/9	20	NS
Sayfan (1990)	NRCT	29	Low	0/16	0/13	?	NS

Suture suture rectopexy without resection, *Resection* resection rectopexy, *RCT* randomized control trial, *NRCT* non randomized control trial, *NS* not significant

recurrence of prolapse. Laparoscopy did not infer an increase in recurrent prolapse. The study highlighted that the recurrence increases with time and the 1, 5, and 10 year recurrence rates were 1 %, 7 % and 29 % respectively.

Function and Quality of Life

The PROSPER trial [1] found that continence, bowel function and quality of life improved regardless of whether resection was performed with posterior rectopexy. Patients undergoing sutured posterior rectopexy reported more frequent usage of laxatives (Table 31.7). Other reports have demonstrated less postoperative constipation when posterior rectopexy is combined with resection [26, 27]. Sayfan et al. [28] reported similar findings in a non-randomized trial, describing increased rates of constipation rates following mesh posterior rectopexy than after posterior rectopexy with resection ($p < 0.05$). The majority of patients in both groups experienced an improvement in continence and there was no statistically significant difference between the groups in regards to continence [26, 27].

Morbidity and Mortality

Mortality was observed in two patients across all three RCTs, including one patient in the resection group and the other in the posterior rectopexy without resection group [1, 27]. The morbidity seen in posterior rectopexy with resection included two anastomotic strictures [27]. There was no statistical significant difference in morbidity or mortality whether posterior rectopexy was performed with or without resection [1, 26–28]. However retrospectively, Lee et al. [7] observed an increase in anastomotic morbidity in the group of patients undergoing resection ($p = 0.009$) [7].

Table 31.7 Functional outcome and morbidity after posterior rectopexy with or without resection

Study	Type	Quality	Incontinence	Constipation	QOL	Morbidity
PROSPER (2013)	RCT	Moderate	RR = R (P = 0.7)	R > RR[a] (P = 0.05)	RR = R (P = 0.1)	–
Luukkonen (1992)	RCT	Low	RR > R (P = NS)	R > RR (P = 0.04)	–	RR = R (P = NS)
McKee (1992)	RCT	Low	RR > R (P = NS)	R > RR[b] (P = 0.06)	–	–
Sayfan (1990)	Non RCT	Low	RR > R (P = NS)	R > RR (P = NS)	–	RR = R (P = NS)
Lee (2014)	RR	Low		–	–	RR > R (P = 0.009)

RR resection rectopexy, *R* rectopexy (mesh/suture), *RCT* randomized control trial, *NS* not significant
[a]Higher use of laxatives reported in the rectopexy group
[b]Data combined from Luukkonen and McKee p = 0.003; OR0.07 95 % CI 0.01–0.4

Laparoscopic Verses Open Rectopexy

Laparoscopic posterior rectopexy has been evaluated in two RCTs [30, 31]. A total of 61 patients were randomized to laparoscopic mesh posterior rectopexy (n = 28) and open mesh posterior rectopexy (n = 32). There were no significant differences detected in recurrence rates, with two recurrences in the open group, one of which was mucosal recurrence [30, 31]; the combined mean follow up was 26 months. Laparoscopic mesh posterior rectopexy was associated with longer operative time, but shorter length of stay ($p < 0.05$) when compared to open cohorts [30, 31]. Continence was improved, without any significant difference between the groups. Open posterior rectopexy significantly increased cardio-respiratory postoperative morbidity compared to laparoscopic cohorts ($p < 0.01$) [31]. There was a trend towards new onset constipation in the open group compared to the laparoscopic group, however this was not significant [30]. Cost was lower with the laparoscopic vs. open procedure ($p < 0.01$) across two different healthcare systems (USA and Australia) [30–32].

Ventral Rectopexy

Laparoscopic ventral rectopexy with mesh is a relatively new abdominal approach for the correction of rectal prolapse [33]. Data regarding this procedure is mostly limited to non-randomized retrospective case series and systematic reviews. The observed recurrence rate ranges between 5-15 % at a median follow-up of 3-61 months [34].

Functional outcomes indicate significant improvements in continence and constipation in the majority of patients. Significant quality of life improvement was documented in a 31 patient prospective review [35] at 1 year follow-up ($p < 0.01$).

The mesh erosion rate was reported at 2 % over a 14 year span in a systemic multicenter review of 2,200 laparoscopic ventral rectopexy; there was no significant differences if using biologic or synthetic mesh [36]. Mortality at 30 days was reported at 0.1 %. As there is a propensity for laparoscopic ventral rectopexy in Europe and laparoscopic posterior rectopexy with resection in North America, results from a non-randomized, multi-institutional international trial comparing the two approaches is ongoing (LaProS study) [2].

Recommendations

- Correction of rectal prolapse through an abdominal approach connfers less recurrence (although higher than previously reported) compared to a perineal approach. However, consideration should be given to perineal procedures in frail patients as morbidity is lower with acceptable function and quality of life. (Evidence quality moderate; conditional recommendation).

- Abdominal approaches can be performed with laparoscopy with similar outcomes. (Evidence quality moderate; strong recommendation).
- Posterior rectopexy with resection and ventral rectopexy have acceptable recurrence rates and improve both quality of life and bowel function. Sutured posterior rectopexy without resection may carry an increased risk for postoperative functional problems, but avoids the risk of anastomotic dehiscence or mesh complications. (Evidence quality moderate; strong recommendation).
- If the perineal approach is chosen, both the Altemeier and Delorme procedures are acceptable in terms of recurrence, functional outcome and quality of life. Although there is a trend towards less recurrence and higher quality of life following Altemeier procedures, there is an increased risk for postoperative morbidity when compared to the Delorme procedure. (Evidence quality low; conditional recommendation).
- Concurrent levatorplasty with Altemeier procedure should be performed. (Evidence quality moderate; strong recommendation).

Personal View

- Women with rectal prolapse have a significant incidences of concomitant genital prolapse and we therefore recommend that the majority of patients undergo a pelvic evaluation by a urogynecologist before proceeding with surgical repair.
- Abdominal approach is preferred for a majority of patients, because of a lower risk for recurrence. Perineal approaches are usually reserved for elderly patients or patients with significant comorbidities.
- The Altemeier procedure is chosen for a majority of patients operated with a perineal technique. The Delorme procedure is reserved for patients with a small prolapse.
- The risk for sexual dysfunction should be discussed with young males with rectal prolapse. This risk is lower with perineal procedures, but will need to be weighed against the higher risk for recurrence.
- Posterior rectopexy can be performed with laparoscopic, robotic or open technique. We prefer open technique using a pfannenstiel incision or robotic technique. These two techniques provides a good mobilization combined with a stable suspension.
- Posterior rectopexy with resection is reserved for patients with significant preoperative constipation, because of the risk for anastomotic problems. Ventral rectopexy is an intriguing alternative for these patients (please see below).
- Ventral rectopexy is an intriguing alternative for rectal prolapse repair, because of improved functional outcome in recent studies. This surgery can be performed with open, laparoscopic or robotic technique. We prefer using the robot, which offers excellent visualization combined with excellent ability for suturing. Patients need to be counseled about the risks with pelvic mesh. We prefer using biologic mesh, which may have a better risk profile, but could increase the risk for recurrence.

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Part VI
Benign Anal Disease

Chapter 32
Optimal Management of the Transsphincteric Anal Fistula

Richard T. Birkett and Jason F. Hall

Introduction

Management of transsphincteric fistulas can pose a difficult challenge for surgeons. The goal is to cure the fistula while retaining functional capacity of the sphincter complex. The Parks system is the classic classification system, which divides fistulas into five types: intersphincteric, transsphincteric (high and low), suprasphincteric, and extrasphincteric (Fig. 32.1), based on the course of the track in relation to the anal sphincter complex [2]. Goals of management include eradicating sepsis, promoting healing of the fistula tract, maintaining continence through preservation of the sphincter complex, and preventing future recurrence. Simple submucosal, intersphincteric, and low transsphincteric fistulas can be managed effectively with conventional fistulotomy and represents the gold standard comparator owing to low incontinence and recurrence rates [3]. However, transsphincteric fistulas cross through the internal and external sphincter, predisposing patients to higher rates of incontinence following fistulotomy. Therefore, a number of alternative approaches have been developed to tackle these complex fistulas although no consensus algorithm for management exists.

In this chapter, the data regarding sphincter-saving approaches to complex transsphincteric fistulas is reviewed. We discuss the following techniques in our review:fistulotomy, seton placement, fibrin glue, plug, endorectaladvancement flap (ERAF) and ligation of the intersphincteric fistula tract procedure (LIFT). Our recommendations are based on data presented in Table 32.1, comparing fistulotomy,

R.T. Birkett, MD
Lahey Hospital and Medical Center, Burlington, MA, USA
e-mail: jason.f.hall@lahey.org

J.F. Hall, MD, MPH, FACS (✉)
Department of Surgery, Boston Medical Center, Boston, MA, USA

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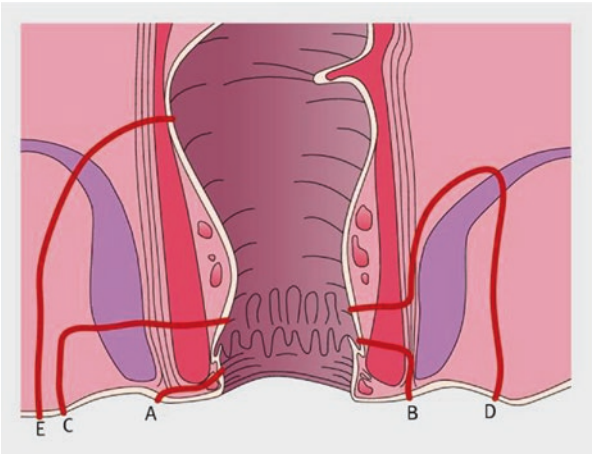

Fig. 32.1 Parks classification (*A*) superficial fistula (*B*) intersphincteric fistula (*C*) transsphincteric fistula (*D*) suprasphinteric fistula (*E*) extrasphincteric fistula (From Simpson et al. [1])

plug, ERAF and LIFT. In addition, we comment on the experience at our institution and our personal approach to this problem (Table 32.2).

Search Strategy

We performed a literature search in the MEDLINE database (using PUBMED) under the search titles "transsphincteric fistula" or "fistula-in-ano". We initially focused on prospective trials randomized studies. Further mining was performed using the reference lists of published systematic reviews. Given the lack of randomized trials involving all treatment interventions, especially the LIFT procedure, we did include multicenter prospective observation studies and multicenter center retrospective review studies. Although discussed in text, we excluded meta-analyses, single-surgeon reviews, single-surgeon observational studies and those published in foreign languages.

Results

Fistulotomy

Fistulotomies are performed by unroofing the track between the internal and external openings (Fig. 32.2). Reported recurrence rates are low. A zero recurrence rate was reported by a single surgeon case series of 38 patients over 5 years [17]. A more recent multicenter retrospective review of 537 patients undergoing fistulotomy for low perianal fistula reports a primary healing rate of 83.6 %, 81.7 % for transsphincteric, and a secondary healing rate of 90.3 % after treatment for recurrence [4].

Table 32.1 Summary of evidence

Author (year)	Population	Procedure	N	Median follow-up	Success	Function	
						change post-op	Between groups
Gottgens [4] (2015)	Low transsphincteric	Fistulotomy	164	38.9 months (6–74.8)	134 (81.7 %)		
Abramowitz [5] (2015)	Low transsphincteric	Fistulotomy	93	12 months		=	
	High transsphincteric	Seton + staged fistulotomy	59			–	
Schwander [6] (2009)	Transsphincteric after seton	Plug	66	12 months	37 (62 %)	=	
Stamos [7] (2015)	Complex transsphincteric	Plug	55	12 months	49 %	+	
Perez [8] (2006)*	High transsphincteric & suprasphincteric	Fistulotomy	28	38 months (24–52)	26 (92.8 %)	=	=
		ERAF	27		25 (92.5 %)	=	
Ortiz [9] (2009)*	High transsphincteric	Plug	15	12 months	3 (20 %)		
		ERAF	16		14 (87.5 %)		
Van Koperen [10] (2011)*	High transsphincteric	Plug	31	11 months (5–27)	9 (29 %)	=	=
		ERAF	29		14 (48 %)	=	
Hall [11] (2014)	Low tanssphincteric	LIFT	17	3 months	14 (82 %)	+	
	High transsphincteric		19		15 (79 %)	+	
Sileri [12] (2014)	Complex fistulas	LIFT	26	20 months (16–24)	19 (73 %)	=	
Han [13] (2015)*	Transsphincteric	LIFT	118	6 months	99 (83.9 %)	=	=
		LIFT-Plug	117		110 (95 %)	=	
Madbouly [14] (2014)*	High transsphincteric	ERAF	35	12 months	23 (65.7 %)	=	=
		LIFT	35		26 (74.3 %)	=	
Mushaya [15] (2012)*	Transsphincteric or complex	ERAF	14	19.2 months (1.7–32.2)	13 (92.9 %)	=	=
		LIFT	25		23 (92 %)	=	

*Randomized study; + improvement incontinence score; – worsening incontinence score; = no statistic difference in incontinence score

Table 32.2 Comparison of available approaches for management of transphincteric fistulas

Pt population	Intervention	Comparator	Outcomes studied
Patients with transsphincteric fistulas	Fistulotomy	Sphincter saving approach	Cure, continence

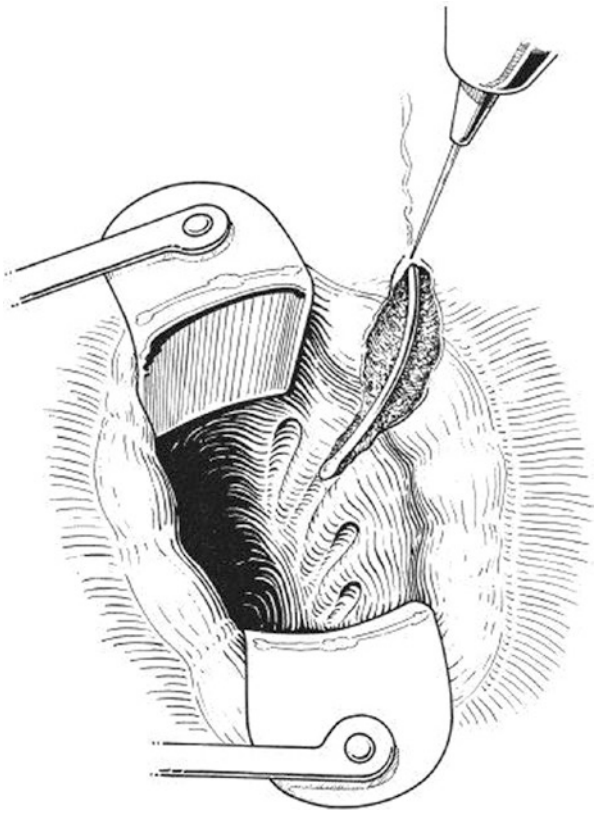

Fig. 32.2 Fistulotomy (Fischer et al. [16])

Incontinence rates following fistulotomy depends on both the amount of muscle divided at the time of operation as well as any preexisting sphincter damage. Although Gottgens et al. reported a major incontinence rate of 28 %, the risk of incontinence in simple fistulas is very low. Abramowitz et al. described only a 1-point increase in Wexner score postoperatively after 1 year in patients undergoing fistulotomy for low fistula with a reported score ≤5 in 69 %. However, the median Wexner score worsened by 3 points for patients with high transsphincteric fistulas, which was statistically significant [5].

Setons

Setons are the oldest recorded surgical approach to fistula management, first described by the Indian Surgeon Shushruta 1200 BC. A seton serves to drain sepsis, enables preservation of the sphincter mechanism and can prepare the patient for a two-stage procedure. A draining seton prevents the internal and external orifices of the fistulas from closing, allowing infection to dissipate. Cutting setons enable slow division of a fistula tract by pressure necrosis of the intervening tissue. Because the division is slow, it is postulated that this leads to greater fibrosis without a significant gap in the sphincter complex.

Short-term healing rates with draining setons have been reported to be between 44 and 83 % [18]. These durability of these results must be questioned as draining setons do little to alter the underlying anatomy and physiology of a fistula tract. While they may reduce symptoms, it is doubtful that they lead to eradication of the fistula tract in any circumstance. A recent retrospective analysis of 121 patients with transsphincteric fistulas reported a 98 % healing rate with cutting setons. Preoperatively, 23 (19 %) of the patients reported incontinence to feces or gas. At follow-up, only 14 (11.6 %) reported seepage of stool or loss of flatus control, 0 and none experienced major continence issues. Of the initial 23 patients that reported continence disturbances preoperatively, symptoms had resolved in 17 patients after surgery (73.9 %). New onset incontinence did occur in eight patients, but all denied change in lifestyle or the need to wear a pad [19].

Although cutting setons have been reported to be effective, their use has been limited due to concerns about subsequent fecal incontinence. A large review of multiple studies on cutting setons including over 500 patients reported an average incontinence rate of 32 % across all types of fistulas and 20.5 % when used for transsphincteric fistulas. However, the definitions and grading of incontinence were missing in over a third of the studies [20]. A UK position statement described similar results with incontinence rates ranging up to 62 % including major incontinence in 10 % reported in seven studies reviewed [21]. Additionally, one must account for the need of interval tightening and associated discomfort caused by cutting setons.

Advancement Flaps

ERAF is an alternative option to avoid division of the sphincter complex. A semicircular flap or U-shaped flap of mucosa, submucosa and a few muscle fibers is raised from the level of the dentate line over a distance of 4–5 cm proximally. The flap is then lifted to expose the fistula tract, which is cored out and the associated muscle defect is sutured closed. The flap is then advanced down to the dentate line and anchored with absorbable sutures.

A recent meta-analysis of 35 studies reported an 80.7 % success rate and 13.2 % incontinence rates for cryptoglandular fistulas, although the quality of the reports

were low [22]. A study on long-term outcomes of advancement flaps in high transsphincteric, suprasphincteric and extrasphincteric fistulas reports a meager success rate of 37 % with a mean follow-up of 72 months [23]. Although this study accumulated a reasonable sample size, it is a single-center observational study and the fistula etiology was Crohn's disease in more than a quarter of the patients. Perez et al., conducted a randomized, prospective trial randomizing 55 patients with high transsphincteric fistulas and suprasphincteric fistulas to ERAF or fistulotomy with sphincter reconstruction and found no difference in recurrence or incontinence rates. The success rates in both groups remarkably exceeded 92 % and there was no change in continence scores between groups [8]. Additional studies comparing ERAF to LIFT will be discussed later in the chapter. The best reported outcomes have been associated with a full-thickness flap in conjunction with fistulectomy, without fibrin glue or preliminary draining seton [24].

Biologic Products

Fibrin glue is another sphincter-sparing option for complex fistulas, however, success rates generally appear to be poor. The glue is a combination of fibrinogen, thrombin and factor XIII which cross-links with collagen in the tissue, sealing the tract and stimulates the growth of fibroblasts and pluripotent endothelial cells promoting collagen deposition and wound healing.

One study looking at long-term results of fibrin glue over an average of 22 months after seton drainage, reported an initial closure rate of 60 % which increased to 69 % with retreatment [25]. In contrast, Buchanan et al. found successful healing in only 3 of 22 patients (14 %) with complex fistulas with fibrin glue after tract curettage [26].

An alternative to fibrin glue is a synthetic anal fistula plug. The plug rolled into a conical configuration, then secured into the primary opening of the fistula tract to promote healing. Schwander et al. followed 66 patients in a multicenter study over 12 months with transsphincteric fistulas treated with seton placement followed by anal fistula plug 8 weeks later and reported a 62 % success rate [6]. A more recent multicenter study of cryptoglandular transsphincteric anal fistulas included 55 patients from 11 centers and reported a 12-month healing rate of 49 %; all had significantly improved Wexner scores by 6 months. There were 8 total and 5 partial plug extrusions [7].

Ortiz et al. compared ERAF with anal fistula plugs. The study was cut short secondary to high recurrence rates in the plug arm whereas only 2 of 116 patients treated with ERAF had recurrence [9]. These results were confirmed in another double-blinded multicenter trial which found a recurrence rate of 71 % using fistula plug vs 52 % with ERAF, although this was not a significant difference given the number of patients completing the study. Interestingly, there were no differences in post-operative pain or incontinence scores [10]. The plug procedure has been abandoned by many owing to poor results.

LIFT Procedure

The LIFT procedure was first described by Rojanasakul et al. in 2007 [27]. The procedure involves dissection in the intersphincteric plane to define and encircle the fistula tract. The fistula is then ligated without division of the sphincter complex. The mean success rate at 10 months was 76.5 %, with a 5.5 % post-operative complication rate in one review [28]. Another recent review analyzed 26 studies which included one randomized controlled trial and 25 cohort/case series. Seven technical variations of the ligation of the intersphincteric fistula tract procedure were identified and classified according to the surgical technique. Primary healing rates ranged from 47 to 95 %. In 12 of these studies, the classic LIFT procedure was used, and healing rates ranged between 61 and 94.4 %. Several technical modifications have been described, including LIFT combined with excision of the intersphincteric tract, coring out of the fistula tract, intraoperative seton, advancement flap, plug and adjunctive use of a bioprosthetic graft; a similar range of success was observed [29].

Early results from a multicenter study in China suggest a higher primary healing rate with placement of a bioprosthetic plug in the tract extending to the external opening. Han et al. randomized over 100 patients to either a LIFT or LIFT-plug arm. Initial results include an 83.9 % success rate after LIFT and 95 % combined with the plug. No difference was found in continence scores; longer follow-up is necessary [13].

A prospective multicenter study of high volume New England centers reported results of operative options for surgical management of anal fistulas. These authors were particularly interested in short term outcomes of the LIFT procedure. They found that of the 43 LIFT procedures, 88 % of were performed for transsphincteric fistulas. Hospital site was the only variable associated with healing. Hospitals that performed more LIFT procedures had higher healing rates. At 3 months, 79 % of high transsphincteric fistulas had healed versus 82 % for low fistulas, with no statistical difference. Patients that had a seton placed preoperatively before LIFT procedure did not appear to have higher healing when compared to patients treated with LIFT alone. Mean continence scores improved in all groups [11]. Sileri et al. found similar results with respect to the success rate after LIFT. This multicenter prospective study reported an 73 % healing rate in 26 patients followed over 20 months, with no change in function.

Two randomized studies compared LIFT to ERAF in managing complex transsphincteric fistulas. Mabdouly et al. found a cure rate of 74.3 % with LIFT versus 65.7 % after ERAF at 1 year. No change in Wexner score was reported, however, mean healing time was shorter (22.6 days) after LIFT than ERAF (32 days) and patients reported less immediate postoperative pain in the LIFT group [14]. An earlier, smaller study found a comparable success rates of over 92 % in both groups, and similar secondary outcomes to other studies. They found that the LIFT group had faster healing times, less postoperative pain and higher patient satisfaction scores in comparison to patients undergoing ERAF.[15]

Conclusion and Personal View

Low transsphincteric fistulas can usually be managed readily with fistulotomy. These patients usually go on to prompt healing with low rates of long term fecal incontinence. More complex fistulas are often very challenging as one must balance the desire for healing with the risk of fecal incontinence. Management should be individualized and tailored to the patient's current bowel habits and sphincter function.

The initial approach for all patients should be control of sepsis and precise evaluation of the anatomy. Examination in the clinic setting or under anesthesia are both effective tools for defining the anatomy of the fistula tract. Occasionally, imaging might be required to delineate the anatomy of a fistula. We often find that placement of a seton helps to clearly delineate the anatomy of the fistula tract as well as reduce local sepsis. Once these objectives have been accomplished, then a rational choice can be made regarding the most appropriate definitive strategy for addressing the fistula.

For high transphincteric fistulas where the fistula traverses more than a third of the external sphincter, we favor a sphincter-saving approach over fistulotomy. Also, patients with low transsphincteric fistulas and higher baseline fecal incontinence scores are typically better served with a sphincter-sparing procedure.

Level 1 data comparing advancement flap to the LIFT procedure are limited. Both randomized trials comparing ERAF to LIFT reported largely equivalent results and involve only short follow-up. Smaller case-series examining each technique are limited by selection bias.

Our approach is to offer ERAF or LIFT to patients with high transsphincteric fistulas or in those with poor sphincter function. Some important technical details merit consideration when making a decision about which technique to use. We have found that identification of the fistula in the intersphincteric groove can be difficult in patients with posterior fistulas. This makes ligation of the fistula track difficult and often leads to technical failure of a LIFT procedure. Thus, we offer most patients with posterior fistulas ERAF. Most other patients can be offered LIFT as we have demonstrated that it can be performed safely with good short term healing rates. In the evaluation and treatment of patients with complex fistulas, there is no substitute for the patient's understanding of the anatomic complexity and technical considerations that are associated with each approach.

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Chapter 33
Benign Anal Disease: Management of the Recurrent Anovaginal/Rectovaginal Fistula

Elise H. Lawson and Patricia L. Roberts

Introduction

Rectovaginal fistula represents a challenging and often frustrating clinical entity for patients and surgeons alike. Despite a plethora of available approaches for repair, rates of non-healing and recurrence remain high. As a result, patients often require multiple attempts at repair before a satisfactory outcome is achieved. The surgical literature is replete with observational studies consisting of single-institution case series; however, there is a lack of level 1 evidence to support definitive recommendations. In this chapter, we summarize the available literature regarding procedures used to treat recurrent rectovaginal fistulas, then, supplement this with recommendations and observations from clinical practice. Specifically, we focused on endorectal/mucosal advancement flaps, tissue transposition techniques, and biologic mesh repair.

Search Strategy

We performed a MEDLINE literature search limited to years 2005–2015 using the search terms "anovaginal fistula" OR "rectovaginal fistula." Abstracts were reviewed for the 166 titles produced by this search strategy. To be included, articles had to be

E.H. Lawson, MD, MSHS
Lahey Hospital and Medical Center, Burlington, MA, USA

P.L. Roberts, MD (✉)
Department of Colon and Rectal Surgery, Lahey Hospital and Medical Center,
41 Mall Rd, Burlington, MA 01805, USA
e-mail: Patricia.l.Roberts@lahey.org

N. Hyman, K. Umanskiy (eds.), *Difficult Decisions in Colorectal Surgery*,
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an original research study addressing the repair of rectovaginal fistula in an adult. We included studies on initial rectovaginal fistula repair because of the paucity of studies specifically focused on recurrent fistula. References were mined to identify additional articles for inclusion. Articles focused on plugs, sealants, diversion alone or simple repair with episioproctotomy/fistulotomy or levatorplasty were excluded due to lack of efficacy of these methods for recurrent rectovaginal fistula. Additionally, we excluded retrospective single-institution experience case review studies describing a heterogeneous mix of approaches to repair. The exception to this was 3 studies focused on Crohn's-related fistula. Ultimately, our search strategy produced 22 studies for inclusion (Table 33.1).

PICO table for rectovaginal fistula

Patient population	Intervention	Comparator	Outcomes studied
Recurrent rectovaginal fistula	Tissue transposition techniques (Martius, gracilis muscle)	Endorectal/mucosal advancement flaps, mesh repair	Rate of non-healing and/or recurrence, postoperative adverse events

Results

A common approach for initial or recurrent rectovaginal fistula is the endorectal or mucosal advancement flap repair. This method involves extending a U-shaped flap of rectal mucosa, and often submucosa, over the internal opening of the fistula. A study by de Pareades [1] described this technique combined with muscular plication in 23 patients (10 initial fistula, 13 recurrent) and reported a success rate of 65 %. The authors further reported that symptoms were not worsened in the 8 patients with a failed repair. Notably, patients with active Crohn's proctitis, malignant or radiation-induced fistula, stricture of the anorectum or an external sphincter defect were excluded from the study.

Similarly, Hull [2] reported a 62 % success rate for full thickness rectal advancement flaps performed on 37 women with rectovaginal fistula resulting from obstetrical trauma or cryptoglandular origin. About half the patients also had a protective stoma. This study also described the authors' experience with episioproctotomy, which is their preferred approach for repair when there is a significant anterior sphincter muscle defect identified by anal endosonography. Though not explicitly stated, the report implies that patients undergoing advancement flap did not have a significant sphincter defect identified preoperatively. Finally, a study by Ellis [3] described the authors' experience with advancement flap repair (mucosal or anodermal) in women with an initial or recurrent fistula but without active Crohn's disease or acute injury. The rate of healing was 62 % for the 29 patients who underwent mucosal advancement flap and 73 % for the 27 patients who underwent anodermal flap. Sphincteroplasty and/or levatorplasty was performed if an associated muscle injury was identified preoperatively.

Table 33.2 Summary of evidence for rectovaginal fistula repair

Author (Year)	Population (time period)	Method of repair	Number of patients	Diverting stoma?	Results	Follow-up	Quality of evidence
De Parades (2011) [1]	Rectovaginal fistula (2003–2008)	Endorectal advancement flap with muscular plication	23 (10 initial, 13 recurrent)	No	15 (65 %) healed	Mean 14 months (2–67)	Low
Hull (2011) [2]	Rectovaginal fistula from obstetrical or cryptoglandular origin (1997–2009)	Rectal advancement flap	37	19 (54 %) with stoma	23 (62 %) healed	Median 39 months (13–70)	Low
Ellis (2008) [3]	Rectovaginal fistula (2000–2006)	Mucosal advancement flap (MAF), anodermal advancement flap (AAF), bioprosthetic interposition mesh repair with or without plug	29 MAF, 15 AAF, 27 bioprosthetic mesh interposition, 7 mesh plus plug	No	Healed: MAF – 18 (62 %) AAF – 11 (73 %) Bio mesh – 22 (81 %) Plug – 6 (86 %)	Mean 11 months (3–26)	Low
Gottgens, (2014) [4]	Recurrent rectovaginal or pouch-vaginal fistula (2009–2012)	Transperineal or transvaginal repair with collagen matrix biomesh	12 (10 transperineal repair, 2 transvaginal)	8 with stoma, 4 without	8 (67 %) healed 1 (8 %) healed after subsequent rectus abdominal transposition 3 (25 %) unhealed or recurrent	Median 22 months (2–45)	Low
Schwander (2009) [5]	Fistula in lower 2/3 of rectovaginal septum (2007–2008)	Surgisis mesh	21 (18 recurrent, 3 initial)	8 (38 %) with stoma	15 (71 %) healed 4 (19 %) healed after subsequent repair 2 (10 %) unhealed or recurrent fistula. 4 (19 %) minor postoperative complications	Mean 12 months (3–18)	Low

(continued)

Table 33.2 (continued)

Author (Year)	Population (time period)	Method of repair	Number of patients	Diverting stoma?	Results	Follow-up	Quality of evidence
Schouten (2009) [6]	Low rectovaginal fistula from obstetrical, iatrogenic or cryptoglandular origin (2006–2009)	Rectal sleeve advancement	8	2 with stoma	5 (63 %) healed.	Median 12 months (3–17)	Low
Lamazza (2015) [7]	Rectovaginal fistula after XRT and anterior resection for rectal cancer (not available)	Endoscopic placement of self-expandable metal stent	15 (11 initial, 4 recurrent)	Yes, for recurrent fistula	12 (80 %) healed 1 (7 %) didn't tolerate stent	Mean 22 months (4–39)	Low
Pitel (2011) [8]	Low rectovaginal fistula (2000–2010)	Martius advancement flap	20 (5 initial, 14 with prior rectal advancement flap, 1 prior Martius flap)	14 with stoma, 6 without	13 (65 %) healed 3 (15 %) minor wound complications.	Median 29 months (2–210)	Low
Songne (2006) [9]	Rectovaginal fistula (1994–2004)	Martius advancement flap	14 (10 initial, 4 recurrent)	Yes	13 (93 %) healed 1 (7 %) healed with subsequent repair	Mean 40 months (8–120)	Low
McNevin (2007) [10]	Rectovaginal fistula (2002–2006)	Martius advancement flap	16	6 with, 10 without	15 (94 %) healed 1 (6 %) recurrent	Mean 75 weeks (24–190)	Low
Cui (2009) [11]	Rectovaginal fistula (2003–2007)	Martius advancement flap	9 (3 initial, 6 recurrent)	Yes, for recurrent fistulas	100 % healed	Median 14 months (6–48)	Low
Troja (2013) [12]	Recurrent rectovaginal, pouch-vaginal or anovaginal fistula after primary closure (2004–2010)	Graciloplasty	10 (5 rectovaginal, 4 pouch-vaginal, 1 anovaginal)	Yes	6 (60 %) healed 1 (10 %) perineal wound defect 1 (10 %) hematoma	Median 50 months (20–63)	Low

Author (Year)	Population (time period)	Method of repair	Number of patients	Diverting stoma?	Results	Follow-up	Quality of evidence
Nassar (2011) [13]	Iatrogenic rectovaginal fistula (2002–2009)	Graciloplasty	11	Yes	11 (100 %) healed 4 (36 %) minor postoperative complications	Mean 35 months (12–67)	Low
Lefevre (2009) [14]	Recurrent rectovaginal fistula (2003–2006)	Graciloplasty	8	Yes	6 (75 %) healed 1 (13 %) healed after subsequent repair 1 (13 %) recurrence	Median 28 months (4–55)	Low
Ulrich (2009) [15]	Recurrent rectovaginal fistula (2003–2008)	Graciloplasty	9	Yes	7 (78 %) healed	Mean 28 month (3–52)	Low
Zmora (2006) [16]	Rectovaginal and pouchvaginal fistula w/history of prior repair or pelvic irradiation (1999–2005)	Graciloplasty	6	4 with, 2 without	5 (83 %) healed 1 (17 %) recurrence 1 (17 %) perineal wound infection	Median 26 months (9–74)	Low
Wexner (2008) [17]	Rectovaginal and pouchvaginal fistula (1995–2007)	Graciloplasty	17 (4 initial, 13 recurrent)	Yes	7 (41 %) healed 2 (12 %) healed after repeat repair 8 (47 %) unhealed 8 (47 %) minor wound complications	Not reported	Low
Schloericke (2011) [18]	Low or mid-rectovaginal fistula (2000–2010)	Transabdominal/ transperineal omental flap	9	Yes (except 1)	8 (89 %) healed 1 (11 %) healed after subsequent repair 2 (22 %) with minor complications	Median 22 months	Low

(continued)

Table 33.2 (continued)

Author (Year)	Population (time period)	Method of repair	Number of patients	Diverting stoma?	Results	Follow-up	Quality of evidence
van der Hagen (2011) [19]	Rectovaginal fistula between middle third of rectum and posterior vaginal fornix (2006–2009)	Laparoscopic excision and omentoplasty	40	2 (5 %) underwent stoma because omentoplasty not feasible	38 (95 %) healed 1 (3 %) necrotic omentum requiring reoperation 1 (3 %) abscess requiring drainage	Median 28 months (10–35)	Low
El-Gazzaz (2009) [20]	Crohn's-related rectovaginal fistula (1997–2007)	Multiple	65	39 with stoma (60 %)	30 (46 %) healed	Median 45 months (13–79)	Low
Ruffolo (2008) [21]	Crohn's-related rectovaginal fistula (1993–2006)	Multiple	52	Some with stoma (number not given)	29 (56 %) healed 13 (25 %) healed after subsequent repair(s)	Median 109 months (24–180)	Low
Löffler (2009) [22]	Crohn's-related rectovaginal fistula (1991–2001)	Multiple	45	No	24 (53 %) healed with initial or subsequent repair	Median 48 months	Low

In the same report, Ellis also described their experience with rectovaginal fistula repair using bioprosthetic mesh with or without a plug in women with an initial or recurrent rectovaginal fistula [3]. Patients with an acute injury were again excluded; however, 7 patients (21 %) with Crohn's disease were included. The mesh was placed as an interposition graft after transecting the fistula tract and closing the rectal and vaginal openings. Sphincteroplasty and/or levatorplasty were again performed as needed. For the 27 patients who underwent mesh repair and the 7 patients who underwent mesh plus plug repair, rates of healing were 81 % and 86 %, respectively.

Use of collagen matrix biomesh as an interposition graft was also described by Göttgens [4] for 12 patients with recurrent rectovaginal fistula from a variety of etiologies, including Crohn's disease. Among this group, 67 % were successfully healed with the mesh approach. Two-thirds of the study group had protective stomas, including all 4 of the patients who underwent a failed repair. In a prospective study by Schwandner [5], 21 patients with initial or recurrent rectovaginal fistula underwent fistulectomy followed by endorectal advancement flap and transvaginal placement of bioprosthetic mesh. Just over one-third of the patients also had a protective stoma. This combined approach resulted in a healing rate of 71 %.

Rectal sleeve advancement is a more invasive treatment option for rectovaginal fistula that involves circumferential mucosectomy, transanal transection of the rectum and rectoanal anastomosis. Schouten [6] described use of this technique to treat 8 women with recurrent rectovaginal fistula and reported a successful healing rate of 63 %. One patient (13 %) developed fecal incontinence postoperatively.

Endoscopic placement of a metallic stent has recently been described as a novel treatment for iatrogenic initial or recurrent rectovaginal fistula [7]. In a series of 15 patients who developed a fistula after undergoing radiation and anterior resection for rectal cancer, Lamazza reported successful healing in 80 % of the women. One patient (7 %) did not tolerate the stent and had to have it removed after 3 days. Notably, 100 % of the 11 patients with an initial rectovaginal fistula were successfully healed by this technique.

A number of techniques for tissue transposition have been described for repair of recurrent rectovaginal fistula. These procedures bring healthy tissue into the rectovaginal septum, essentially creating a well-vascularized barrier between the rectum and vagina. The Martius advancement flap is one such technique, in which the bulbocavernosus muscle and surrounding fibroadipose tissue is harvested from the labia majora and tunneled into the rectovaginal septum, preserving the vascular pedicle. In a series of 20 patients with initial or recurrent rectovaginal fistula from a variety of etiologies who underwent repair with a Martius advancement flap, Pitel [8] reported a successful healing rate of 65 %. The majority of patients had a protective stoma at the time of surgery and 3 patients (15 %) had minor wound complications. In a similarly heterogeneous group of 14 patients, Songne [9] reported a successful healing rate of 93 %. The one patient with recurrence was successfully healed with a repeat Martius advancement flap procedure from the contralateral side. Of note, all patients in this study had a protective stoma. McNevin [10] and

Cui [11] have reported similarly high successful healing rates of 94 % in 16 patients and 100 % in 9 patients, respectively, with initial or recurrent rectovaginal fistula. In McNevin's study, just over a third of the patients had a protective stoma, while in Cui's study, a protective stoma was only used for patients with a recurrent fistula.

Gracilis muscle transposition, or graciloplasty, is another tissue transposition technique in which the gracilis muscle is mobilized from the medial thigh and transposed into a defect created by a perineal incision after excising the fistula. In a series reported by Troja [12], 10 patients with recurrent rectovaginal, pouch-vaginal or anovaginal fistula underwent graciloplasty, with a success rate of 60 %. All patients had a protective stoma. Nassar [13] reported a 100 % rate of healing for 11 patients with an iatrogenic postoperative rectovaginal fistula who underwent graciloplasty with protective stoma. For a group of 8 patients with recurrent rectovaginal fistula due to Crohn's disease, obstetrical injury or iatrogenic injury, Lefevre [14] reported a 75 % successful healing rate after graciloplasty with protective stoma. Using this same approach, Ulrich [15] reported a successful healing rate of 78 % in a similar population of 9 patients with recurrent rectovaginal fistula. Zmora [16] reported a successful healing rate of 83 % for 6 patients with history of a previous failed repair or pelvic irradiation who underwent graciloplasty. Notably, the one patient with recurrence in this study did not have a protective stoma. Finally, among 17 patients with a recurrent rectovaginal or pouch-vaginal fistula, Wexner [17] reported 41 % successful healing after graciloplasty. Successful healing was achieved in 75 % of a subgroup of 8 patients without Crohn's disease.

Mobilization of the greater omentum for use as an interposition flap in the rectovaginal space has also been described. Schloericke [18] reported using a transabdominal/transperineal approach for low or mid rectovaginal fistulas, in which the omental flap is first harvested transabdominally then fixed in the rectovaginal space transperineally after dissection of the fistula. The reported successful healing rate was 89 % for the 9 patients who underwent this procedure, and the one patient with a recurrence was successfully healed with repeat repair. Nearly all patients had a protective stoma. For 40 patients with a fistula between the middle third of the rectum and the posterior vaginal fornix, van der Hagen [19] described attempting a laparoscopic fistulectomy followed by omental interposition into the rectovaginal septum. Two patients (5 %) ultimately underwent diversion instead as intraoperatively the omentum was found to be unsuitable for omentoplasty. One patient developed necrosis of the omental flap requiring reoperation, and another patient developed an abscess requiring drainage. Overall, the successful healing rate was 95 %.

Crohn's-related rectovaginal fistulas are particularly challenging to treat. Our literature search produced three reports specifically focused on this patient population. El-Gazzaz [20] described the Cleveland Clinic experience with 65 women with Crohn's disease and a rectovaginal fistula over a 10 year period. A variety of treatment approaches were undertaken and the overall rate of successful healing was 46 %. Mucosal advancement flap was the most commonly performed procedure (47 patients) and was associated with a rate of healing of 43 %. On multivariate

analysis, smoking and steroids were associated with recurrence while use of immunomodulators was associated with successful healing. Ruffolo [21] reported a successful healing rate of 56 % among 52 women with Crohn's related rectovaginal fistula who underwent a range of repairs. Successful healing was achieved in an additional 25 % of the patient population after subsequent repair(s). As in the previous study, mucosal advancement flap was the most commonly performed procedure. Finally, in a series of 45 women with Crohn's related rectovaginal fistula, Löffler [22] reported a successful healing rate of 53 % after one or more attempts at repair.

Recommendations Based on the Data

- Patients with a recurrent rectovaginal fistula should be assessed for the presence of a sphincter defect and, if identified, the defect should be addressed at the time of definitive repair (evidence low; weak recommendation).
- Endorectal advancement flap is a safe procedure for recurrent rectovaginal fistula but may not have high efficacy (evidence low; weak recommendation).
- For patients with multiple failed rectovaginal fistula repairs, consider fecal diversion with a protective stoma at the time of further attempts at repair (evidence low; weak recommendation).
- Repair of recurrent rectovaginal fistula with biologic mesh is a safe procedure (evidence low; weak recommendation).
- Repair of recurrent rectovaginal fistula with tissue transposition such as Martius flap or graciloplasty is safe and may have greater efficacy than other less invasive repair techniques (evidence low; weak recommendation).
- Patients with Crohn's-related rectovaginal fistula should not undergo definitive repair in the face of active proctitis (evidence low; weak recommendation).

A Personal View of the Data

Rectovaginal fistulas are difficult to treat with no clear consensus on the best method of repair and no level 1 evidence to guide the surgeon. As the best reported outcomes result in recurrent fistula and/or breakdown of the repair in 1 in 4 women overall, and up to 1 in 2 women with Crohn's who undergo repair, the preoperative discussion with the patient should be extensive and include a detailed discussion of the potential results. Furthermore, if a rectovaginal fistula recurs after repair, it is our clinical experience that it is often initially larger than the original fistula and usually more symptomatic. This results in great distress to the patient who often wishes to have a repeat repair as soon as possible; in our opinion, it is generally best to wait at least 3 months to allow the tissues to become less inflamed and to optimize the chance of a successful repair.

Our approach to recurrent rectovaginal fistulas is first to assess why the repair failed. Were there technical aspects of the repair that resulted in fistula recurrence? Was the appropriate procedure selected? Is there a sphincter defect that was not recognized? For advancement flaps, necrosis of the distal extent or entire flap or hematoma of the flap may cause failure in addition to inadvertent button-holing of the flap during dissection. Our preference is to incorporate part of the internal sphincter in the flap, which results in a thicker flap, in an attempt to get better healing and coverage of the internal opening of the fistula. On occasion, the flap may not have been adequately mobilized and tension on the distal portion of the flap may result in dehiscence and failure of the repair. In women with a rectovaginal fistula from obstetric injury, a sphincter defect (which is more the rule than the exception) that is not addressed at the time of repair is an additional cause of flap failure.

There is increasingly a push to use setons prior to a definitive anal fistula repair, such as the LIFT procedure. We have not found setons useful for the majority of patients with rectovaginal fistulas as the tract is quite short and any associated abscess generally well drained through the short tract. The exception is women with Crohn's disease, who in addition to a rectovaginal fistula may have additional fistulas (resulting in a so-called watering can perineum) and require setons for long term drainage.

There is no clear consensus on the best repair for recurrent rectovaginal fistula and we approach each patient on a case-by-case basis. We use a fairly simple approach of "if it didn't work the first time, try something different the next time." Thus, if an advancement flap was not successful the first time, we would generally not repeat the procedure and would instead proceed to another option such as episioproctotomy.

We generally recommend proximal fecal diversion for the majority of patients with rectovaginal fistula and Crohn's disease and use it selectively for women who have failed prior repairs. If a prior repair was associated with a wound infection, there is a potential advantage to proximal diversion with a subsequent repair to ameliorate the consequences of the wound infection and optimally improve the chances of a successful outcome. Anecdotally, morbidly obese patients seem to have a much higher incidence of wound infection, and while stoma creation has its own challenges in this group, we generally recommend proximal fecal diversion in this cohort of patients.

For recurrent fistulas, it is important to bring well-vascularized tissue into the rectovaginal septum. If patients have had multiple repairs, this area is generally quite scarred and tissue transposition is needed. Gracilis flaps are most commonly performed, but have significant morbidity and a lengthy recovery period. The pudendal thigh flap, or Singapore flap, is another potential option for tissue transposition and we have increasingly used this technique for patients with recurrent fistulas. There are few reports of this technique in the literature [23]. Tissue transposition techniques and other repairs may be associated with dyspareunia and perceptions of changes in body image. These outcomes are not routinely reported but are increasingly important patient reported outcomes to consider in assessing the optimal repair for this challenging condition.

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Chapter 34
Benign Anal Disease: When to Operate on the Patient with an Anal Fissure

David J. Berler and Randolph M. Steinhagen

Introduction and Problem

Anal fissures have been reported to affect an estimated 235,000 individuals per year, though the true incidence is likely higher. The majority of anal fissures are associated with high internal anal sphincter tone. The etiology is thought to be related to local trauma caused by hard stool and/or related to chronic ischemia associated with increased sphincter pressures. While most acute fissures heal spontaneously with stool bulking, local care, and topical treatments, the management of chronic fissures, specifically the decision on when lateral internal sphincterotomy (LIS) is appropriate, represents a clinical challenge.

While non-surgical therapies, such as botulinum toxin and calcium channel blockers are safe and more effective than placebo in healing fissures, lateral internal sphincterotomy has been shown to be far superior in promoting healing and is associated with the lowest rates of recurrence. However, the decision to recommend sphincterotomy should not be made lightly, as there is always concern that the procedure will be associated with some degree of incontinence. Given the choice between a painful fissure and a permanent deficit in continence, many patients may prefer coping with the pain of the fissure. The true incidence and extent of continence disturbances following surgical sphincterotomy is often disputed; this leads to the difficulty in deciding when to recommend it.

D.J. Berler, MD
Department of Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, USA

R.M. Steinhagen, MD (✉)
Division of Colon and Rectal Surgery, Department of Surgery, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY 10029, USA
e-mail: randolph.steinhagen@mountsinai.org

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Search Methods

All data and studies were collected via searching the MEDLINE and Pubmed search engines for numerous terms including 'anal fissure,' 'continence,' 'sphincterotomy,' 'constipation,' 'advancement flap,' and 'recurrence.' Preferential inclusion and higher level of quality were given to studies that were prospective, randomized, published between 2004 and 2015 in journals based within the US and Europe, as well as in English. Twenty-three such studies, including two Cochrane reviews, were identified and were included as a basis for the set of recommendations listed at the end of this chapter. A standard PICO table outlining the clinical question explored is illustrated below.

P (patients)	I (intervention)	C (comparator)	O (outcomes)
Patients with chronic anal fissure	Surgical management	Medical management	Cure, recurrence, postoperative incontinence

Results

Lifestyle modifications consisting of sitz baths, implementing a high fiber diet, increasing fluid intake, and the use of stool-bulking agents, have been shown to be safe and effective in promoting spontaneous healing in 90 % of patients with an acute anal fissure. For the remaining 10 % who progress to chronic fissure, treatments include those that are primarily medical (topical calcium channel blockers, nitroglycerin ointment, botulinum toxin injection) or surgical, typically lateral internal sphincterotomy.

A 2012 Cochrane review of 75 randomized clinical trials included over 5,000 patients with chronic fissures who were either treated with surgery or conventional medical therapies [1]. Nitroglycerine ointment was found to be marginally though significantly superior to placebo in achieving healing (48.9 % vs. 35.5 %, $p < 0.0009$). However, late recurrence developed in 50 % of these patients. Similar efficacy has been observed with topical calcium channel blockers and botulinum toxin injection. Such nonsurgical interventions lead to resolution of symptoms in up to 60 % of affected patients, making them worthwhile to attempt in patients with fissures of less than 12 months duration. The evidence supports the concept that they should typically be tried prior to surgery, given that they are safe and may be effective. Most surgeons do not advocate surgery as first-line therapy, primarily because of concerns related to incontinence.

However, it is well recognized that no medical therapies have enduring cure rates that are at all comparable to those associated with LIS (80–95 %, depending on the case series). Indeed, numerous studies have demonstrated the superiority of surgery in both the healing of and prevention of recurrence of chronic fissures [2–5]. The previously described Cochrane review of 75 RCTs found an odds-ratio of 0.11

(95 % CI 0.06–0.23) when comparing non-healing, defined as persistence or recurrence, at a median of 2 months in patients who underwent medical therapies compared to those who underwent any form of surgery for anal fissure [1].

A prospective randomized trial of 142 patients with anal fissure compared healing rates and defecatory pain following treatment with either LIS or anal dilation plus topical nifedipine [6]. 68.9 % of patients in the nifedipine group and 88.2 % of patients in the LIS group were healed by 8 weeks ($p = 0.0077$). Those who underwent LIS had significantly less pain with defecation at 3 and 7 days. A parallel, randomized controlled trial of 99 patients with chronic fissure found no significant difference in healing rates in patients with fissures of less than 12 months duration who underwent botulinum toxin injection with supplemental calcium channel blocker therapy compared to those who underwent LIS. However, in patients who had chronic fissures for more than 12 months, the healing rate was significantly higher in the LIS group (86 % vs 23 %, $p < 0.001$) [7].

Of all the medical therapies that are currently available, botulinum toxin injection has increasingly been used as first-line therapy for recalcitrant anal fissures, and nitroglycerine ointment may act in synergy with botulinum toxin [8]. Still, there is currently no consensus on the ideal dosage, precise location of injection (external vs internal sphincter), and number of injections of botulinum toxin needed to achieve optimal results. Higher doses do seem to correspond with higher healing rates and are just as safe as lower doses, though the recurrence rate remains higher than that following LIS (up to 42 %), making LIS a superior procedure for cure. Incontinence scores are higher in patients treated with LIS [8], however, incontinence to stool and flatus is also a potential complication of botulinum toxin injection, which occurs in up to 18 % of cases.

With the goal being to promote permanent cure while minimizing the likelihood of a disturbance in continence, some have advocated combined fissurectomy with botulinum toxin injection as a viable alternative to LIS. In a prospective nonrandomized study of 105 patients who underwent this procedure, 95 % of patients had resolution or improvement of symptoms at 12-weeks; 93 % had no complications; however 7 % developed postoperative incontinence to stool and/or flatus which proved to be transient (all patients had restored continence at 12 weeks) [9]. The authors argue that even though LIS remains the procedure with the highest cure and lowest recurrence rates, botulinum toxin injection with fissurectomy has similar efficacy and may be preferable given that it does not permanently alter the anal musculature, as LIS does. The latter consideration is important since muscular tone diminishes with aging (further increasing the probability of late incontinence) and LIS may distort planes for future anorectal surgeries that may become necessary. While other studies have demonstrated similar findings [10, 11], it remains difficult to make a broad recommendation on fissurectomy with botulinum toxin injection as an alternative to LIS due to a paucity of adequately-powered, prospective studies. Similarly, pneumatic dilation as a means to reduce the hypertonicity of the internal sphincter has also been explored as a nonsurgical means to healing. While the initial data seems promising with 94 % of patients reporting healing between 3 and 5 weeks, the few trials that have been reported are underpowered [12, 13].

The tradeoff for the high efficacy of LIS is an increased risk for incontinence. After all, diminishing anal canal resting pressure is the primary mechanism by which surgery heals chronic anal fissures. Long-term manometric studies have established that preoperative resting anal pressure is high in patients with fissures and significantly declines following LIS. The sphincter tone and resting pressure gradually increase over a 12-month period, but they nevertheless remain elevated relative to normal controls without fissures. This makes incontinence in such patients possible, though still unlikely [14]. Retrospective studies have postulated that the likelihood of incontinence following LIS is unpredictable, though a history of vaginal delivery may increase this risk [15]. A recent systematic review of 22 studies including over 4500 patients who underwent LIS for chronic fissure showed an overall postoperative continence disturbance rate in 14 %, with a mean follow-up time of 24–124 months (flatus incontinence 9 %, soilage/seepage 6 %, and accidental defecation in 0.91 %) [16].

Still, most agree that the majority of incontinence following LIS is a transient phenomenon, and that the risk of this is far outweighed by the risk of failed, prolonged medical management with continuing distress of patients related to an unhealed symptomatic fissure. A retrospective cohort study of 38 patients who underwent LIS between 1998 and 2004 found that long-term symptomatic incontinence was reported by only two patients (5.6 %) [17]. The authors' final recommendation is that patients with risk factors for the development of incontinence (preoperative incontinence, multiparous women) should arguably be treated with non-surgical therapies prior to LIS. Finally, there is speculation that incontinence may actually be a feature of the underlying condition itself, and is not solely a complication of surgical management [18].

The degree of sphincter division may proportionately dictate the likelihood of the development of postoperative incontinence. Numerous prospective studies have found that partial sphincterotomy, limited to division just beyond the fissure apex, correlates with a lower risk of postoperative incontinence than does complete sphincterotomy to the level of the dentate line [14–18]. In general, internal sphincterotomy to the level of the dentate line is associated with higher rates of healing as well as more rapid healing of chronic fissures, although it is associated with a higher risk for incontinence than is partial sphincterotomy [19]. A 2011 Cochrane review of 27 studies, including 2,056 patients, concluded that open and closed partial lateral sphincterotomy were equally efficacious and not different in terms of the risk of developing postoperative incontinence. The conclusion is that more data are needed to determine the effectiveness of alternate procedures such as posterior internal sphincterotomy, anterior levatorplasty, and bilateral internal sphincterotomy [20].

There has been recent interest in alternate surgical treatments for chronic fissures that do not carry as substantial a risk for even transient incontinence, as does LIS. Fissurectomy with advancement flap, particularly in patients without internal sphincter hypertonia, has been advocated as a promising option for such patients. One study of 26 patients with fissures refractory to medical therapy showed that fissurectomy with advancement flap led to complete healing by 30 days, and that the

intensity of pain with defecation was substantially diminished. At 1 year, only three patients reported ongoing incontinence [21]. The obvious problem, of course, is that the etiology behind the large majority of chronic fissures is high internal sphincter tone. Fissurectomy with advancement flap does not address this, and therefore, most patients would conceivably neither benefit nor heal from such treatment.

Other prospective studies have suggested that what has been called "modified LIS" (partial sphincterotomy to the level of the fissure apex with dermal advancement flap) results in better healing and less postoperative discomfort than does isolated, conventional LIS to the dentate line. One such study of 32 patients found that modified sphincterotomy with a VY flap from perianal skin was associated with less postoperative defecatory pain and faster objective healing than was conventional LIS ($p < 0.01$) [22]. Similar findings have been reported by others [23, 24]. For obvious reasons, modified LIS carries less risk for postoperative incontinence than does conventional LIS. It may be useful and more appropriate in patients with preoperative incontinence or known risk factors for developing incontinence postoperatively (prior vaginal delivery, older age). There have been some low-powered studies suggesting that fissurectomy with advancement flap may be effective as a first line procedure in patients with chronic fissures, irrespective of anal sphincter tone [25, 26].

Recommendations

1. *Medical therapy is safe and should be attempted prior to surgical intervention for chronic anal fissure.* **Evidence high; strong recommendation**.
2. *No medical therapies possess the efficacy for healing chronic anal fissures as does surgery, and surgery should be considered in patients with fissures that fail to heal in response to medical therapy.* **Evidence high; strong recommendation**.
3. *Botulinum toxin injection in the setting of chronic fissures is superior to placebo and to other medical therapies with respect to healing and recurrence. A standard for optimal delivery has not been established. Results are usually inferior to LIS.* **Evidence moderate; weak recommendation**.
4. *Although the risk of incontinence exists with LIS, this risk is largely overstated and should not discourage its use for definitive management in patients with chronic fissure that have failed nonsurgical therapies.* **Evidence high; strong recommendation**.
5. *Patients with chronic anal fissures, anal hypertonia, and no preoperative risk factors for incontinence should undergo LIS.* **Evidence high; strong recommendation**.
6. *In patients with chronic anal fissure and diminished anal tone, fissurectomy with anal advancement flap or modified LIS with advancement flap should be considered as an alternative to LIS.* **Evidence moderate; weak recommendation**.
7. *Pneumatic dilation may lower sphincter tone and induce healing of chronic anal fissures without causing incontinence.* **Evidence low; weak recommendation**.

A Personal View of the Problem and the Data

The vast majority of patients who have a symptomatic anal fissure seek advice and treatment for what they or their referring providers refer to as 'hemorrhoids.' Taking a complete history and performing a thorough physical exam is the key to making the correct diagnosis. It is important to educate patients about the nature of their condition and how it differs from hemorrhoids. Since the majority of fissures will heal with non-operative management, patients should be advised that surgery is not mandatory and that nonsurgical treatments are generally the preferred first line therapy. The importance of a high fiber diet and drinking sufficient quantities of liquids cannot be overemphasized.

For most, the addition of a fiber supplement such as psyllium and/or a stool softener such as docusate will be beneficial. Often, a topical medication such as nitroglycerine or diltiazem is prescribed from the outset. Since most patients are concerned that cutting any portion of the sphincter will leave them incontinent, they should be reassured that the reason they have a fissure is that their sphincter is excessively tight. They are informed that, while cutting a portion of the sphincter will reduce the pressure, the surgery will leave them with a sphincter pressure that is still often higher than normal. The data shows that the incidence of clinically meaningful incontinence after partial LIS is extremely low, and that is also my own experience. Still, while we know that the surgery is very effective and the risks are small, we never push a patient to have surgery; We tell them that it is available and it will always be their decision as to if and when it should be utilized.

Nonsurgical therapies which reduce internal anal sphincter tone, can be predictive of the likelihood of success with sphincterotomy. It is critical to choose patients appropriately. If the sphincter tone is lax, then other etiologies for the fissure must be considered and sphincterotomy is likely to have a poor outcome. The few patients with chronic fissures and low resting tone or preexisting incontinence who fail nonoperative therapy, are best managed with fissurectomy and advancement flap. There is another group of patients who initially respond well to nonoperative management, but then the fissure recurs as do the symptoms. These patients should typically repeat the therapies that were effective, but if the recurrences are too frequent and the asymptomatic intervals too short, sphincterotomy will be an effective long-term solution.

Although the risk of any degree of incontinence in appropriately selected patients is very low, this should never be minimized and the patient should never feel that this is not a significant concern. Patients want to be treated by a surgeon who is not in a rush to operate, and by one who is as concerned about their ability to control their bowels as they are themselves.

Anal fissure: literature search results

First author	Year	Study design	Interval	Patients (n)	LIS n (%)	Medical management n (%)	Follow-up time (months)	Cure rate (M, S) %	Recurrence rate (M, S) %	Incontinence rate (M, S) %
Libertiny	2002	Prospective, RCT	1998	70	35 (50)	35 (50) GTN	24	(54.3, 100)*	(5.26, 2.86)	NA
Mentes	2003	Prospective, RCT	NA	111	50 (45)	61 (55) BTI	2, 6, 12	(86.9, 98)	(24.6, 6)	(0, 16)*
Arroyo	2005	Prospective, RCT	1998–2000	80	40 (50)	40 (50) BTI	36	(45, 92.5)*	(0,0)	(0, 5)
Iswariah	2005	Prospective, RCT	2000–2002	38	21 (55.3)	17 (44.7) BTI	6, 26-week	(86, 91)*	(53, 9.5)*	See study
Derosa	2013	Prospective, RCT	2008–2010	142	68 (47.9)	74 (52.1) TCCB	2, 4, 8-week	(68.9, 88.2)*	(23, 11.7)	(0, 3)
Gamdokar	2015	Prospective, RCT	2010–2012	99	50 (50.5)	49 (49.5) TCCB + BTI	2, 6, 12	(65, 94)* [Overall]	(10.2, 0)*	(0,2)
Barnes	2015	Prospective cohort	2008–2012	102	0	102 (100) Fiss + BTI	12	66.7	0	0
Lindsey	2004	Prospective cohort	2001–2003	31	0	31 (100) Fiss. + BTI	16-week	93	NA	7
Scholz	2007	Retrospective	2001–2004	40	0	40 (100) Fiss. + BTI	12	95	10.6	0
Renzi	2005	Prospective cohort	1999–2002	33	0	33 (100) PBD	26 (mean)	94	3	6
Yucel	2009	Prospective, RCT	2004–2005	40	20 (50)	20 (50) PBD	2	(90, 85)	(10, 5)	(0,0)

(continued)

Anal fissure: literature search results (continued)

First author	Year	Study design	Interval	Patients (n)	LIS n (%)	Medical management n (%)	Follow-up time (months)	Cure rate (M, S) %	Recurrence rate (M, S) %	Incontinence rate (M, S) %
Kement	2011	Retrospective review	2003–2006	253	253 (100)	0	23 (mean)	NA	NA	11.7
Garg	2013	Metaanalysis	1969–2012	4512	4512 (100)	0	24–124 (mean)	68–100	NA	15
Davies	2014	Retrospective	1998–2004	38	38 (100)	0	5-years (mean)	92	8	5.6
Mentes	2005	Prospective, RCT	NA	80	To apex: 40 (50) To dentate line: 40 (50)	0	1, 2, 12	Apex: 97.5 Dentate: 100	Apex: 13.2 Dentate: 0	Postop AIS, apex: 0.42 Postop AIS, dentate: 0.58* [both mean]
Patti	2010	Prospective cohort	2002–2007	26	26 (100) Fiss. + AF	0	1, 6, 12	100	0	11.5
Theodoropoulos	2015	Prospective, nonrandomized	2005–2012	62	LIS: 32 (51.6) LIS + AF: 30 (48.4)	0	57.9 (LIS), 20.6 (LIS + AF)	LIS: 100 LIS + AF: 100	LIS: 6.2 LIS + AF: 0*	LIS: 28.1 LIS + AF: 6.6*
Magdy	2012	Prospective, RCT	2009–2010	150	LIS: 50 (33.3) AF: 50 (33.3) LIS + AF: 50 (33.3)	0	3, 6, 12	LIS: 84 AF: 48 LIS + AF: 94*	LIS: 4 AF: 22 LIS + AF: 2*	LIS: 14 AF: 0 LIS + AF: 2*

Patel	2011	Retrospective	NA	100	LIS: 50 (50) Fiss + AF: 50, (50)	0	20–22	LIS: 88 Fiss + AF: 96	NA	LIS: 0 Fiss + AF: 0
Patti	2012	Prospective cohort	2002–2008	48	Fiss + AF: 48 (100)	0	24	100	8	12.5
Giordano	2009	Prospective	2000–2007	51	SCAFA: 51 (100)	0	2, 4, 6+	98	5.9	0
Nelson	2012	Metaanalysis	1966–2010	979 (15 studies)	Overall cure rate with surgery: 89 % (adjusted for drop-outs: 95 %) Overall risk of incontinence: 9–10 %					

Statistically significant differences in healing, recurrence, and incontinence rates are bolded and adjoined to an asterisk (*)
In the event of multiple follow-up times, all results listed denote data corresponding to the longest follow-up point
Parameters not reported in an above-listed study are marked 'NA'
Key: *M* medical management, *S* surgical management, *GTN* topical glyceryl trinitrate, *TCCB* topical calcium channel blocker, *BTI* botulinum toxin injection, *PBD* pneumatic balloon dilation, *Fiss.* fissurectomy, *AF* anorectal advancement flap, *SCAFA* simple cutaneous advancement flap anoplasty, *RCT* randomized controlled trial, *AIS* anal incontinence score

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Chapter 35
Anal Fissure: Recurrence After Lateral Internal Sphincterotomy

Christy Cauley and Liliana Bordeianou

Introduction

Anal fissure is a common cause of perianal pain. When patients fail medical treatments, surgical management through a lateral internal sphincterotomy (LIS) provides relief with cure rates as high as 96–100% [1–5]. However, some patients present with recurrent anal fissures after surgical treatment. This represents a difficult problem for the patient and their colorectal surgeon. While cure of the painful anal fissure is the ultimate goal, repeat interventions come with the potential increased risk of incontinence.

In recommending a treatment solution to patients with recurrent anal fissure, the surgeon must evaluate the patient carefully and weigh the decrement to quality of life from continued pain with chronic fissure versus the risk of incontinence. The first step in determining the proper treatment for these patients is to ensure that there is not an alternative underlying cause for the fissure. This can be done by performing a focused history and physical exam. Due to the significant pain associated with anal fissure, exam under anesthesia is often appropriate. Secondary etiologies of anal fissure, such as inflammatory bowel disease, syphilis, tuberculosis, leukemia, and human immunodeficiency virus, and alternative diagnoses, such as cancer, can thus be ruled out in refractory cases. Furthermore, examination under anesthesia

C. Cauley
Colorectal Surgery Program, Department of Surgery, Massachusetts General Hospital (MGH), 15 Parkman Street, ACC 460, Boston, MA 02114, USA

L. Bordeianou, MD, MPH (✉)
Colorectal Surgery Program, Department of Surgery, Massachusetts General Hospital (MGH), 15 Parkman Street, ACC 460, Boston, MA 02114, USA

MGH Center for Pelvic Floor Disorders, Boston, MA, USA
e-mail: lbordeianou@mgh.harvard.edu

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can allow for inspection of the extent of the fissure and completeness of previous LIS. This may provide important insight into why previous interventions were unsuccessful. In addition, biopsy of the fissure may be performed if cancer is suspected.

In addition to an exam under anesthesia, we also advocate for adjunct testing with anal manometry and anal ultrasound. The anal ultrasound can help quantify the extent of the previous LIS. Inadequate sphincterotomy is thought to be a common cause of recurrent fissure. Anal manometry, which is done in an awake patient who can hopefully tolerate the insertion of the probe into their anus, can help determine if the fissure is associated with low or high resting sphincter tone. Resting anal pressure of the internal anal sphincter can be useful in identifying the cause of anal fissure. Primary anal fissure is due to compression of end arteries associated with elevated resting pressure, while sphincter hypotonia is usually due to secondary problems, such as anal trauma, previous anal surgery, anal stricture with secondary anal canal tearing with defecation, or infection. The findings of these adjunct studies have important implications on treatment decisions, though not all patients can tolerate these additional exams. In these instances the surgeon must still use their clinical judgement in deciding on the presence or absence of sphincter hypertonia.

Treatment Options

As described above, the treatment of recurrent fissures should be based on the presence or absence of hypertonia. Patients with high resting sphincter tone can still benefit from interventions aiming to improve blood flow. Repeat sphincterotomy, which involves the permanent destruction of of additional muscle fibers within the internal sphincter, or botulinum toxin injection which causes temporary flaccid paralysis of these muscle fibers, can achieve this goal by decreasing the resting pressure generated by the sphincter muscle. In contrast, patients with internal sphincter hypotonia will not benefit from decreasing sphincter muscle tone further. Instead, these patients are more likely to benefit from attempts at replacing their diseased anoderm with healthy tissue.

In this chapter we will discuss the current evidence supporting these treatment options and their outcomes for patients with recurrent anal fissure after failure of prior lateral internal sphincterotomy.

Search Strategy

A literature search was performed querying the Cochrane Library and Pubmed to identify guidelines and studies on treatments of recurrent anal fissure. The search terms “anal fissure” and “surgery” were used in the Cochrane Library to identify relevant articles. Search terms “recurrent” or “redo” and “anal fissure” as part of the

article title were performed in Pubmed. Two case series describing treatment of patients with recurrent anal fissure were identified on Pubmed. No articles discussing treatment of recurrent anal fissure were identified at the Cochrane Library. The two case series identified on Pubmed included (1) a case series describing the use of botulinum toxin after LIS and its outcomes with no comparison group and (2) a case series study of redo LIS with no comparison group. In addition the reference lists of these two articles were reviewed to identify further studies addressing treatment of patients with failure of LIS, and no references were identified. There were no limits placed on the search for type of article, language, or dates. Due to the lack of published research on this patient population the majority of this chapter will discuss expert opinion on this topic due to very low quality evidence.

Results

The first study of patients with recurrent anal fissure following LIS was published in 2008 by Brisinda and colleagues [6]. It describes the injection of lyophilized type A botulinum toxin (either 30 units of Botox® or 90 units of Dysport®) into the internal anal sphincter at two sites, on either side of the anterior or posterior midline depending on the fissure location. Patients with posterior fissures received anterior injections and patients with anterior fissures received posterior injections. Eighty patients received the described treatment and those who had persistent symptoms at the 2-month follow-up evaluation (21 patients) received re-treatment with a higher dose of botulinum toxin (either 50 units of Botox® or 150 units of Dysport®). The authors found that 68 % of patients had complete healing at 1 month after the procedure with 10 % reporting mild incontinence of flatus, which improved at 2 months. In 5 year follow-up there were no reported recurrences. This study has several limitations. The study did not provide any comparison group and no preoperative continence assessment was performed. In addition, the conclusion that there was a lack of recurrence with an average 5 year follow-up was determined by no patients returning to the clinic to report symptoms. There was no documented effort to contact patients to see if they presented to another hospital system and there were no comments on patients lost to follow-up for the study.

The second case series discussing patients with recurrent fissure after surgery addresses the use of repeat LIS. This study, published in 2015, describes the outcomes of a 57 patient cohort who received repeat LIS by a single surgeon [7]. Incontinence was assessed pre- and postoperatively using the modified Cleveland Clinic Incontinence Score. In addition, overall satisfaction and pre- and postoperative quality of life scores were obtained on a 10 point scale. One patient (2 %) reported fissure recurrence after repeat LIS and 19 % of patients reported a complication, including minor bleeding, urinary retention, urinary infection, and fecal impaction. Regarding incontinence, 53 % of patients had preoperative incontinence and these patients reported improved or unchanged incontinence postoperatively. Of patients with no preoperative continence issues, 2 of 27 (7.4 %) reported the

development of minor incontinence postoperatively, one for gas and the other for gas and seepage. This study also reported an improvement in overall quality of life score from 5.7 preoperatively to 9.3 out of 10 ($p < 0.001$) postoperatively. Limitations of this study included the lack of a comparison group and its report of outcomes from a single surgeon. In addition, no specific information about the validity of the satisfaction or quality of life questionnaire was provided in the study methods.

Recommendations Based on Current Data

The current data available is of very low quality; therefore, no firm, evidence based recommendation can be made regarding treatment of recurrent anal fissure after surgical intervention. Specifically, recommendation for or against the use of botulinum toxin or repeat LIS cannot be confidently made due to the very low quality of the available evidence. Decision aids may be useful in helping patients decide what treatment will be most beneficial for them, delineating the risk of future recurrence and risk of incontinence after repeat interventions. Colorectal surgeons treating this condition should practice shared decision making with their patients since no clear evidence exists regarding outcomes of interventions in these patients.

A Personal View of the Data

The data available are from single institution case series that lack comparison groups. In addition, both of these studies had a small sample size and one of the studies reported outcomes from a single surgeon. Due to the limitations of these studies, it is difficult to draw evidence based conclusions from the available data. Therefore, our recommendations here are based on expert opinion integrating personal experience, the data presented in this query, and published data discussing outcomes after primary anal fissure treatment.

In patients who present with hypertonia despite prior LIS, we advocate consideration of repeat LIS on the contralateral side. Repeat LIS was shown in the case series cited above to have a 98 % cure rate with a low rate of new onset incontinence (7.4 %). In addition, the authors were able to show a significantly improved overall quality of life for these patients. While this study reports that its findings are from a prospectively maintained database, it suffers from the lack of a comparison treatment group and discloses outcomes from only one surgeon at a single site. However, the authors' findings are consistent with previous literature published on the outcomes of patients with primary chronic anal fissure treated with LIS. Specifically, there were similar rates of complications at 19 % compared to 7–42 % [8–10] and new incontinence of 7 % compared to 10–14 % [11, 12].

We do not typically use botulinum toxin as a treatment for recurrent anal fissure. While the case series cited above states that 68 % of patients were able to heal their

recurrent fissures with the use of botulinum toxin, a recent systematic review revealed that this therapy is only slightly better at healing fissures than placebo for first time fissures [13]. Because there is no comparison to placebo or alternative treatment in this case series, it is hard to know if these findings were significant. Further studies using a comparison group are needed to show the true effect of botulinum toxin in these recurrent anal fissure patients.

For patients presenting with hypotonia or severe incontinence already, neither repeat LIS nor Botox injections are appropriate. For these patients, we advocate consideration of anal advancement flaps. We have no data to support this advice aside from the previous studies comparing outcomes of anal advancement flap with LIS as the standard treatment of de novo anal fissures. These studies found equivalent outcomes between the two groups [14, 15]. The postoperative complication rate in the flap group was 10 % compared to 18 % in the LIS group and the fissure cure rate was 96 % in the flap group compared to 88 % in the LIS group in a retrospective study in 2011 [14]. Due to small sample size in the treatment groups (n = 50 in each treatment arm), these differences did not reach statistical significance. The other study, published in 1995, revealed similar results with an incontinence rate of zero in both groups and equivalent failure rates of 0 % in the LIS group and 3 of 20 (15 %) in the anal advancement flap group. Clearly, further studies of anal advancement flaps, LIS and redo LIS with manometric baseline data should be performed to establish the efficacy of this treatment versus others.

Conclusion

When considering different treatment options for recurrent anal fissure it is important to recognize that inadequate primary LIS may be the cause of the recurrence. Over the years, several variations of LIS including open, closed, tailored, and the standard approaches to sphincter division have been developed in an attempt to decrease the risk of incontinence. By performing a less complete sphincter division, surgeons are likely placing patients at an increased risk of treatment failure. The case series cited above demonstrate that repeat standard LIS can provide the patient with a low recurrence rate as well as low risk of incontinence, though one must only consider this option in the setting of clearly documented hypertonia.

In patients presenting with unhealed fissures and hypotonia, anal advancement flaps may be a better option. We do not recommend botulinum toxin injection for any anal fissure patient due to the temporary nature of the therapy, and its unknown benefit in chronic fissures. The lack of published research on patients with recurrent anal fissure brings to light the need to perform future cohort studies comparing treatments with particular attention paid to preoperative stratification for sphincter tonicity. This would better enable colorectal surgeons to provide more realistic information to patients regarding key outcomes including rates of cure, rates of new incontinence, and patient satisfaction or quality of life (Tables 35.1 and 35.2).

Table 35.1 PICO outline for clinical problem

Patient population	Intervention	Comparator	Outcomes studied
Patients with recurrent fissure after Lateral Internal Sphincterotomy	Repeat LIS	1. Advancement flap 2. Botox	Cure, continence, patient satisfaction

Table 35.2 Results of literature search

Authors	Year published	Study type	# of patients	Treatments compared	Failure rate	New incontinence rate	Other outcomes measured
Brisinda et al.	2008	Case Series	80	Botulinum Toxin Inject vs. No comparison provided	22 % at 1 month	Baseline incontinence not measured; 10 % incontinence at 1 month; none long term	NA
Liang et al.	2015	Case Series	57	Lateral Internal sphincterotomy vs. No comparison provided	2 %	7.4 %	Patient Satisfaction: Significantly improved after intervention

Summary for Box

No recommendation can be made regarding treatment of recurrent anal fissure after lateral internal sphincterotomy. (evidence quality: very low).

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Chapter 36
Benign Anal Disease: Third Degree Hemorrhoids – Who Really Needs Surgery?

Aneel Damle and Justin Maykel

Introduction

Surgeons posess a wide variety of therapeutic options to treat hemorrhoids. Grade I/II hemorrhoids can usually be readily managed with dietary modification and/or office based treatments whereas grade IV hemorrhoids commonly require surgery. However, there are no clear-cut guidelines for the optimal treatment of grade III hemorrhoids. Further complicating matters, the hemorrhoid grading system developed by Goligher in 1954 (grades I-IV) does not account for key factors that may drive decision making, such as size or whether the hemorrhoids are isolated or circumferential [1].

The surgeon must decide when office-based techniques are most appropriate as opposed to surgical intervention [2]. In broad terms, excisional hemorrhoidectomy (EH), has an excellent success rate, but is associated with a significant amount of postprocedural pain and related disability, not to mention cost [3]. Newer operative techniques such as the procedure for prolapse and hemorrhoids (PPH) or Doppler-guided hemorrhoidal artery ligation (DGHAL) may be associated with less postoperative pain but carry higher recurrence rates. Office based techniques such as rubber band ligation (RBL), sclerotherapy or infrared coagulation offer a relative safe and simple approach for many patients, although long-term durability

A. Damle, MD, MBA
Division of Colon and Rectal Surgery, University of Massachusetts Medical Center, 55 Lake Avenue North, Worcester, MA 01655, USA

J. Maykel, MD (✉)
Division of Colon and Rectal Surgery, University of Massachusetts Medical Center, 67 Belmont Street, Worcester, MA 01605, USA
e-mail: maykelj@ummhc.org

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remains a concern. RBL is relatively contra-indicated in patients using clopidogrel, warfarin, or heparin due to the significant incidence of post-procedure bleeding [4]. However, of the available office-based procedures, RBL is typically the most effective option and has been used as the comparison group to surgical hemorrhoidectomy [5].

Complications may result from any technique and can range from minor to life-threatening. They include bleeding, urinary retention, wound infection, incontinence, anal-stricture, ectropion, and local sepsis [3]. To appropriately answer the question of who should have surgery for grade III hemorrhoids, we must evaluate the ability of a treatment to control symptoms, the re-treatment rate, postoperative pain, complication rates, disability, and patient satisfaction (Table 36.1).

Search Strategy/Methods

A literature search of MEDLINE, PubMed, the Cochrane Database of Collected Reviews, and Google Scholar was performed using English language articles from January 2000 to present. Search terms included hemorrhoids, internal and external hemorrhoids, hemorrhoid disease, rubber band ligation, hemorrhoidectomy, hemorroidopexy, and Doppler-guided hemorrhoidectomy. Selected references from articles identified in the primary literature search were used when relevant. Literature was evaluated using the GRADE evidence quality classification system [6]. Post-hoc data analysis was conducted using Fisher's exact test.

Results

High quality evidence comparing office techniques to surgical hemorrhoidectomy for grade III hemorrhoids is lacking. The majority of the available evidence focuses on EH versus RBL. A recent Cochrane Review comparing these two groups was able to include only three of 1186 abstracts reviewed as most studies failed to meet inclusion criteria or contained methodological problems [7]. Of these studies, only two evaluated grade III hemorrhoids. There is a similar lack of high quality data comparing other operative techniques such as PPH or DGHAL to RBL. The following discussion includes the results of available studies (Table 36.2).

Table 36.1 Identification of patient population, intervention, comparison, and outcomes

Patient population	Intervention	Comparator	Outcomes studied
Patients with 3rd degree hemorrhoids	Hemorrhoidectomy	Rubber Band Ligation	Symptom control and morbidity

Table 36.2 Results of studies comparing surgery to office management of grade III hemorrhoids

Study	Group	No. of patients (Gr 3/total)	Results	Quality of evidence
Murie et al. [14]	EH vs RBL	56/88	RR 0.12 for prolapse for grade III (95 % CI, 0.02–0.87, p = 0.04) RR 0.55 for bleeding for all patients (95 % CI, 0.2–1.3, p = 0.2) RR 1.54 for pain > 48 h for all patients (95 % CI, 1.2–1.9, p < 0.01) WMD + 29 days off work for all patients (95 % CI, 21.2–36.8, p < 0.01)	Low
Lewis et al. [15]	EH vs RBL	56[a]	RR 0.40 for short-term symptom recurrence (95 % CI, 0.2–0.7, p < 0.01) RR 0.18 for long-term symptom recurrence (95 % CI, 0.1–0.4, p < 0.01) RR 3.75 for pain requiring systemic analgesia (95 % CI, 2.1–6.8, p < 0.01)	Low
Gagloo et al. [17]	EH vs RBL	38/100	RR 0.25 for prolapsed for grade III (95 % CI, 0.1–0.8, p = 0.02) RR 5.0 for requiring post-operative analgesia for all patients (95 % CI, 2.8–8.7, p < 0.01)	Low
Peng et al. [19]	PPH vs RBL	55/65	RR 0.21 for bleeding symptoms 2 weeks post-op (95 % CI, 0.1–0.4, p < 0.01)	Moderate

Gr grade, *RR* relative risk, *WMD* weighted mean difference

[a]A total of 112 patients were in the study, but patients who had anal dilation or cryotherapy were excluded from ad-hoc analysis

Control of Symptoms

Excisional hemorrhoidectomy is often referred to as the "gold standard" for the treatment of hemorrhoids when it comes to control of symptoms [8]. A large retrospective case series of 693 patients who underwent EH (Ferguson closed technique) for grade III and IV hemorrhoids reported a recurrence rate of 1 % and 3 % at 1 and 2 years [9]. When compared to other surgical techniques such as PPH, a meta-analysis demonstrated that patients undergoing EH were significantly less likely to complain of ongoing hemorrhoidal symptoms than those who underwent PPH (6 trials, 388 patients, OR 0.52, 95 % CI, 0.3–0.91; p = 0.02) [10]. DGHAL has also been shown to have a high recurrence rate with 31 % of patients having symptoms within the subsequent 5 years [11]. Conversely, a recent clinical trial comparing EH to DGHAL with mucopexy demonstrated no difference in symptoms including pain and bleeding at 2 years post-procedure [12].

RBL has also been shown to control symptoms for many individuals, but to a lesser extent. A retrospective study of 701 patients showed an overall success rate (alleviation of symptoms) of 70 % [13]. When only patients with grade III hemor-

rhoids were included, the success rate decreased to 59 %. Three studies were identified that compared outcomes of EH directly to RBL. Murie et al. evaluated 100 patients with either grade II or III hemorrhoids and randomized them to EH or RBL [14]. Of the 56 patients with grade III hemorrhoids, 97 % of patients undergoing EH had no symptoms of prolapse at 1 year compared to 70 % in the RBL group ($p=0.04$). When adding in the patients with grade II hemorrhoids, 86 % of EH patients had no bleeding at 1 year compared to 74 % in the RBL group ($p=0.28$).

Lewis et al. compared EH with anal dilatation, RBL and cryotherapy [15]. Of the 26 patients undergoing EH, 100 % had fewer symptoms and 65 % had no symptoms at 1 year, as opposed to 67 % and 13 % for RBL. In the long-term (6 months–5 years) 100 % of EH patients had fewer symptoms and 86 % had no symptoms. Only 40 % of RBL patients had fewer symptoms and 23 % were symptom free. No patients in the EH group required further treatment compared to 80 % in the RBL group.

A systematic review of the two aforementioned trials demonstrated greater efficacy for EH over RBL for the treatment of grade III hemorrhoids (2 trials, 116 patients, RR 1.23, 95 % CI 1.0–1.5, $p=0.01$). However, this difference was not seen with grade II hemorrhoids (1 trial, 32 patients, RR 1.07, 95 % CI 0.9–1.2, $p=0.32$) [16].

A 2011 study randomized 100 patients with grade II/III hemorrhoids to EH or RBL [17]. Of the grade III patients (38 patients), 12.5 % of the EH group experienced recurrent prolapse symptoms after 6 months compared to 50 % in the RBL group. Although no statistical analysis was included in the study, post-hoc analysis reveals this is a statistically significant finding ($p=0.03$). Consistent with the systematic review is the finding that RBL leads to better results with grade II hemorrhoids compared to grade III (77 % vs. 50 % without prolapse at 6 months, respectively).

In a comparison of PPH with RBL, there was a significant decrease in the percentage of patients experiencing the symptoms of bleeding from hemorrhoids at 2-weeks post-procedure in the PPH group (27 % vs. 68 %, $p<0.005$). This difference was not seen for prolapse, pruritis, or wound discharge [18]. By 2 months, there was no difference in symptoms experienced in either group.

We did not identify any published results comparing DGHAL to RBL. However, there is currently a multi-center randomized controlled trial that has been completed comparing these two interventions for grade II and III hemorrhoids, with results pending [19].

Post-Treatment Pain and Complications

A systematic review of trials comparing EH to RBL for grade II/III hemorrhoids (including Murie and Lewis, et al.) demonstrated significantly more patients that underwent EH experienced post-operative pain (3 trials, 212 patients, RR 1.94, 95 % CI 1.62–2.33, $p<0.001$) [16]. There was no statistically significant difference

in other postoperative complications such as urinary retention, hemorrhage, or anal stenosis. A meta-analysis of the same three trials revealed similar results [5]. Gagloo et al. found 100 % of patients undergoing EH required postoperative analgesia compared to 20 % of patients after RBL [17]. Severe pain from RBL may result from placement of the band below the dentate line, which precludes the banding of external hemorrhoids [3].

While EH has been repeatedly shown to be associated with more postoperative pain than RBL, a recent Cochrane Review has demonstrated a significant decrease in pain when hemorrhoidectomy is performed with a LigaSure device [20]. Pain scores on the first post-operative day showed a WMD of −2.07 (10 studies, 835 patients, CI −2.77–1.38). There was no relevant difference in other postoperative complications. A study comparing DGHAL *with* mucopexy to EH demonstrated no significant difference in post-operative pain scores up to 2 weeks [12].

In a comparison of PPH with RBL, PPH was associated with a higher maximal pain score at discharge (5 vs 2, $p < 0.001$) and at 2 weeks (5 vs 0, $p < 0.001$). However, by 2 months, no patient in either group complained of pain. There was no difference in other complications such as urinary retention, bleeding, anal stenosis, or change in continence. However, his study was not sufficiently powered for these endpoints [18].

Lifestyle (Return to Work and Patient Satisfaction)

Murie et al. reported that 100 % of working patients undergoing EH lost time from work with a mean of 32 days compared to 44 % of the RBL group with an average time away from work of 3 days (SD 7 days-$p < 0.01$) [14]. However, the newer techniques of hemorrhoid surgery have considerably improved return to work times. A Cochrane review comparing LigaSure hemorrhoidectomy to standard EH demonstrated a return to work 4.88 days earlier (4 studies, 451 patients, CI 2.18–7.59). When comparing DGHAL to EH, DGHAL patients returned to work after 10 days compared to 22 days in the EH group ($p = 0.09$) [12].

A systematic review demonstrated similar overall patient satisfaction in both EH and RBL patients (RR 1.02, 2 studies, 148 patients, 95 % CI, 0.94–1.10) [16]. Gagloo, et al. reported 70 % of patients considered EH an “excellent” modality compared to 64 % for RBL [17]. There was no difference noted between PPH and RBL in terms of patient satisfaction at discharge, 2 weeks, 2 or 6 months [18].

Cost

None of the identified studies comparing EH to RBL evaluated cost. However, in the current healthcare climate, cost of therapy must be a consideration. Factors that may impact cost include operative time, equipment, and need for further treatment. In

addition, the time of convalescence financially impacts patients, and the economy as a whole.

There is considerable variation of operative time based on surgical technique. Multiple studies have demonstrated EH to have longer operative times than other techniques such as PPH [21]. However, when accounting for equipment costs, EH was demonstrated to be less expensive than PPH ($252 vs. $504) [22]. The addition of disposable LigaSure diathermy forceps adds an additional $225 per operation to EH [23].

RBL does not require operating room time and the cost of equipment is minimal. However, a long-term study of over 700 patients demonstrated that 30 % of patients require re-treatment with a median 2 bandings per patient and a range of 1–17 bands placed [13]. Also, as previous studies have demonstrated increased pain with multiple bandings in a single session, patients often need to be brought back for several sessions [13, 24, 25]. However, as stated above, RBL does allow a considerably earlier return to work, reducing lost wages.

Recommendations

There are insufficient randomized controlled trials to make a strong recommendation based on high-quality evidence. However, there are trends in the literature sufficient for recommendations.

Recommendation 1
Most patients with uncomplicated grade III internal hemorrhoids may be effectively treated with office procedures as first line treatment after appropriate medical therapy. Strong recommendation based on moderate quality evidence.

Due to the relatively low complication rate, decreased pain, faster return to work and reasonable efficacy, office techniques such as rubber band ligation may be an appropriate first option for many patients. While not as efficacious as surgical hemorrhoidectomy, many patients may succeed without a trip to the operating room. This technique does burn any bridges and therapy may always be escalated to surgical management.

Recommendation 2
Patients with large multi-column grade III hemorrhoids or a mixed internal/external component should undergo surgical hemorrhoidectomy. Strong recommendation based on moderate quality evidence.

Large hemorrhoids may not be treated as effectively with office-based procedures. This may be due to the small size of the ligation barrel limiting the size of the hemorrhoid banded [26]. In these cases, surgical hemorrhoidectomy is the better choice to remove all affected tissue. In addition, as multi-column disease may require multiple banding episodes, these patients may be good candidates for surgery. Finally, as rubber band ligation should not be applied below the dentate line, patients who seek treatment for mixed component hemorrhoids should preferably undergo surgery.

Recommendation 3
Patients who are unable to tolerate or have failed office-based techniques should undergo surgical hemorrhoidectomy. Strong recommendation based on moderate quality evidence.

While office based procedures such as rubber band ligation may have the advantages of decreased invasiveness, many patients require repeat therapy. In addition, while the risk of late bleeding after RBL is similar in patients who take no antithrombotic therapy and those who hold antithrombotic therapy, not all patients are able to do so [27]. Patient preference may play a large role in how many times this is done. In patients who continue to be symptomatic from their hemorrhoids or no longer wish to have repeat procedures, surgical therapy is appropriate.

Expert Opinion

When we see patients with symptomatic grade III hemorrhoids, they are typically complaining of tissue prolapse, bleeding, and mucous drainage. Occasionally they will complain of pain from hemorrhoidal engorgement with straining. By the time the rectal mucosal prolapse requires manual reduction, we do not think that non operative treatment alone, such as fiber supplementation, will likely provide successful and durable relief of symptoms.

Patients with discrete, localized internal grade III hemorrhoids will be offered in-office rubber band ligation, using a suction banding device. The rubber band is positioned directly above the dentate line and the suction is held long enough to fill the chamber fully with excess hemorrhoid tissue/rectal mucosa. Although caution has been expressed re banding more than one column at a single session due to an increased risk of complications and/or pain, we routinely band the two most prominent columns at the initial session. This approach expedites the successful treatment of the hemorrhoids while minimizing return office visits and additional procedures. We warn all patients they should expect 48 h of rectal “pressure” but do not prescribe pain medications beyond Tylenol. We caution them regarding the risks of bleeding, pain, and infection, although serious complications are rare. We see patients back in

1 month for repeat banding if necessary, recognizing that the majority of patients will not return when the initial RBL has successfully resolved their symptoms. When patients are anticoagulated on medications beyond aspirin, we hold the anticoagulation prior to RBL due to the risk of hematoma and bleeding.

When patients present with symptomatic, circumferential internal grade III hemorrhoids or when they do not tolerate in office anoscopy and/or RBL, we typically offer them PPH hemorrhoidectomy. When the purse string stitch is properly placed one cm above the hemorrhoids themselves, we have found this to be a very successful and durable option for symtomatic grade III hemorrhoids. This provides a single-procedure solution for extensive disease, as opposed to serial RBL sessions. Patient pain experience varies based on location of the staple line as well as variability of anal canal innervation. An alternative remains Doppler-guided hemorrhoid artery ligation; the addition of a mucopexy significantly improves outcomes and long term success.

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Chapter 37
Which Patients with Fecal Incontinence Require Physiologic Workup?

Tracy Hull and Nouf Y. Akeel

Introduction

Anal physiology testing is part of the initial diagnostic workup used in patients presenting with fecal incontinence (FI) but the value in defining the disease severity, predicting and assessing treatment outcomes has been debated [1]. This chapter will present the available evidence in the literature to define the role of anal physiology testing for FI.

Search Strategy

PubMed was queried using different combinations of search terms. The search terms were: faecal/fecal incontinence, anal incontinence, assessment, testing, evaluation, fecal incontinence/diagnosis, outcome and process assessment (Health Care), diagnostic techniques and procedures, diagnosis, physical examination, diagnostic techniques, digestive system workup, diagnostic evaluation, predictive value of test, physiological test, physiologic workup, manometry, anal manometry, anorectal manometry, balloon expulsion, pudendal nerve terminal motor latency, costs and cost analysis, cost, and quality of life. The filters used were: English; adult: 19+ years; dates: January 1994-present; and humans. References of relevant articles were also reviewed.

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T. Hull (✉) • N.Y. Akeel, MD
Department of Colon and Rectal Surgery, Digestive Disease Institute, The Cleveland Clinic Foundation, Cleveland, OH, USA
e-mail: hullt@ccf.org

N. Hyman, K. Umanskiy (eds.), *Difficult Decisions in Colorectal Surgery*,
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P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with fecal incontinence.	Physiologic workup.	Clinical Decision Making.	Diagnosing the underlying cause. Predicting treatment outcome.

Results

We feel that obtaining a detailed history and physical exam is usually the most important determinant that influences the decision making [2, 3]. Therefore when considering a diagnostic test, the key question is whether this test will affect the overall management plan.

Some studies reported that physiologic testing could guide the physician in treating patients with FI. Vaizey and Kamm prospectively studied 100 patients to evaluate the impact of anorectal investigations (this included anal ultrasound) on the management decisions. They found that the information provided by anorectal physiologic assessment had an impact on management in patients with benign anorectal disorders. However, carefully evaluating their study, even though anorectal assessment had an important diagnostic and prognostic role in managing patients with benign anorectal disorders, endoanal ultrasound was actually the driving test that changed their plans in FI patients (n = 51); anorectal physiology helped guide decision making for patients with constipation [4]. Therefore, anorectal physiology testing did not really seem to influence FI decisions.

Wexner and Jorge conducted a prospective study on 308 patients presenting with various complaints (constipation, fecal incontinence and chronic intractable rectal pain) to assess the usefulness of colorectal physiological studies to identify all relevant causes that could be treated [5]. Out of 308 patients, 80 presented with FI. The etiology of FI was revealed by history and physical examination alone in 9 patients (11 %) and by physiological testing (anal manometry, cinedefaecography, anal electromyography and pudendal nerve terminal motor latency PNTML) in 44 (55 %). The etiology remained undiagnosed in 27 patients (34 %) even after testing. The causes of FI were loss of muscle fibers (26 %), neuropathy (13 %), combined muscle loss and neuropathy (19 %), and rectoanal intussusception (9 %). They concluded that physical examination might detect anorectal scarring, attenuation of the rectovaginal septum/anal sphincters, and poor contraction of the sphincter; however clinical evaluation cannot confirm the presence of iatrogenic injury. Physical examination also was not capable of detecting pudendal neuropathy. In their view, findings of colorectal physiological testing permit assignment of patients to treatment regimens. It is important to note that this study also included more investigations than just anal physiology and they reported using all this data when making their conclusion. Therefore the role of anal physiology could not be determined.

On the other hand, more recent studies reported no benefit to physiologic testing for FI. Lam et al. [3] prospectively assessed 600 patients referred for anorectal testing and compared those with and without FI (48 % with fecal incontinence and 87 % female) in order to formulate a statistical model to determine which factors would predict FI, particularly after a stoma closure. In regards to anorectal physiology testing, women with FI had lower anal pressures, shorter sphincter length, and smaller rectal capacity. Men with FI had lower anal pressures. Incontinent and continent patients had a broad overlap in anorectal physiology testing. They did find that all patients with a rectal capacity <60 cc had FI and of those with maximum basal and squeeze pressures ≤20 mmHg, only 4 % were continent. They used six items to create a statistical model for FI (female, age, stool consistency, maximum rest and squeeze pressures, rectal capacity, and anal sphincter defects). They then used this model on 5 women to accurately predict the risk of FI following stoma closure. While this study did demonstrate some utility for anal physiology testing, this was used in combination with other tests and consideration of patient characteristics.

Similar findings were also reported by Raza and Bielefeldt [6]. They reviewed 298 patients who had anorectal manometry mainly for FI (51 %) and constipation (42 %). Patients with fecal incontinence had significantly lower pressures compared to individuals with constipation, but the data overlapped significantly. The sensitivity of resting and squeeze pressures were 50 and 59 %, respectively while the specificity for low squeeze pressures was only 69 %. They concluded that manometry should not be used routinely because it has poor discriminatory power.

Zutshi et al. conducted a retrospective study on 53 women who had a sphincter repair. They reported that anal manometry did not correlate with severity of incontinence nor did it assess or predict response to treatment [1]. Bordeianou et al. looked at the relationship between anorectal manometry, fecal incontinence severity (FISI scores), and findings at endoanal ultrasound in 351 women [7]. They found FISI scores were equally severe in patients with or without a sphincter defect; a weak correlation was observed between resting anal pressure and the severity of defects on anal ultrasound; and no correlation existed between maximum squeeze pressure and FISI scores. In the subset of patients with a sphincter defect (n = 148), a weak and negative correlation was reported between the mean resting pressures and maximum resting pressures, the size of the internal and external sphincter defects, as well as the size of the perineal body.

In a Cochrane review evaluating the effects of sacral nerve stimulation (SNS) for FI and constipation, anorectal manometry did not appear to predict which patients would benefit from SNS and the authors concluded that testing with anorectal manometry did not appear to provide clinically useful information [8].

Anal manometry has many limitations. One drawback is that it is very difficult to compare results between institutions because manometric findings are not standardized; the normal range of values varies at each institution [9]. There are no normal values stratified by sex and age [10] and different companies manufacture different types of machines that also adds to the variability.

Intact pudendal nerves may contribute to the success of FI treatment such as SNS or sphincter repair. However PNTML reflects the activity of the fastest fibers, which

makes it a poor indicator of damage to the entire range of nerves that supply the sphincter complex. Additionally it is operator dependent. This has led many investigators to no longer recommended PNTML when evaluating FI [11–13]. In a systematic review by Glasgow and Lowry, 900 patients from 16 studies (2 case control, 1 prospective and 13 retrospective studies) were included as they looked at the outcomes of anal sphincter repair for FI [14]. In five studies, pudendal neuropathy, resting and squeeze anal pressures, anal canal length, and rectal compliance did not predict long-term outcomes following sphincteroplasty [15–19]. However, there was one retrospective study that reported pudendal neuropathy predicted the outcome after sphincter repair for FI [20].

Recommendations Based on the Data

The majority of published studies examining the role of physiologic workup in FI are retrospective (low quality of evidence). FI is multifactorial in etiology and since there is no gold standard test of the overall continence mechanism [10], this makes as assessment of utility more challenging. The available clinical assessment tools also have a subjective component which adds to the challenge of using them for management decisions. Based on this review, we provide a weak recommendation against the use of anal physiology testing routinely. Anorectal physiologic testing does not generally harm the patient; however, most of the available data shows no impact for choosing treatment or predicting outcomes. There may be some benefit when combined with a total anorectal assessment and testing. Results of anal physiology testing overall do not correlate with the severity of symptoms nor does it assess response to treatment.

Summary of Recommendation Options

Strength of recommendation	Implications for patients	Implications for clinicians	Implications for policy makers
Weak against anal physiology testing.	It does not cause harm but may not improve outcome.	In some circumstances, it may aid treatment recommendation.	Should be considered but used selectively.

A Personal View of the Data

At our institution we start all work-up for patients with FI utilizing a detailed history and physical exam. We believe this is the most important factor in discerning contributing factors and making management decision in FI. We do obtain anal physiology testing; however as we have gained more data and experience, we do not feel it overall guides our therapy for FI. One exception would be FI related to rectal dysfunction. When looking at first perception of a balloon inflated in the rectum, urge to defecate, and maximum tolerated volume, a rectum that is hypersensitive may push stool past a sphincter that has acceptable tone on physical exam. This finding would prompt us to communicate with the physical therapist so appropriate therapy can be used to try to desensitize the rectum. Also suppositories that decrease spasticity may be considered. Conversely, for patients detected to have a hyposensitive rectum with a maximum tolerated volume of >300 cc (the limit of what the balloon can hold), FI can be a result of overflow which may be difficult to detect by history and physical exam only. For patients with a hyposensitive rectum, communication with the physical therapist is essential so they work on appropriate retraining. Also enema therapy may be more efficacious in this group.

We do not feel overall that resting pressures and squeeze pressures are helpful. We also agree that PNTML does not correlate with what we find on physical exam. For instance when doing a digital and asking a patient to contract against the examining finger there may be no movement at all in the levator or sphincter complex, but the PNTML may be normal. Nearly all patients should initially be offered conservative management which consists of dietary adjustments, antidiarrheal medications, enema therapy, skin care, and physical therapy retraining. If conservative measures fail, then patients are considered for further workup and treatment. We used to feel that anal ultrasound was our preferred test, but with the popularity of SNS for treatment, we do not rely on this test as much as in the past (Tables 37.1 and 37.2).

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Table 37.1 Anal physiology in diagnosis of FI

Author	Year	Patients	Study type	Results	Quality of evidence	Comment
Dobben et al. [21]	2007	FI (n = 312)	Prospective	Anal inspection and digital rectal examination DRE can give accurate information about anal sphincters but do not detect EAS defects <90°.	Low	Anal inspection and DRE in some centers done by residents, gynecologists, or gastroenterologist. The clinicians were unblinded to patients' history.
Raza and Bielefeldt [6]	2009	FI vs. chronic constipation and others (n = 298)	Retrospective	Manometric findings have low sensitivity and specificity and do not discriminate well between continent and incontinent patients.	Low	
Pehl et al. [22]	2012	Healthy controls (n = 144) vs. FI patients (n = 599)	Retrospective	Single data from the entire spectrum of manometry information is moderate for the pressure data and poor for the sensory data. The entire data set has excellent sensitivity (91.4 %) and moderate specificity (62.5 %).	Low	

Author	Year	Patients	Study type	Results	Quality of evidence	Comment
Lam et al. [3]	2012	FI vs. continent patients (n = 600)	Prospective	There was a large overlap between incontinent and continent patients.	Moderate	
Lam et al. [23]	2012	FI (n = 218)	Prospective	Anal manometry did not detect anorectal sphincter defects. Anorectal manometry and ultrasound do not correlate well with FI scores.	Moderate	

Table 37.2 Anal physiology in predicting FI treatment outcomes

Study	Year	Type of treatment	Type of study	Results	Quality of evidence	Comment
Buie et al. [24]	2001	Anterior sphincteroplasty (n = 191)	Retrospective	Anorectal manometry and PNTML are not predictive of postoperative function.	Low	33 % of the patients did not have manometry and 53 % did not have PNTML
Gearhart et al. [25]	2005	Sphincter repair (n = 20)	Prospective	The physiologic parameters are not predictive of functional outcome.	Moderate	
Zutshi et al. [1]	2010	Sphincter repair (n = 53)	Retrospective	No correlation of pre- and postoperative manometric parameters with incontinence scores.	Low	
Glasgow and Lowry [14]	2012	Anal sphincter repair (n = 900)	Systematic review	No consistent predictive factors for outcomes were identified.	Moderate	
Bols et al. [26]	2012	Physiotherapy (n = 80)	Secondary analysis of a randomized trial	Results of physical examination, diagnostic tests, and physiotherapy assessment were not predictive of outcomes.	Moderate	
Feretis and Chapman [27]	2013	Biofeedback (n = 137)	Retrospective	Anorectal investigations are of doubtful role in patient selection for biofeedback therapy.	Low	

Study	Year	Type of treatment	Type of study	Results	Quality of evidence	Comment
Roy et al. [28]	2014	SNS (n = 60)	Prospective	No pre-treatment or post-treatment assessment parameters that predict the outcome of SNS.	Moderate	
Quezada et al. [29]	2015	SNS (n = 60)	Retrospective	Anal physiology testing, PNTML and ultrasonography were not predictive of clinical outcomes of SNS.	Low	

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Chapter 38
Benign Anal Disease: Who Are the Right Candidates for Sacral Nerve Stimulation?

Teresa C. Rice and Ian M. Paquette

Introduction

Fecal incontinence (FI) is defined as the involuntary passage of stool or flatus over at least 1 month's duration [1, 2]. It is a physically and socially debilitating condition that affects between 1 and 15 % of adult patients [3–5]. The disease can dramatically limit an individual's activity, negatively impacting quality of life and resulting in significant morbidity. The etiology of FI is often multifactorial and consequently management of the disease is complex. Initial therapy typically begins with conservative measures including dietary or medical management [6–8] and biofeedback [9, 10]. However, when patients do not respond to these initial measures, consideration is given to surgical management including sacral nerve stimulation (SNS), sphincteroplasty [11], sphincter replacement strategies [12, 13], or stoma creation [14, 15]. Sacral nerve stimulation was initially developed for management of urinary incontinence but was first used for the successful treatment of FI by Matzel et al. in 1995 [16]. Due to its reported long-term efficacy and low morbidity, SNS continues to develop as an emerging and promising technique for the management of severe FI. Here, we aim to identify which patients with FI would benefit from SNS. Further, we describe the utility of SNS for management of FI in the subset of patients with a complete external sphincter defect.

T.C. Rice, MD
Department of Surgery, University of Cincinnati College of Medicine, Cincinnati, OH, USA

I.M. Paquette, MD (✉)
Division of Colon and Rectal Surgery, University of Cincinnati College of Medicine, Cincinnati, OH 45219, USA
e-mail: ian.paquette@uc.edu

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Table 38.1 PICO Table

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with FI	Sacral nerve stimulation	All other interventions	Success of therapy, decrease in FI episodes, change in CCIS, morbidity

Search Strategy

A systematic review of MEDLINE, PubMed, and the Cochrane Database of Collected Reviews was performed from 1995 through December 2015. Search terms included "fecal incontinence" and "sacral nerve stimulation" or "sacral neuromodulation" or "percutaneous nerve evaluation". All English language manuscripts and studies in adult patients were reviewed. Case reports were excluded from review. The primary outcome examined was success of therapy based on greater than 50 % improvement in FI severity following permanent implantation with SNS. Other outcomes examined included changes in the Cleveland Clinic Florida Incontinence Score (CCIS) [17] (0–20, 0 – perfect continence; 20 – severe incontinence) and decrease in episodes of fecal incontinence (Table 38.1). Each study was graded on its quality of evidence based on the GRADE approach [18].

Results

In the SNS studies reviewed, 55–100 % percent of patients had a successful peripheral nerve evaluation (PNE) test as defined by >50 % improvement in FI severity during the testing phase. A successful PNE test is highly predictive of a successful permanent implant. Preoperative anal physiology testing and ultrasonography do not appear to be predictive of SNS success for the management of fecal incontinence [19]. Factors associated with failure of PNE testing phase include increased age [20, 21], defects in the external anal sphincter [20, 22], and repeated PNE attempts [20, 22]. However, if a PNE test was successful, the aforementioned factors were not associated with reduced success of a permanent implant [22].

Of the SNS studies reviewed, the majority were prospective case studies with only two randomized trials [23, 24]. Most studies were of moderate to low quality evidence by the GRADE approach [18] and were limited by the lack of a direct comparator. In a randomized double blind crossover trial, there was a significant improvement in frequency of episodes, symptom severity, and quality of life during the device ON versus device OFF phase, indicating that improvement was due to the device and not due to placebo [23]. When SNS was compared to optimal medical management in a randomized controlled trial, those treated with SNS had a statistically significant improvement in weekly fecal incontinence episodes (from 9.5 to 3.1) and an improvement in quality of life [24]. Further, 47.2 % of patients achieved perfect continence with SNS. In contrast, the optimal medical management group had no improvement in fecal incontinence, nor quality of life scores. Meurette et al.

compared SNS to artificial bowel sphincter (ABS) and noted that the SNS had higher postoperative CCIS scores (9.4 vs. 4.7), but less constipation and a similar improvement in quality of life [25]. Additionally, there was no significant morbidity in the SNS group while 53 % of patients in the ABS group required further surgical revision due to mechanical failure or ulceration/erosion of the anal canal. Aside from these studies, there are no other direct comparative studies of SNS versus alternative therapies.

The success rates for SNS based upon an improvement of at least 50 % in FI severity following permanent implantation are shown in Table 38.2, in a per protocol analysis (success of patients who received a full-system implantation). Overall, 54–100 % of patients undergoing permanent implantation experienced a statistically significant greater than 50 % improvement of FI in all follow up stages. Perfect continence was achieved in 4–73 % of patients. Table 38.2 demonstrates an improvement in CCIS score across all follow up lengths. SNS therapy for FI was shown to be effective in studies with follow-up as long as 9 years [51, 78], though patients need ongoing follow up; many patients will need a battery change or lead revision over time [82].

Traditionally, patients with FI secondary to sphincter injury were managed with sphincteroplasty and good short-term results were achieved [11]. However, additional studies demonstrated a decline in long-term efficacy [92–94]. As a result, the utility of sphincteroplasty has been questioned as SNS has emerged as a novel, minimally invasive therapy. Recent studies have demonstrated that SNS can be effective even in patients with sphincter injury as seen in Table 38.3. These results were achieved in patients with defects up to 180°. Additionally, SNS was proposed as a treatment option for patients following failed sphincteroplasty. In a study that compared SNS, artificial bowel sphincter (ABS), and repeat sphincteroplasty, no difference was found between CCIS scores or quality of life at follow up [105]. No head to head comparison of SNS versus sphincteroplasty has been conducted to date.

Few studies have been performed to evaluate efficacy of SNS in the setting of rectal prolapse [106, 107]. One small study demonstrated that SNS was less efficacious in patients with high-grade rectal prolapse [106]. However, a more recent prospective study has demonstrated that when SNS is performed following laparoscopic ventral rectopexy, 55.7 % of patients were able to achieve greater than 50 % improvement in FI at 1 year follow up [107]. While initial prospective case series have had encouraging results in the setting of FI following LAR for rectal cancer [108, 109], or in severe perianal Crohn's disease [96], large prospective studies are necessary to validate the success of SNS in these select patient populations.

Recommendations Based on the Data

In summary, SNS is a relatively safe procedure with no reported mortality and low complication rates. The most commonly reported adverse events include pain at the implantation site and infection [60, 70]. An advantage of SNS treatment is the

Table 38.2 Outcomes following permanent implantation with sacral nerve stimulator

Study	Study type	Grade	Temp PNE/ Perm implant	F/U (months)	% Patient improvement		CCIS		FI episodes	
					>50 %	100 % continent	Baseline	F/U	Baseline	F/U
Kenefick [26]	PS	Low	15/15	24	–	73.3			11	0
Ripetti [27]	PS	Low	21/4	15	100		12.2		12	2
Ratto [28]	PS	Low	10/10	–						
Matzel [29]	PS	Low	37/34	23.9	88	39.4			16.4	2
Jarrett [30]	PS	Low	59/46	12	100	41.3	14	6	7.5	1
Rasmussen [31]	PS	Low	43/37	6	86		16	6		
Uludag [32]	PS	Low	75/50	12					7.5	0.67
Altomare [33]	PS	Low	14/14	24					7	1
Jarrett [34]	PS	Low	13/12	12	–	41.7			9.33	2.39
Jarrett [35]	PS	Low	16/16	24	100	25			12	1.5
Leroi [23]	RCT	High	34/28	6	–	26.3	16	8.5	7	1
Hetzer [36]	PS	Low	20/13	1	100		14	4		
Uludag [37]	PS	Low	14/14	1	100				8.7	0.67
Michelsen [38]	PS	Low	29/29	6	100		16	4		
Faucheron [39]	PS	Low	40/29	6	–		17	6		
Kenefick [40]	PS	Low	19/19	24	100	73.7			12	0
Holzer [41]	PS	Low	36/29	35	–				7	2
Gourcerol [21]	PS	Low	61/33	12	69	21	14.4		5	1
Hetzer [42]	PS	Low	44/37	13	91.9		14	5	8	2
Melenhorst [43]	PS	Mod	134/100	25.5	81				31.3	4.8
Navarro [44]	PS	Low	26/24	12	100		15	4.87		
Tjandra [24]	RCT	High	60/53	12	71	47.2	16	1	10	3
Jarrett [45]	PS	Low	8/8	26.5	75				5.5	1.5

Study	Study type	Grade	Temp PNE/ Perm implant	F/U (months)	% Patient improvement		CCIS		FI episodes	
					>50 %	100 % continent	Baseline	F/U	Baseline	F/U
O'Riordan [46]	PS	Low	14/10	–	100		16	5		
Munoz-Duyos [47]	PS	Low	47/29	34.7	86.2	48.3			7.1	<1
Dudding [48]	PS	Low	70/51	24	85.4	39.6			6	0.5
Roman [49]	PS	Low	18/18	3	77.8		14.9	4.9		
Stelzner [50]	PS	Low	20/13	10					9.9	4.5
Meurette [25]	PS	Mod	A: 15	43						A: 5.6
			B:27/15	15						B: SNS
Matzel [51]	PS	Low	12/12	118	77.8	44.4	17	10		
Altomare [52]	PS	Low	94/60	74	74	18	15	5	4	1
Govaert [53]	PS	Mod	208/145	31	80					
Vallet [54]	PS	Low	45/32	33	71.9	4.3	16.1	10		
Oom [55]	PS	Low	46/37	32	81.1	5.4			9	0
Koch [56]	PS	Low	35/19	24	89.5	21			11	2
Otto [57]	PS	Low	14/14	6			16.3	9.6		
Wexner [58]	PS	Mod	133/120	28			39[a]	30[a]	9.4	2.9
Michelsen [59]	PS	Mod	177/142	24	54		16	10		
Wexner [60]	PS	Mod	133/120	28	83	41			9	2
Maeda [61]	PS	Mod	191/191	–			16		14.5	
Faucheron [62]	PS	Mod	123/87	48.5			13	8.2		
Lombardi [63]	RS	Low	16/11	38	100	27.3	19.91	6.82	5	1
Uludag [64]	PS	Low	12/12	6			13.09	4.91	4.55	1.32

(continued)

Study	Study type	Grade	Temp PNE/ Perm implant	F/U (months)	% Patient improvement		CCIS		FI episodes	
					>50 %	100 % continent	Baseline	F/U	Baseline	F/U
Uludag [65]	PS	Low	50/50	85	84				8	0
Soria-Aledo [66]	PS	Low	23/23	–					3.1	0.5
Gallas [67]	PS	Mod	200/200	12	67.3		12	7		
Hollingshead [68]	PS	Low	113/86	21.5	83		15	9	9	1
Lim [69]	PS	Low	80/53	54			11.5	8		
Mellgren [70]	PS	Mod	133/120	3	86	40	39.9[a]	29[a]	9.4	1.7
Maeda [71]	PS	Mod	245/176	13						
Boyle [72]	PS	Low	50/37	17	81.8	39.4	15	8	14	2
Wong [73]	RS	Low	91/61	31			14.3	7.6		
Devroede [74]	PS	Mod	133/120	39	85.9	33.3	39.9[a]	28[a]	9.4	1.9
Faucheron [75]	PS	Low	57/49	62.8			14.1	6.9		
George [76]	PS	Low	30/23	44	100	56	19[a]	10[a]	10	0
Dueland-Jakobsen [77]	PS	Mod	129/129	46	75	36			19	2.5
George [78]	PS	Low	25/23	114			20	8	22	0
Santoro [79]	PS	Low	28/28	6		68	16	3	14.7	0.4
Benson-Cooper [80]	PS	Low	29/27	10.7					7.25	1
Damon [81]	PS	Mod	119/102	48	75.5					
Hull [82]	PS	Mod	133/120	60	88.9	36.1	38[a]	28[a]		
McNevin [83]	PS	Low	33/29	–					19	3
Moya [84]	PS	Low	50/50	55.5			15	4		

Study	Study type	Grade	Temp PNE/ Perm implant	F/U (months)	% Patient improvement		CCIS		FI episodes	
					>50 %	100 % continent	Baseline	F/U	Baseline	F/U
Maeda [85]	PS	Mod	141/101	60	59.4		16	6	22.5	2
Ruiz Carmona [86]	PS	Low	49/33	37			16.04	5.6		
Roy [87]	PS	Low	89/60	36	55					
Quezada [19]	RS	Low	60/55	12			15	4		
Gorissen [88]	PS	Low	82/61	13	98.4		*31*[a]	*27*[a]		
Altomare [89]	PS	Mod	407/272	84	85.1		16	7	7	0.25
Dueland-Jakobsen [90]	PS	Mod	164/164	22			15	9	12	1
Johnson [91]	PS	Mod	152/145	12	94.4	18	14	3		

PS prospective, *RS* retrospective, *RCT* randomized control trial, *ABS* artificial bowel sphincter, *A* Treated with artificial bowel sphincter, *B* treated with SNS, *mod* moderate

[a]Fecal incontinence score index used to assess fecal severity

Table 38.3 Outcomes following permanent implantation of sacral nerve stimulator in patients with anal sphincter defect

Study	Study type	Grade	Temp PNE/ Perm implant	F/U (months)	% Patient improvement		CCIS		FI episodes		Defect
					>50 %	100 % continent	Baseline	F/U	Baseline	F/U	
Conaghan [95]	PS	Low	5/3	3	100	67			6	0.7	EAS 90–120°
Dudding [22]	PS	Low	81/58	29	56.9	15			9.9	1	Not reported
Vitton [96]	PS	Low	5/3	14	100		15	6	7	2	IAS, EAS <180°
Chan [97]	PS	Low	A: 21	12			15.7	1	A:13.8	A: 5	A: EAS <120°
			B: 32						B: 6.7	B:2	B: Intact
Melenhorst	R	Mod	A: 20/16	29.2	69				26.6	12.5	Post repair
[98]			B: 20/14	22.6	79				24.9	4.1	A: EAS <120°
Jarrett [45]	PS	Low	8/8	26.5	75				5.5	1.5	B: EAS 30–150°
Boyle [99]	PS	Low	15/13		77		12	9	15	3	IAS, EAS <180°
Govaert [20]	RS	Low	245/173	34.7	77						Mean EAS 65°
Ratto [100]	PS	Mod	14[a]	60	85.7		16.4	7.7			IAS, EAS <180°
			10/10	33	100		18.3	9.7			IAS, EAS <180°
Brouwer [101]	PS	Low	55/55	37	100		15	6			EAS, not reported
Dudding [102]	PS	Low	9/8	4	77.8	33.3			6.1	1.7	IAS > 30°
Pascual [103]	PS	Low	50/48	17.02	93.8		18	4			Not reported

(continued)

Table 38.3 (continued)

Study	Study type	Grade	Temp PNE/ Perm implant	F/U (months)	% Patient improvement		CCIS		FI episodes		Defect
					>50 %	100 % continent	Baseline	F/U	Baseline	F/U	
Iachetta [104]	PS	Low	A: 9/6	6			12	1			A: Disrupted
			B: 11/8	6			14.1	3.5			B: Intact
Quezada [19]	RS	Low	60/55	12			15	4			Mean EAS 113°
Hong [105]	R	Mod	33 RS	31			17.5	11.5			
			11 ABS	31	45		18.7	8.6			
			15 SNS	31	67		17.6	9.1			

PS prospective, *R* retrospective, RS, *ABS* artificial bowel sphincter, *EAS* external anal sphincter, *IAS* internal anal sphincter, *mod* moderate

[a]Patients receiving sphincteroplasty as comparator group

ability to trial the therapy before permanent implantation, with a successful test being highly predictive of successful permanent implantation. Further, the ability to modify stimulation parameters following implantation allows physicians to reduce adverse effects. SNS is an effective treatment in patients who are non-responsive to medical or conservative management of fecal incontinence. Patients with severe FI may undergo SNS as first line surgical management, though comparative studies to other modalities are lacking. The use of SNS to treat FI in subgroups of patients such as post-LAR for rectal cancer, or in patients with rectal prolapse, is inconclusive and require additional studies in order to validate initial reports.

Recommendations

1. SNS may be considered a first line surgical option in patients with severe fecal incontinence with or without a sphincter defect. (evidence quality moderate; strong recommendation, 1B).

A Personal View of the Data

Once a patient has failed conservative measures for FI, it is up to the surgeon to devise a treatment plan with potential to improve quality of life. Based upon the data presented above, the ASCRS clinical practice guideline recommendation [110], and vast personal experience, I would consider SNS to be a first line therapy for patients with severe FI who have failed conservative measures. Importantly, studies have failed to show any single factor, which is predictive of response to SNS other than the patient's response to a temporary test stimulation [19]. Aside from its very high success rate, the other main advantage of this procedure is the opportunity for the patient to use the therapy during a trial period. This period allows the patient and the surgeon to be sure that they are choosing a regimen that will provide them a successful outcome. For patients with severe FI, refractory to conservative measures and no sphincter defect, I proceed with a test stimulation for SNS. I choose to use the ambulatory based percutaneous nerve evaluation (PNE), which places a temporary lead under local anesthesia, and can be accomplished in the office setting. Patients with a successful PNE test would then proceed with a full-system implantation, while the 10–15 % of patients with an inconclusive PNE would proceed with a surgically placed test lead in the operating room, followed by a 2-week test stimulation.

Currently, the main alternative treatment is sphincteroplasty. For a patient with a sphincter defect, the decision is whether to correct the defect, or proceed with SNS. SNS outcomes are highly successful even with a sphincter defect. In a younger patient with an obstetric sphincter disruption in the prior year, I think that a sphincter repair is a reasonable first line treatment, reserving SNS for the longer-term

sphincter repair failures. The other indication for sphincter repair would be for a near cloacal defect, which may be causing issues such as dyspareunia or body image issues in addition to the FI. In older patients, or patients without a clear reason to repair the sphincter, my preference is to proceed directly to a trial of SNS due to its lower morbidity profile and excellent long-term results. However, direct comparisons of SNS to other modalities are currently lacking in the literature.

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Chapter 39
When Is an Anal Sphincter Repair Indicated?

Jan Rakinic and V. Prasad Poola

This chapter will discuss anal sphincter repair in adult fecal incontinence. Populations not discussed include children, patients with anorectal malformations, and patients who have undergone rectal resection or pelvic radiation.

Introduction

Any adult patient with a disturbance in fecal continence must have a directed history taken and appropriate physical examination conducted. Initial therapy usually consists of dietary manipulation, bulking agents, and occasionally antidiarrheal medications. The details of these important parts of the therapeutic strategy are well described elsewhere. Etiology of fecal incontinence and presence of a demonstrable sphincter defect are key points is to identify, as these will impact therapeutic decisions as well as expected outcomes. Endoanal sonography is most commonly used to identify anal sphincter defects.

If best conservative management is not sufficient for control of moderate to severe fecal incontinence symptoms, further interventions may be discussed. Noninvasive therapies include biofeedback or pelvic floor retraining. While these therapies are very low risk, expected improvement is modest, variable, and seems to deteriorate over the short to medium term [1–4]. Standardized pelvic floor function testing has a limited role in predicting success of biofeedback or pelvic floor retraining [5]. In addition, literature suggests that these therapies are less effective in patients with sphincter defects [6].

J. Rakinic, MD, FACS, FASCRS (✉) • V.P. Poola, MD
Southern Illinois Department of Surgery, Division of General Surgery, Section of Colorectal Surgery, Southern Illinois University School of Medicine, Springfield, IL, USA
e-mail: jrakinic@siumed.edu

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Patients with moderate to severe fecal incontinence and a demonstrated sphincter defect who have not had sufficient response to noninvasive management methods may be candidates for other, more invasive forms of treatment. The use of bulking agents injected into the submucosa overlying the sphincter, or targeted radiofrequency energy applications to the same area, appear to be low-risk interventions. However, benefits and short-term outcomes are modest [7, 8]. Additionally, surgeons have concerns that these modalities alter the tissue planes in the anal canal and so may be reluctant to employ them in patients who are or may become candidates for anal sphincter repair.

Surgical Approaches to Fecal Incontinence

Surgical sphincter repair and sacral nerve stimulation are the most frequently performed surgical procedures for adult fecal incontinence. In contemplating intervention for fecal incontinence, treatment must be individualized for each patient. Functional and quality of life (QOL) related outcomes as well as potential complications of treatment must be considered. This chapter will present an outline for surgeon clinicians to use in determining whether a patient may be best served by an anal sphincter repair, with discussion of patient population (those with a sphincter defect), intervention (anal sphincter repair), comparator (sacral nerve stimulation), and outcomes (improvement in fecal continence).

Patient population	Intervention	Comparator	Outcomes evaluated
Pts with sphincter defect and FI	Sphincter repair	SNS	QOL, decreased incontinence episodes

Anal Sphincter Repair

For the patient with moderate to severe fecal incontinence and a demonstrated sphincter defect in whom best conservative management has not produced sufficient improvement, anal sphincter repair may be considered. A number of authors have reported good to excellent short term results in 60–80 % of patients as evaluated by follow-up questionnaires and QOL measures over 35 years of accumulated data (See Table 39.1) [9–18]. However, the reports are generally small series with retrospective data collection, and few have any comparison groups. It is important to note that most surgeons exclude gaps over 120° from repair.

Important information regarding the longer term durability of anal sphincter repair has been accumulated in the past 13 years [17–23]. The proportion of patients reporting good to excellent outcomes in the long term, approximately 10 years after sphincteroplasty, varies from 14 to 62 % (See Table 39.2.). This is significantly less than that reported in the short term, suggesting that function after anal sphincter

Table 39.1 Short term (up to 5 years) outcomes of sphincteroplasty

Author/year	N	% Excellent/good	% Fair	% Poor
Fleshman (1991)	55	72	22	6
Wexner (1991)	16	76	19	5
Engel (1994)	55	79	–	21
Oliveira (1996)	55	71	9	20
Felt-Bersma (1996)	18	72	–	28
Nikiteas (1996)	42	60	17	24
Sitzler (1996)	31	74	–	26
Ternent (1997)	16	44	31	25
Zorcolo (2005)	93	65	9	27
Barisic (2006)	65	74	17	9

Table 39.2 Long term (10 year) outcomes of sphincteroplasty

Author/year	N	% Excellent/good	% Fair	% Poor
Halverson (2002)	49	14	32	54
Bravo Gutierrez (2004)	130	22	19	57
Zorcolo (2005)	62	45	10	45
Barisic (2006)	65	48	13	39
Maslekar (2007)	64	62	24	15
Mevik (2009)	25	36	–	–
Oom (2009)	120	38	23	40

repair tends to deteriorate over time. However, available literature is limited, and as with the data on short term outcomes, these reports are mostly small series with retrospective data collection and few have any comparison groups. In addition, patient populations and methods of assessing outcomes are heterogeneous, which makes it difficult to draw clear conclusions.

Predicting Outcome After Anal Sphincter Repair

With the realization that long term outcome after anal sphincter repair appears to deteriorate over time, a number of authors have attempted to define what variables might predict outcome. Of nine studies that evaluated the effect of age at surgery on outcome [17, 20–22, 24–27], four [20, 22, 24, 27] reported poorer outcome in patients over age 50. One [24] of three studies that looked at parity [17, 24, 28] found that patients with a history of two or more vaginal births had a poorer outcome after sphincteroplasty. Obstetric injury etiology was associated with better outcome compared to other causes of incontinence in one study that commented on this [22]; however, the number of patients with differing etiologies was small. An observational study of estrogen therapy in postmenopausal women with fecal

incontinence found symptomatic improvement in 90 % after 6 months of hormone replacement therapy, with increases in resting and squeeze pressures and an increase in maximum tolerated rectal volume [29]. The patients with an identifiable sphincter defect had no difference in outcome. However, the potential application of this to the population of patients who are candidates for sphincteroplasty is not clear. All authors felt that older patients should still be considered for anal sphincter repair, though the risk of a possible inferior outcome should be discussed.

Several studies assessed outcome related to initial physiologic and anatomic variables, including resting and squeeze pressures, anal canal length, rectal compliance, pudendal neuropathy, and presence of internal anal sphincter defect [17, 19–21, 25, 28]. None found resting or squeeze pressures, anal canal length, rectal compliance, or presence of internal anal sphincter defect predictive of outcome. Only one [30] of the five studies that evaluated pudendal neuropathy [17, 21, 25, 28, 30] reported that this was predictive of a poorer outcome. However, all authors felt that anal sphincter repair should be offered to patients with pudendal neuropathy, with a discussion of possible poorer outcome.

There is little solid information regarding predictive value of technical aspects of anal sphincter repair. Most surgeons perform overlapping repair. One study [22] evaluated outcome after overlapping repair vs end-to-end repair of the sphincter. No predictive effect was identified. Maslekar et al. [21] felt their good results (86 % good outcome at 7 years) were related to their technique of dissecting each sphincter separately, though they did not include any comparison group. Three studies compared outcomes using fecal diversion with repair performed without diversion [28, 30, 31]. No predictive effect regarding outcome was seen; fecal diversion is not routinely used in anal sphincter repair in the United States.

Relationship of Short and Long Term Outcomes

There does appear to be a predictive relationship between short and long term outcomes. Vaizey et al. [31] found that patients who had good outcomes in short term tended to have more durable outcomes, compared to those who did poorly initially. Malouf et al. [28] reported that the Parks score at 15 months after anal sphincter repair was predictive of long term success. Bravo Gutierrez et al. [20] found that a poor outcome at 3 years after surgery was a strong predictor of poor long term outcome.

Repeat Sphincteroplasty Outcomes

Identification of a recurrent or persistent anal sphincter defect after sphincteroplasty is important, as these patients may be offered a repeat anal sphincter repair. Giordano et al. [32] reported on 36 patients who underwent a repeat sphincter repair after

demonstration of a persistent sphincter defect. The repeat repair group reported good (50 %) and adequate (11 %) function at a median of 20 months, compared with the patients undergoing first-time repair (58 % good, 17 % adequate). Vaizey et al. [31] reported on 23 patients with a repeat anal sphincter repair. Twenty-one were evaluable at 20 months after repeat repair. One was fully continent, 12 reported 50 % or more symptom improvement over preoperative function, and four were unchanged. Hong et al. [33] reported retrospectively on 59 patients with failed sphincteroplasty. In this cohort, 33 underwent repeat sphincteroplasty, 11 had artificial bowel sphincter (ABS) implant, and 15 underwent sacral nerve stimulation (SNS). Observed improvements in continence were similar; however, the rate of complications and reoperations was significantly lower in the repeat sphincteroplasty group, leading the authors to suggest that repeat sphincteroplasty should be considered the first choice in the management of failed anal sphincter repair. However, function after repeat sphincteroplasty may deteriorate over time more markedly than after a first repair [34].

Reporting and Comparing Outcomes

Comparing outcomes of anal sphincter repair is made more difficult by the heterogeneity of the measures utilized in reporting. Many methods of assessment are common, and while those most widely used contain elements of incontinence frequency and severity, not all include patient-defined quality of life measures. However, the quality of life determination may be the most important consideration for the patient who must weigh the effect on daily life activities against the possible risks of treatment. Evaluation of function in 62 patients a mean of 70 months after anal sphincter repair showed that while 70 % had objective clinical improvement, only 55 % considered their bowel control improved and only 45 % were satisfied with the outcome [17]. The authors note that urgency was the most important symptom related to patient satisfaction after anal sphincter repair: 24 of 26 patients in whom urgency had improved reported that they were happy with the outcome.

Sacral Nerve Stimulation

Sacral nerve stimulation (SNS) has been suggested as the first line of treatment in adult fecal incontinence regardless of etiology, in part related to the reported deterioration of function after sphincteroplasty. However, the data on SNS for adult fecal incontinence is still maturing, and concerns exist regarding the rates of complications and reoperation. In a study of 61 patients who underwent temporary electrode stimulation for refractory fecal incontinence, only 35 (57 %) attained the 50 % or greater improvement in incontinent episodes needed to proceed to permanent implant [35]. Of the 33 patients in this study who eventually underwent

permanent implant, 31 % failed to reach the 50 % reduction threshold defined as success. Younger age was related to success with temporary stimulation. A neurologic disorder as etiology for incontinence was related to success with permanent implant.

SNS was compared to optimal medical therapy in a randomized study including 60 patients with severe fecal incontinence in each arm [36]. Ninety percent (54 patients) in the SNS group reached the threshold of 50 % improvement of incontinent episodes; 53 were implanted with 47 % reporting perfect continence. There were no septic complications at a mean follow up of 12 months. There was no significant improvement reported in the medical therapy group.

A short version Cochrane review of SNS for fecal incontinence published in 2008 included two small crossover studies [37]. The authors concluded that while results were very limited, it suggested that SNS could improve fecal continence in selected patients. However, it was also noted that temporary percutaneous stimulation did not always successfully identify those for whom a permanent implant would be beneficial, exposing some group of patients to having an ineffective invasive procedure and foreign body implant.

Several longer term reports on SNS results from a multi-institutional study group illuminate the risk of adverse events and significant complications requiring reoperation. The most common device or therapy related adverse events were implant site pain (28 %), paresthesia (15 %), change in stimulation sensation (12 %), and infection (10 %) [38]. Of particular note, infection carries a 50 % risk of permanent system explantation [39]. Additionally, 36 % of patients followed for at least 5 years required a device revision, replacement, or explant [40].

The most recent Cochrane review of SNS for fecal incontinence included four crossover trials and two parallel group trials. The authors concluded that the limited evidence from the included trials suggested SNS could improve continence in a proportion of patients with fecal incontinence. However, authors also noted the frequency of reported adverse events ranged from 15 to 21 % [41].

Discussion

Direct comparison of data regarding anal sphincter repair and SNS is difficult. Most of the studies of sphincteroplasty are small, single institution, often retrospective, and the populations included and measures used to quantify outcome are heterogeneous. This is underscored by the conclusions of the most recent Cochrane review of surgery for fecal incontinence in adults, which comments on the lack of high quality randomized controlled trials for fecal incontinence surgery [42]. While short to medium term outcomes for anal sphincter repair are good, function deteriorates over time. However, long term outcomes still seem at least as good as the definition of SNS “success”, and patient quality of life and reported satisfaction remain high.

Many of the published studies of SNS in fecal incontinence are small crossover or parallel trials, with a lack of comparison to anal sphincter repair. The included

populations are heterogeneous, and the outcome measures often differ from those used in the evaluation of anal sphincter repair outcomes. The frequency with which patients achieve the 50 % reduction threshold to proceed to permanent electrode implant varies, with predictive factors not clearly identified, and success with temporary implant does not guarantee success with permanent implant. Finally, the risk of complications leading to reoperation appears to be 15–20 %.

Conclusions

A. In patients with a demonstrated sphincter defect, if best conservative management is not sufficient for control of moderate to severe fecal incontinence symptoms, sphincteroplasty should be strongly considered. Discussion of possible worse short and long term outcomes should be undertaken with patients over age 50 (or 60), and possibly also for those with pudendal neuropathy. Grade of strength of recommendation is STRONG.
B. Outcomes of sphincteroplasty are at least as good as SNS outcomes with fewer complications requiring reoperation. Grade of strength of recommendation is STRONG.
C. Those who fail sphincteroplasty can be considered for repeat sphincteroplasty with the expectation of reasonable results. Grade of recommendation is CONDITIONAL.
D. Sphincteroplasty is unlikely to produce improvement for flatus incontinence.

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Part VII
Quality Improvement

Chapter 40
Checklists in Surgery

Eric A. Sparks and Harry T. Papaconstantinou

Introduction

Nearly two decades have passed since the publication of To Err is Human [1], and there has been considerable subsequent interest in research and interventions to describe and prevent health care associated injuries and improve patient outcomes. The WHO launched its "Safe Surgery Saves Lives" campaign in 2008 as a means to prevent unnecessary mortality and improve outcomes for surgical patients [2]. This program resulted in the WHO Surgical Safety Checklist (SSC) [3], which has been widely considered successful in reducing the rates of perioperative complications and mortality. Use of the WHO and similar checklists has now become widespread. However, not all investigations have confirmed their utility and checklists have certainly met some resistance wherever implemented. The purpose of this chapter is to (1) summarize the current body of literature describing the use of surgical checklists and (2) offer expert opinion as to what role checklists may serve for the practicing colorectal surgeon.

E.A. Sparks, MD
Department of Surgery, Baylor Scott & White Healthcare, Scott & White Memorial Hospital, Temple, TX, USA

H.T. Papaconstantinou, MD (✉)
Department of Surgery, Baylor Scott & White Healthcare, Texas A&M University College of Medicine, Baylor Scott & White Memorial Hospital,
2401 South 31st Street, Temple, TX 76508, USA
e-mail: hpapaconstantinou@sw.org

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Methods and Search Strategy

Prior to literature search, a PICO table and four specific questions were formulated as shown below. The literature review was performed under guidelines suggested by the GRADE approach. A systematic literature search was undertaken using MEDLINE via PUBMED and the Cochrane Library. Publications in English dated from January 2000 to May 2015 were included. MeSH search terms and their combination included "checklist", "safety", "randomized control trial", "mortality", "morbidity", "surgery", and "colorectal." Specific database functions such were used to maximize the search. Reference lists of retrieved articles were further screened for additional publications. All identified studies involving evaluation of implementation of, attitudes towards, or outcomes following use of surgical safety checklists were reviewed in depth. The PICO table defined below was used to guide literature search and interpretation of findings.

Question 1: Do surgical checklists reduce perioperative morbidity & mortality?
Question 2: Do surgical checklists have other costs or benefits?
Question 3: Are there costs or barriers to use of surgical checklists?
Question 4: Do surgical checklists offer specific benefits to colorectal surgery?

P (patients)	I (intervention)	C (comparator)	O (outcomes)
All adult patients undergoing colon resection	Use of checklists for quality improvement	Historical management systems without checklists	Mortality Morbidity Errors (wrong site, procedure, etc) Cost Efficiency Attitudes and barriers

Results

Question 1: Do surgical checklists reduce perioperative morbidity & mortality?

The WHO surgical safety checklist was implemented in 2008. In 2009, Haynes' et al. published a landmark study which began a growing mountain of evidence to support the use of these checklists [2]. This study prospectively collected data on approximately 4000 patients from a diverse group of eight hospitals worldwide before and after implementation of the SSC. The authors demonstrated reductions in death (1.5–0.8 %, $p = 0.003$) and inpatient complications (11.0–7.0 %, $p < 0.001$) with checklist use. Many of the studies that followed have been prospective or retrospective observational studies to evaluate the results of SCC implementation in more specific clinical settings (Table 40.1).

While no prospective randomized control studies have been (or likely will be) done, Gillespie et al. performed a robust meta-analysis including seven prospective

Table 40.1 Question 1: Do surgical checklists reduce perioperative mortality & mortality?

Author/year	Study design	n/type of procedure	Outcome measures	Conclusions	Quality of evidence
Gillespie et al. (2014) [4]	Meta-analysis	37,339/general	Major complications, mortality, minor complications	Use of a SSC reduces all complications, wound infections, blood loss. No significant reductions in mortality, pneumonia, or unplanned reoperation.	High
Kwok et al. (2013) [5]	Prospective cohort	2145/general	Process adherence, major 30 days complications, intraoperative hypoxemia	SSC implementation resulted in a decrease in overall, infectious, and noninfectious complications in a resource-limited setting	Moderate
Bliss et al. (2012) [6]	Prospective cohort	319/general	Checklist completion, 30 days morbidity, adverse events	Implementation of SSC results in reduction in adverse events from expected (NSQIP data) rates.	Moderate
Weiser et al. (2010) [7]	Prospective cohort	1750/general	30 day morbidities and mortality	SSC implementation reduces overall complication rate and mortality	Moderate
Haynes et al. (2009) [2]	Prospective cohort	7688/general	30 day morbidities and mortality	SSC implementation significantly reduced inpatient morbidity and mortality in a group of 8 international hospitals	Moderate
Haugen et al. (2015) [8]	Prospective cohort	2212/general	30 day morbidities and mortality	SSC implementation significantly reduced inpatient morbidity and mortality using a model to adjust for possible confounders	Moderate

(continued)

Table 40.1 (continued)

Author/year	Study design	n/type of procedure	Outcome measures	Conclusions	Quality of evidence
Tillman et al. (2013) [9]	Prospective cohort	824/general	Compliance with SCIP Measures	Implementation of SSC improves compliance with SSI reduction strategies and may reduce SSI rates in colorectal procedures	Moderate
Askarian et al. (2011) [10]	Prospective cohort	294/general	Any complication	SSC implementation decreases perioperative complications in a small Iranian hospital	Moderate
Sewell et al. (2011) [3]	Prospective cohort	965/ orthopedics	Any complication, mortality	SSC was not associated with a significant reduction in early complications and mortality in patients undergoing orthopaedic surgery	Moderate
Yuan et al. (2012) [11]	Prospective cohort	481/general	Any complication, mortality	SSC implementation is associated with variable improvements in surgical process compliance and surgical outcomes	Moderate
McCarroll et al. (2015) [12]	Retrospective cohort	89/ laparoscopic/ robotic	30 day readmission Length of stay Operative time	Decreased readmissions (13.5 % vs 4.1 %), no difference in LOS or OR time	Very low
Garcia-Paris et al. (2015) [13]	Retrospective cohort	134/podiatric	LOS, SSI, antibiotic use in podiatric surgery	Use of a SSC improves correct use of antibiotics, reduces SSI's, and reduces LOS	Very low
Reames et al. (2015) [14]	Retrospective cohort	64,891/general	SSI, wound complications, all complications, 30 day mortality	Implementation of a checklist tool did not affect adverse outcomes, potentially due to failed implementation	Low

Loor et al. (2012) [15]	Retrospective cohort	5812/cardiac	Reoperation for bleeding	Implementation of SSC significantly reduces operations for rebleeding	Moderate
van Klei et al. (2012) [16]	Retrospective cohort	25,513/general	mortality	SSC implementation reduces in-hospital mortality, and effect is related to checklist compliance	Moderate
Kim et al. (2015) [17]	Retrospective cohort	637/general	Overall complications, hypoxemia, adherence to safety processes	SSC implementation at a resource-limited hospital improves communication, adherence to safety processes, and complications with no reduction in mortality. Improvements were greater after two years than after 6 months	Low
Dell'Atti et al. (2013) [18]	Retrospective cohort	324/urologic	All complications, intrahospital mortality	SSC implementation led to a reduction in overall complication rate and mortality	Very low
Haynes et al. (2015) [19]	Opinion	n/a/general	n/a	Checklists are effective if barriers to implementation are overcome	Very low
Garg et al. (2013) [20]	Opinion	n/a/general	n/a	Intraoperative crisis checklist is perceived to fascilitate response to massive hemorrhage	Very low
Ladak et al. (2014) [21]	Opinion	n/a/general	n/a	Perceived need for checklists to improve preoperative workup and planning	Very low
Panesar et al. (2009) [22]	Opinion	n/a/general	n/a	Adoption of SSC is effective and should be adopted throughout the UK	Very low

Table 40.2 Question 2: Do surgical checklists offer other benefits?

Author/year	Study design	n/type of procedure	Outcome measures	Conclusions	Quality of evidence
Tillman et al. (2013) [9]	Prospective cohort	824/general procedures	Compliance with SCIP measures	Implementation of SSC improves compliance with SSI reduction strategies and may reduce SSI rates in colorectal procedures	Moderate
Kim et al. (2015) [17]	Prospective cohort	637/general procedures	Overall complications, hypoxemia, adherence to safety processes	SSC implementation at a resource-limited hospital improves communication, adherence to safety processes, and complications with no reduction in mortality. Improvements were greater after 2 years than after 6 months	Low
Semel et al. (2010) [24]	Prospective cohort	n/a	Cost of SSC implementation	Theoretical hospital cost of SSC implementation is recovered if five major complications are prevented	Low
McCarroll et al. (2015) [12]	Meta-analysis	89/robotic/laparoscopic	30 day readmission Length of stay Operative time	Decreased readmissions (13.5 % vs 4.1 %), no difference in LOS or OR time	Very low

cohort studies of 37,339 patients, concluding that SSC's significantly reduce post-operative complications [4]. Van Klei et al. reported a significant reduction in mortality when checklists were fully completed [16]. Lastly, in an attempt to remove confounders, Haugen et al. described an elaborate protocol for SSC implementation, finding significant reductions in morbidity and length of stay [8]. Collectively, these studies indicate that implementation of surgical safety checklists likely improves post-operative outcomes including mortality rates.

However, the benefits above have not been demonstrated in all studies. Several investigators have suggested necessary conditions under which morbidity and mortality can be reduced. Surgical safety checklists are designed primarily to prevent deaths from perioperative errors, which are rare events. Therefore, the intervention of introducing checklists should be with the expectation of population-level benefits, and that a large cohort size will be required to demonstrate effectiveness. Second, some authors have demonstrated effectiveness by examining higher-risk populations (e.g., complicated procedures, unplanned procedures, colorectal operations, and procedures at limited-resource hospitals [3, 5, 9, 10, 12, 15, 17]) or by studying more common or impactful outcomes (e.g., re-operation, infection rates, length of stay [5, 9, 10, 12–18]). Safety culture and attitudes may also play a role in checklists and patient outcome. Haynes et al. updated their original work with a survey of attitudes toward the SSC and found essentially a dose-response curve in which changes in outcomes were directly associated with team perceptions of successful checklist implementation [23]. Fidelity of checklist use and completion has been shown to have a direct correlation with reduction in morbidity [16]. Therefore, the evidence clearly indicates that checklists reduce morbidity and mortality effectively, as long as they are being used as intended.

Question 2: Do surgical checklists have other costs or benefits?

In addition to preventing morbidity and mortality, other indirect measures of quality have been shown to improve with SSC use (Table 40.2). Standardized perioperative processes of care have been shown to improve outcomes. Performance measures including antibiotic timing, intraoperative hypothermia management, and hypoxemia have all been shown to improve with checklist implementation [5, 9, 17]. As a further indication of SSC success, implementation has improved perceptions of perioperative patient safety and communication among operative teams [17, 23].

The vocal critics who oppose the conception of surgical safety checklists have expressed concerns and negative perceptions in the form of anecdotal evidence, surveys, and opinion papers. Some believe that use of a checklist in the operating room is ineffective, unnecessary, and reduces operating room efficiency [25]. Even though there are studies that have failed to demonstrate effectiveness, the concerns brought forth by these critics have not been objectively validated and in some cases directly refuted. Two cohort studies have shown no difference in operative times before and after SSC implementation [12, 26]. This seems intuitive since the checklist itself takes only a few minutes. Results from our institution indicate that SSC implementation did not affect first-start in room on time performance or same day cancellations [9]. Furthermore, the cost of SSC has been investigated. Semel

et al. calculated a cost-savings of $103,829 per year assuming prevention of five major complications during 4000 non-cardiac operations [24]. Therefore, checklists have the added benefit of improving performance of standardized care, perception of patient safety, and communication among team members without adversely affecting operating room efficiency or cost.

Question 3: Are there costs or barriers to use of surgical checklists?

From the inception of checklist utilization, barriers to their use have been present (Table 40.3). The most obvious of these is non-use or failure to complete the checklist [6, 27]. However, "checklist mentality" leads to misuse even after a high completion rate is achieved. Several investigators have audited checklists and team behavior, universally finding poor checklist fidelity [16, 37, 39]. This may be a direct result of checkbox fatigue where the process turns from one of patient safety and benefit to one of mundane automatic (or mindless) checking of a box.

Many specific barriers have been identified which inhibit a culture of SSC compliance. Ineffective education at the time of implementation may hinder adoption, while educational interventions are capable of improving compliance [38]. Checklist-specific factors including non-redundancy, inclusion of only critical and actionable items, and ease of use are described most effectively in Atul Gawande's "Checklist for Checklists" [43]. In the end, investigators have almost universally concluded that leadership buy-in remains the most significant barrier to checklist use [34, 40, 41].

Fundamentally, one may reasonably assume that outcome improvements cannot be seen without proper use of the checklist. Frequent audits of checklist use with cyclical user-feedback and re-education are proposed to help overcome these barriers. Although the barriers to ideal checklist use are numerous, they are well-defined and can be overcome by a carefully designed and implemented checklist process.

Question 4: Do surgical checklists offer specific benefits to colorectal surgery?

Limited data exist to describe the effects of SSC use specific to the field of colorectal surgery (Table 40.4). Tillman et al. performed a prospective cohort study demonstrating improvement in compliance with SCIP SSI-reduction strategies in general surgery patients. In the subpopulation of 183 patients undergoing colectomy, SCIP compliance increased and SSI's decreased (24.1 % vs 11.5 %, $p = 0.03$) after implementation of a surgical safety checklist [9]. O'Mahoney et al. performed a retrospective descriptive study using a checklist to evaluate operative steps of laparoscopic colon resections. They demonstrated feasibility/reproducibility of this tool to identify and document completion of key surgical steps. The authors propose that this standardization offers easier implementation of quality improvement projects in colorectal surgery [44]. As such, the benefits of checklist use are likely applicable beyond those specifically attributed to the well-studied WHO Surgical Safety Checklist. The place of this tool in the field of colorectal surgery is discussed in further detail in the "personal view of the data" section of this review.

Since checklists are excellent tools to ensure performance of complex tasks; it is intuitive that their use in multidisciplinary disease management plans can be powerful. Rectal cancer is a wonderful example as multiple diagnostic and treatment steps

Table 40.3 Question 3: Are there costs or barriers to use of surgical checklists?

Author/year	Study design	n/type of procedure	Outcome measures	Conclusions	Quality of evidence
Oak et al. (2015) [27]	Prospective case series	3000/ general	Pediatric surgery: major errors, "near misses", checklist compliance	0 major errors, 0.3 % near misses, high rate of incompletion or errors	Low
Biskup et al. (2015) [28]	Retrospective cohort	2166/ plastics	30 days complications	Checklist does not reduce complication rates, likely due to checklist item applicability	Low
Haynes et al. (2015) [19]	Opinion	n/a	n/a	Checklists are effective if barriers to implementation are overcome	Very Low
Mahmood et al. (2015) [29]	Retrospective case series	51/ general	Checklist compliance	Checklist completion overestimates actual practice compliance.	Low
Johnston et al. (2004) [30]	Prospective case series	63/ general	Checklist compliance (audit)	Audit tool was successful, compliance with checklist standards varied from 0 to 100 %	Low
Shapiro et al. (2013) [31]	Opinion	n/a	n/a	Checklists are needed for office-based surgeries	Very Low
Abdel-Rehim et al. (2011) [32]	Retrospective cohort	90/ general	Checklist compliance	Use of the WHO SSC improves perioperative use of surgical "Time out"	Very Low
Mahaffey et al. (2010) [25]	Opinion	n/a	n/a	Proper use of a checklist is dificult to maintain; SSC's are distracting and ineffective.	Very Low
Panesar et al. (2009) [22]	Opinion	n/a	n/a	Adoption of SSC is effective and should be adopted throughout the UK	Very Low
de Vries et al. (2008) [33]	Opinion	n/a	n/a	Checklists should be empoyed in surgical care beyond the operative phase	Very Low
Kim et al. (2015) [17]	Retrospective cohort	637/ general	Overall complications, hypoxemia, adherence to safety processes	SSC implementation at a resource-limited hospital improves communication, adherence to safety processes, and complications with no reduction in mortality. Improvements were greater after 2 years than after 6 months	Low

(continued)

Table 40.3 (continued)

Author/year	Study design	n/type of procedure	Outcome measures	Conclusions	Quality of evidence
Russ et al. (2015) [34]	Prospective case series	874/ general	Compliance with checklist steps (audit)	SSC is frequently incompletely or inappropriately performed. Senior leadership performed best and should champion SSC use	Low
Russ et al. (2015) [35]	Survey	119/ general	Attitudes towards SSC use	checklist characteristics, methods of implementation, senior staff support, and post-implementation monitoring are important factors to SSC compliance	Low
Putnam et al. (2014) [36]	Prospective cohort	873/ general	Checklist compliance	Interventions to improve checklist compliance are effective	Low
Papaconstantinou et al. (2013) [26]	Retrospective cohort	35,570/ general	OR efficiency	Implementation of SSC does not negatively impact OR efficiency	Moderate
Sparks et al. (2013) [37]	Retrospective cohort	671/ general	Checklist compliance	Accuracy of checklist completion remains poor after high participation and completion rates are achieved	Low
Sheena et al. (2012) [38]	Prospective cohort	72/ENT	checklist compliance	Educational intervention improves checklist compliance	Moderate
Levy et al. (2012) [39]	Prospective cohort	142/ general	Checklist fidelity	Despite 100 % documentation, process compliance is poorer (60–97 %).	Moderate
Conley et al. (2011) [40]	Survey	n/a	Preceptions of barriers to SSC implementation	SSC success is related to effectiveness of implementation which hinges on buy-in of leadership	Low
Vats et al. (2010) [41]	Opinion	n/a	n/a	SSC use is frequently poor. Barriers to effective SSC implementation include insufficient education, lack of leadership buy-in, perceived inefficiency, and duplicated steps.	Low
Terry et al. (2009) [42]	Opinion	n/a	n/a	Acceptance and implementation of SSC's is spreading, yet physician resistance remains frequent	Very Low
Haynes et al. (2011) [23]	Survey	281/ general	Attitudes towards SSC use	Reduction in complications is directly associated with attidues towards SSC use	Low

Table 40.4 Question 4: Do surgical checklists offer specific benefits to colorectal surgery?

Author/year	Study design	n/type of procedure	Outcome measures	Conclusions	Quality of evidence
Tillman et al. (2013) [9]	Prospective cohort	824/general procedures	Compliance with SCIP Measures	Implementation of SSC improves compliance with SSI reduction strategies and may reduce SSI rates in colorectal procedures	Moderate
O'Mahoney et al. (2015) [44]	Retrospective cohort	16/colorectal procedures	Compliance with operative steps	Checklists help definite and document key steps of laparoscopic surgery	Low

exist, treating team members are interdependent on each other, and multidisciplinary input and communication is crucial to optimal outcomes.

Recommendations from the Data

1. Implementation of surgical safety checklists likely improves post-operative outcomes including mortality rates (Level 2a). Outcomes at highest risk are the most likely to see these benefits (Level 2b). Success hinges on achieving high rates of participation and proper checklist use (Level 2b).
2. Surgical safety checklists do not increase operative times and are not hindrances to the operative team (Level 2b). These tools likely improve efficiency, multidisciplinary communication, and compliance with universal quality improvement initiatives in addition to reducing surgical errors (Level 2b).
3. There are a host of physical and cultural barriers to checklist implementation (Level 2b). These barriers may be overcome by cyclical auditing of checklist use, feedback, and re-education (Level 2b).
4. Surgical safety checklists may offer specific benefits when applied to colorectal surgery (Level 2b). Checklists will likely play a broader role as an invaluable tool for quality improvement in surgery and ensuring proper delivery of care by complex multidisciplinary teams (Level 5).

Personal View of the Data

Surgical care is becoming more and more complicated. As humans, our memory is fallible especially in stressful and complex situations. This is clearly true in surgical patients, and recent efforts to optimize outcomes have become more focused on

standardization of care. Surgical checklists have proven to be an invaluable tool for standardizing the processes of care and improving performance on quality measures. They accomplish this directly, by ensuring that specific tasks are accomplished, and indirectly, by improving communication among multidisciplinary teams. Through these effects, checklists clearly have the ability to reduce morbidity and mortality and improve outcomes.

The checklist, however, does not accomplish these goals by itself; it is not a magic carpet. Human factors affect adoption and effective use, and incorporate the patient safety culture, ownership of process, and team member buy-in. In fact, despite the seemingly simple nature of a checklist, potential pitfalls are numerous. We have found both anecdotally and based on literature review that the following steps are crucial for successful checklist implementation and use.

1. Multidisciplinary planned approach to checklist design and content. You must get buy-in from all stake holders and participants. This will enhance enthusiasm, performance and successful adoption of the checklist.
2. Development of a checklist which meets the recommendations of "Checklist for Checklists" Gawande's "Checklist for Checklists". The first and perhaps most important step here is determining that each checklist item is "a critical safety step and in great danger of being missed", "not adequately checked by other mechanisms", "actionable, with a specific response required", and "can be affected by the use of a checklist". Our opinion is that many checklists which suffer from checkbox fatigue and poor fidelity, if examined, will fail to meet many of these requirements.
3. Leadership must "walk the walk and talk the talk". Physician champions and leaders must embrace and perform the checklist in the proper fashion. Team members look to their leader to see how they respond and perform. A highly visible leader that is perceived as cutting corners or not embracing the checklist and process severely erodes the acceptance, adoption and performance by the remainder of the team.
4. Extensive team education and simulation prior to use. Successful adoption of checklists requires explaining ***why*** something is being done, and must be followed by showing ***how*** it is performed. We have found that simulation is the easiest way to show the how and allows for direct and immediate feedback on performance.
5. Carefully planned and staged implementation strategy. After thorough education and simulation, the implementation phase is another opportunity to avoid checklist failure. At our institution, checklists were rolled out in select operating rooms to gather early feedback prior to making system-wide changes. This controlled approach appeared to ease cultural adoption of the new procedures.
6. Frequent auditing of checklist participation ***and*** fidelity. You get what you inspect, not what you expect. Regular auditing is vital to sustainability of practice. Auditing should be active, not passive, with direct feedback to the team on performance and how to improve. If team members are cutting corners or not performing the checklist as intended, and this is not pointed out and addressed,

it will be perceived as the way it should be done. This concept of "normalization of deviance" is likely why many institutions, including our own, have seen performance erode over time after implementation. Feedback of compliance and outcomes should be shared with the team and augmented with continuing education. Celebration of successes is important to improve morale, justify continued use, and create a positive culture of safety.

7. Iterations of steps 1–6 to continuously improve the checklist and enhance the involved processes. Checklists need an appropriate balance of flexibility and rigidity. For flexibility, we consider this adaptation to an ever changing environment, needs, and evidence of benefit. We believe that checklist change must be a structured process and requires a formal request for change with appropriate data to support the change. This is evaluated by physician champions and team leaders with rapid feedback regarding decision with supporting information. The rigidity is in maintaining the integrity and focus of the checklist. Wide deviations can erode into the spirit and intent of the checklist eliminating support for "why" it is being done.

Of all these steps, we have found that investment, support, and exemplary participation and performance of physician champions from all teams appear to be the most critical and most frequently missed step. This chapter focuses significantly on the surgical safety checklist; however, we believe that checklists play a broader role for colon and rectal surgeons. Checklists allow standardization of care and data collection for research and quality improvement. Opportunities are present for design of new checklist tools which help bridge the gaps between scientifically supported "best practice" and what is actually provided in routine care.

One potential application is the Rectal Cancer Centers of Excellence initiative. Checklists are perfect for this situation as they provide a strict protocol for guidance and objective performance data to tie to outcomes. Our goal in this chapter has been to provide a better understanding of the successes and pitfalls of checklists so that colon and rectal surgeons become champions of theses quality improvement initiatives and consider them a new tool which helps reduce variability in care and provides an opportunity to improve outcomes.

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Chapter 41
Quality Improvement: Where Are We with Bowel Preps for Patients Undergoing Colon Resection?

Anthony J. Senagore

Introduction

Colorectal surgeons have strived for reductions in postoperative septic complication rates and especially the incidence of anastomotic dehiscence since the inception of bowel surgery [1]. Bowel antisepsis as a means to this end was first advocated by Poth in the 1940s [2]. Thirty years later, Barker and Everett advocated for MBP because of their belief that gross fecal loading of the bowel was associated with an increased incidence of wound infection [3, 4]. As a result of this work, MBP became almost uniformly accepted as a dogma going forward [5]. The classic article which codified the role of mechanical bowel prep with oral antibiotics was the three armed study performed by Condon et al. They compared oral mechanical bowel prep with either intravenous cephalothin alone; oral neomycin and erythromycin alone; or both intravenous and oral regimens [6]. Although the intravenous antibiotic chosen was limited in bacterial coverage, the combined strategy was superior nonetheless.

Coppa et al. studied 350 patients randomized to intravenous cefoxitin (broader coverage gram negative and anaerobes) with or without oral neomycin and erythromycin in conjunction with a mechanical bowel prep [7]. The dual regimen was superior for superficial wound infection (11 % versus 5 %). Finally, Schoetz et al. performed the reverse study, randomizing 190 patients to receive neomycin and erythromycin orally with and without intravenous cefoxitin. Wound infection and leak rates were higher in the group receiving only oral antibiotics [8]. These data led to the era of combined mechanical bowel prep, with both oral and intravenous prophylactic antibiotics. Over the last decade, the necessity for mechanical bowel prep

A.J. Senagore, MD, MBA
Department of Surgery, UTMB- Galveston, Galveston, TX, USA
e-mail: anthony.senagore@cmich.edu

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has been questioned along with contemporaneous data reinvestigating the relative role of mechanical prep with or without oral antibiotics.

Patients undergoing colon resection	Bowel prep	No bowel prep	SSI, leak rate, dehiscence, complications

Search Strategy

Search DATA SOURCES: Embase, PubMed, and the Cochrane Library were searched using the terms oral, antibiotics/antimicrobial, colorectal/rectal/colon/rectum, and surgery/operation. Time frame 2014–2016.

MAIN OUTCOME MEASURES: Anastomotic leakage, all-cause mortality, wound infection, peritonitis/intra-abdominal abscess, reoperation, surgical site infection, quality of life, length of stay, and adverse events were measured.

Patients	Intervention	Comparator	Outcomes
Patients undergoing colectomy	No bowel prep	Mechanical bowel prep with or without oral antibiotics	Anastomotic leak, mortality, wound infection, surgical site infection, ileus, reoperation, quality of life, length of stay, and adverse events.

Results

Contant et al. studied 1431 patients undergoing open colorectal resection randomized to intravenous antibiotics (aerobic and anaerobic coverage) with or without MBP [9]. The data demonstrated a significant increase in the rate of intra-abdominal abscess without MBP (2.5 % vs 0.3 %), however there was no significant difference in superficial wound infection (no-MBP-14 % vs MBP- 13.8 %) or anastomotic leak (no-MBP-5.4 % vs MBP-4.8 %). The authors concluded that mechanical bowel preparation can be safely avoided. Jungl et al. performed a similarly designed study of 1505 open colectomy patients and also concluded that there was no significant difference in wound infection (MBP- 7.8 % vs N-MBP- 6.4 %) or anastomotic leak (MBP-2 % vs no-MBP 2.6 %) [10]. The recent meta-analysis by Bucher et al. included 7 RCTs available in the literature. This meta-analysis revealed a higher incidence of anastomotic dehiscence in patients receiving MBP, 5.6 % (36/642), vs no MBP 2.8 % (18/655) (P = .03; OR, 1.85 [95 % CI, 1.06–3.22]) [11]. However, using a number need to treat analysis (NNT) and an incidence of 5 % for anastomotic leaks, 32 patients (95 % CI, 19–306) would have to be operated on without MBP to prevent one leak in a patient receiving MBP before surgery. The rate of intra-abdominal infection (peritonitis or abscess) was similar in the MBP group, 3.7 % (17/458), compared with the no-MBP group, 2.0 % (9/461) (OR, 1.69 [95 %

CI, 0.76–3.75]; P = .18). The rate of wound infection was slightly higher in patients receiving MBP, 7.5 % (48/642), vs no MBP, 5.5 % (36/655) (OR, 1.38 [95 % CI, 0.89–2.15]; P = .15). General complication and extra-abdominal morbidity rates were not significantly different in any of these studies; this finding was confirmed in the meta-analysis. Because of the significant impact of anastomotic leaks, the Bucher meta-analysis would favor the avoidance of MBP in terms of mortality rates (OR, 1.42 [95 % CI, 0.37–5.45]; P = .60). The systematic review performed by Wille-Jorgenson arrived at the same conclusion [12].

A major limitation of the "no bowel prep" philosophy was the failure to understand that these data were obtained in the absence of the documented superior treatment arm, mechanical bowel prep with oral antibiotics. Therefore, the more accurate conclusion from these data is that bowel prep without oral antibiotics is equivalent to no mechanical bowel prep. The recent report from the Michigan Surgical Quality Consortium which analyzed 2062 elective colectomies between January 2008 and June 2009 compared 49.6 % of patients with mechanical prep only to 36.4 % with mechanical prep and oral antibiotics [13]. Patients receiving oral antibiotics were less likely to have any SSI (4.5 % vs. 11.8 %, p = 0.0001), to have an organ space infection (1.8 % vs. 4.2 %, p = 0.044) and to have a superficial SSI (2.6 % vs. 7.6 %, p = 0.001). Interestingly, patients receiving bowel prep with oral antibiotics were also less likely to have a prolonged ileus (3.9 % vs. 8.6 %, p = 0.011). Fry recently reviewed the published literature and found MBP alone did not reduce SSIs in nine prospective randomized trials between 2000 and 2010 [14]. He then performed a meta-analysis of nine randomized clinical trials of MBP which showed the superiority of oral and intravenous antibiotics versus only intravenous antibiotics [odds ratio 0.47 (95 % CI: 0.16–0.77, p < 0.0001)]. Furthermore the rate of SSIs decreased by 6.18 % (95 % CI: 3.43–8.94) with MBP using oral and intravenous antibiotics [14].

More recently, there has been a concerted effort to revisit the impact of bowel prep with antibiotics as part of quality improvement projects. Althumari performed an analysis of the American College of Surgeons National Surgical Quality Improvement Program Colectomy Targeted Participant Use Data File for 2012 and 2013 [15]. The analysis of 19,686 patients (25.7 % no bowel prep; 40.7 % received MBP only; 3.3 % oral antibiotics only; 30.3 % received MBP plus oral antibiotics). Patients who received MBP plus oral antibiotics had a lower incidence of superficial SSI, deep SSI, organ space SSI, any SSI, anastomotic leak, postoperative ileus, sepsis, readmission and reoperation compared with patients who received neither (all P < 0.01). The reduction in SSI incidence was associated with a reduction in wound dehiscence, anastomotic leak, pneumonia, prolonged requirement of mechanical ventilator, sepsis, septic shock, readmission, and reoperation. Kiran analyzed a portion of the same National Surgical Quality Improvement Program-targeted colectomy data and also concluded that mechanical bowel prep with oral antibiotics reduced the rates of SSI, anastomotic leak, and ileus by nearly half [16].

Wick et al. evaluated the impact of the implementation of a pathway designed to improve patient outcomes which adopted a mechanical bowel preparation with oral antibiotics at their institution. Compared to a historical control group, there was a

significant reduction in SSI (18.8 % vs 7.3 %). Collins et al. analyzed long term data from a 1999 to 2005 randomized study comparing mechanical bowel preparation (no oral antibiotics) to no prep and demonstrated that prep was associated with significantly fewer recurrences, and better cancer-specific and overall survival in the MBP group after 10 years [17]. Finally, a more recent meta-analysis assessing seven randomized controlled trials that consisted of 1769 cases determined that both total surgical site infection and incisional surgical site infection were significantly reduced in patients who received oral and systemic antibiotics with a mechanical bowel preparation (total: 7.2 % vs 16.0 %, $p < 0.00001$; incisional: 4.6 % vs 12.1 %, $p < 0.00001$) [18]. Therefore, the current body of data would support the re-introduction (or continued practice) of the combination of mechanical bowel prep with oral antibiotics as well as prophylactic intravenous antibiotics for optimal outcomes including surgical site infection and the related secondary complications in colectomy patients.

Study	Patients	Outcome classification	Typical risk No prep	Typical risk MBP/oral ABX	Quality of evidence
Contant et al. *Lancet*. 2007; 370(9605): 2112–2117	Elective colorectal surgical resection patients	Mechanical prep with either PEG or magnesium citrate vs no Prep; Anastomotic leak	Leak 37/684 (5.4 %)	Leak- 32/670 (4.8 %)	High quality PRCT; however no study arm with prep and oral antibiotics
Jung et al. *British Journal of Surgery* 2007; 94: 689–695	Elective colorectal surgical resection patients	Primary end point- SSI; Secondary- adverse outcomes	SSI- 16.1 % ND in other periop complications	SSI- 15.1 %	HIgh quality PRCT; however no study arm with prep and oral antibiotics
Cochrane Review – Antimicrobial prophylaxis for colorectal surgery (Review) 2009- [19]	Colorectal surgical resection patients	SSI	Oral/IV vs IV	RR 0.55 with combination	High quality comparison of multiple outcomes favoring MBP and oral ABX
Fry DE. *American Journal of Surgery*. 2011;202(2): 225–232	Meta-analysis of 9 studies comparing MBP with and without oral antibiotics	SSI		OR in favor of combined mechanical prep and oral abx for SSI reduction	High quality meta analysis

Study	Patients	Outcome classification	Typical risk No prep	Typical risk MBP/oral ABX	Quality of evidence
Englesbe MJ. *Annals of Surgery* 2010; 252(3): 514–520.	Propensity analysis based on quality database of colorectal surgery patients	SSI risk and associated complications	SSI- 11.8 % Organ Space- 4.2 % Superficial- 7.2 % Ileus- 8.6 %	SSI- 4.5 % Organ Space- 1.8 % Superficial- 2.6 % Ileus- 3.9 %	High quality audited database

Recommendations Based on Data

Based upon the available data, it appears that the initial rigorous work by Nichols and Condon as well as other investigators regarding the efficacy of mechanical bowel preparation, oral antibiotics, and broad spectrum prophylactic intravenous antibiotics has been reaffirmed. The controversy over the need for mechanical bowel preparation in recent years was, in retrospect, supported by incomplete studies which did not include an arm with oral antibiotics. These studies were conceived on the incorrect assumption that modern, broad spectrum intravenous prophylactic antibiotics were sufficient to reduce surgical site infection. The importance of selective GI decontamination is an important component of both enhanced recovery and quality improvement in colorectal surgery.

Strength of recommendation	Implications for patients	Implications for clinicians	Implications for policy makers
Strong in favor of combined mechanical bowel preparation and oral antibiotics; The large PRCT's advocating equipoise for prep/ no prep did not include the important component of oral antibiotics with the prep	Most patients undergoing colectomy would desire a combined MBP/oral ABX prep when offered the informed consent discussion regarding the risk of SSI and associated complications. This approach should be part of the patient education within an enhanced recovery program.	The robust quality data base studies comparing historical approaches to broad implementation of MBP/oral ABX prep are consistent with single center studies performing quality improvement. The consistent and significant decrease in SSI and related complications is compelling and should be widely adopted.	This single component (MBP/ oral ABX prep) is the most important single aspect of any strategy for reducing SSI in colectomy. It is low cost and high reward and should be strongly advocated as a process measure within a greater enhanced recovery protocol for colectomy.

A Personal View of the Literature

The journey of initial adoption of a MBP/oral antibiotic strategy based on high quality prospective randomized studies, followed by the subsequent refutation of that strategy also based on high quality prospective randomized studies is a an excellent object lesson for future quality initiatives. If one looks back at the Nichols/Condon era, all combinations were assessed: no mechanical bowel prep; no prep/oral antibiotics; prep alone; and prep with oral antibiotics. Interestingly, the more modern high quality studies failed to appreciate the strength of the prior research and the need to at least compare the study arm (i.e., no prep) to the gold standard (prep with oral antibiotics). The data describes both the journey away from the successful practice of prep with oral antibiotics with a resulting increase in SSI to the journey back with improved outcomes. At least for my practice, I have maintained this successful process measure as part of a global enhanced recovery protocol with excellent outcomes. This should be a platform for future quality studies where the gold standard should be put up against a comparator with a clear definition of the outcomes to be impacted. Innovation is important but it should be structured in a way that the new approach is at least equal, if not superior both from an outcome and cost perspective.

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Chapter 42
Quality Improvement: Are Fast Track Pathways for Laparoscopic Surgery Needed?

Avery S. Walker, Michael Keating, and Scott R. Steele

Introduction

Multiple studies have been performed demonstrating the benefits of an enhanced recovery program following a wide breadth of surgical disciplines, including more recent reports showing significant benefits of enhanced recovery protocols for patients undergoing a laparoscopic colectomy. This has held true in both comparisons of an open versus minimally invasive approach, as well as when comparing enhanced recovery pathways to traditional perioperative care strategies. While most providers are now well versed in the concept of enhanced recovery, the individual practice and components often vary in number and nature. However, the basic principles of ensuring this program spans the preoperative, intraoperative, and postoperative settings, along with a multidisciplinary mandated "buy-in", are necessary to ensure maximal effectiveness regardless of the institution or procedure.

While enhanced recovery protocols may include anywhere from 8 to 26 different components, almost all begin with detailed patient education on expectations and outcomes in the outpatient setting prior to pursuing optimal perioperative techniques, early enteral nutrition, and early mobilization. Initially described by

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A.S. Walker, MD
Department of Surgery, Brian Allgood Army Community Hospital, Yongsan, South Korea

M. Keating, BA
Case Western Reserve University School of Medicine, Cleveland, OH, USA

S.R. Steele, MD (✉)
Department of Colon and Rectal Surgery, Case Western University, Cleveland, OH, USA
e-mail: harkersteele@mac.com

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Professor Kehlet in the setting of open abdominal surgery, the impact that this "fast track" protocol in the setting of a minimally invasive/laparoscopic approach has also been questioned. To answer this latter question, this chapter focuses on patients who undergo laparoscopic colectomy under the tenets of an enhanced recovery pathway compared to those patients who progress through traditional perioperative management strategies following a laparoscopic approach. The outcomes we primarily evaluated within these programs include overall length of stay, morbidity, and readmission rates--all in an effort to accelerate recovery without compromising patient safety.

Search Strategy

A systematic database search utilizing the Cochrane Collaborative Library, OVID, and PubMed databases was performed to identify all trials of interest from January 2009 to December 2015. This time period was selected in an effort to provide the most up-to-date information balanced with allowing enough time from the initiation and evolution of enhanced recovery programs in the early 2000s. Randomized controlled trials (RCTs) and observational studies were provided the most weight, though not the sole inclusionary criteria. The following keyword combinations were used: "fast track"; "enhanced recovery"; "laparoscopic"; "colorectal"; "colon"; "rectal"; "traditional open surgery"; and "laparotomy". MeSH terms included "minimally invasive"; "laparoscopy*"; "treatment outcome"; "colonic/surgery"; "colectomy/rehabilitation"; "length of stay"; "outcome assessment"; "postoperative care"; "preoperative care"; "patient readmission"; "laparoscopic colectomy" and "enhanced recovery pathway". In addition, we hand-searched reference lists of related systematic reviews since 2001 to identify relevant additional studies. Final studies were selected based on the PICO (Population, Intervention, Comparator, Outcomes) framework as listed in Table 42.1. Although not exclusionary, primary authors focused on all English language manuscripts and studies of adults. The primary authors formulated recommendations with the final grade of recommendation selected using the GRADE system (Table 42.2).

Table 42.1 PICO chart

P (patients)	I (intervention)	C (comparator)	O (outcomes)
Patients undergoing colorectal surgery	1. Laparoscopic-assisted approach or 2. Enhanced recovery program/fast track pathway	1. Traditional open surgery or 2. Conventional postoperative care	Total hospital stay, postoperative stay, complications, readmissions

Note: Studies were included where either (1) a fast track pathway was in place and they compared open vs. laparoscopic approach or (2) laparoscopic colorectal surgery was being performed and the analysis focused whether or not the addition of a fast track pathway changed outcomes

Table 42.2 The GRADE system – grading recommendations

	Description	Benefit vs. risk and burdens	Methodologic quality of supporting evidence	Implications
1A	Strong recommendation, High quality evidence	Benefits clearly outweigh risk and burdens or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B	Strong recommendation, Moderate quality evidence	Benefits clearly outweigh risk and burdens or vice versa	RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C	Strong recommendation, Low or very low quality evidence	Benefits clearly outweigh risk and burdens or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2A	Weak recommendation, High quality evidence	Benefits closely balanced with risks and burdens	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B	Weak recommendations, Moderate quality evidence	Benefits closely balanced with risks and burdens	RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C	Weak recommendation, Low or very low quality evidence	Uncertainty in the estimates of benefits, risks and burden; benefits, risk and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

Adapted from Guyatt et al. [1]

Results

The definition of an enhanced recovery pathway for colon and rectal surgery was established by the Consensus Review of Optimal Perioperative Care in Colorectal Surgery Group in 2009. This was a succinct and easily adaptable list which describes the 20 aspects of the enhanced recovery protocol [2]. Our focus was whether adding an enhanced recovery/fast track pathway to patients undergoing laparoscopic techniques add any benefits when compared to those undergoing laparoscopy in the absence of a fast track pathway (Table 42.3).

It is well known that using a laparoscopic approach for colorectal surgery is associated with shorter hospital stays, decreased postoperative complications, and decreased pain when compared to open surgery [9–12]. It is also well established that adding an enhanced recovery protocol to open colorectal surgery results in better patient outcomes. In theory, the addition of an enhanced recovery protocol should produce better outcomes for laparoscopic surgery as well; however, the lack of tier 1 randomized controlled trials makes this presumption difficult to definitively prove. In reality, most studies are retrospective reviews, underpowered, or lack an appropriate number of fast track elements.

However, Zhao et al. attempted to strengthen the literature by combining the data with a meta-analysis in August of 2014 [6].The authors were able to identify and deem eligible five randomized controlled trials and five clinical controlled trials for a total of 1,317 patients. The patients all underwent laparoscopic colorectal surgery, with 696 participating in an enhanced recovery protocol and 621 patients undergoing traditional care. Importantly, all patients underwent a minimally invasive approach. In addition, all studies within the meta-analysis were determined to range in quality from moderate to high. Primary hospital stay (−1.64 days; 95 % CI, −2.25 to−1.03; $p<0.001$), time to first flatus (−0.40 day; 95 % CI, −0.77 to−0.04; $p=0.03$), time to first bowel movement (−0.98 day; 95 % CI, −1.45 to−0.52; $p<0.001$), and complication rate (RR, 0.67; 95 % CI, 0.56–0.80; $p<0.001$) were all improved when an enhanced recovery program was applied in addition to the laparoscopic technique. Readmission rate and 30-day mortality were found to be nonsignificant, which has been consistent with other studies comparing enhanced recovery protocols within colorectal surgery. Another interesting aspect of this meta-analysis was that complication rates were found to be significantly reduced--a finding in which no other meta-analysis had identified before. The authors ultimately concluded that not only can an enhanced recovery protocol be combined with laparoscopic colorectal surgery to decrease primary hospital stay, increase time to first flatus and bowel movements, but also that using laparoscopy within these protocols may actually increase *patient safety* when compared to traditional perioperative colorectal care.

When looking at some of the existing primary data, a study by Vlug and colleagues provides a closer comparative evaluation. Vlug and associates provided one of the first studies looking specifically at laparoscopy versus open techniques within enhanced recovery protocols in the 2011 entitled LAparoscopy and/or FAst track

Table 42.3 GRADE profile for laparoscopic colorectal surgery in enhanced recovery protocols

Study year	Study type	Patients numbers	Outcomes	Quality of evidence
Zhuang et al. (2015) [3]	Meta-analysis	598 patients Lap vs. Open in ERAS program	Laparoscopic surgery ↓Total hospital stay ↓# of complications	Moderate
Lei et al. (2015) [4]	Meta-analysis	714 Patients 373 FT Lap 341 FT Open	Lap surgery – shorter post op stay and shorter overall hospital stay	Moderate
Tiefenthal et al. (2015) [5]	Prospective Clinical Trial	292 Patients Lap within ERAS program	↓Pain control ↓Hospital stay	Moderate
Zhao et al. (2014) [6]	Meta-analysis	1,317 Patients 696 Lap/ERAS 621 LAP/ traditional care	↓Primary hospital stay ↓Time to first flatus ↓Time to first bowel movement ↓Complications	Moderate-High
Vlug et al. (2012) [7]	RCT	400 Patients 193 Lap/Open FT 207 Lap/Open standard	Factors ↓ total hospital stay Female Sex **Laparoscopic resection** Normal diet on POD 1, 2, 3 Enforced Mobilization	Low-moderate
Vlug et al. (2011) [8]	RCT	400 Patients Lap FT Lap standard Open FT Open standard	Laparoscopy within ERAS protocol ↓hospital stay to 5 days vs. 7 days in the Open and ERAS protocol	Moderate

RCT randomized controlled trial, *ERAS* enhanced recovery after surgery pathway, *Lap* laparoscopic, *FT* fast track pathway

multimodal management versus standard care (LAFA trial) [13]. The authors stratified 400 patients into 4 treatment groups: laparoscopic/fast track, open/fast track, laparoscopic/standard, and open/standard with the primary goal to find a minimum difference of 1 day in hospital stay [13]. They showed a total hospital stay of 5 days in the laparoscopic/fast tract group versus 7 days for the open/fast track group ($p < 0.001$), concluding that optimal perioperative treatment includes a laparoscopic resection within an enhanced recovery protocol [13]. On regression analysis, laparoscopy was the only independent predictive factor to reduce hospital stay and morbidity [13]. When specifically comparing laparoscopic with fast track, versus laparoscopic with standard perioperative care, the median hospital stay was lower in the fast track cohort at 5 days (interquartile range: 4–8) versus 6 days (range: 4.5–9.5). However, secondary outcomes including postoperative hospital stay, morbidity, reoperation, readmission, in-hospital mortality, and quality of life did not differ significantly amongst the groups.

In 2012, Vlug and colleagues followed up with a more specific question given the potentially confounding elements of the enhanced recovery recommendations and attempted to ferret out which aspects of the enhanced recovery protocol predicted early recovery after colon cancer surgery [7]. Using patients from the LAFA trial, all patients who were randomized to fast track care (n = 193) and standard care (n = 207) were analyzed to determine whether one single item or a set of items independently predicted "enhanced recovery" as defined by total postoperative hospital stay as the primary outcome [7]. Six baseline characteristics (female gender, age, ASA, BMI, laparoscopic operation, and right-sided resections) along with the achieved fast-track elements were entered in a univariate linear regression analysis. Those with a $p < 0.100$ were subsequently entered in a multivariate linear regression analysis, which identified female gender, laparoscopic resection, normal diet at postoperative days 1, 2, and 3, and enforced mobilization at postoperative days 1, 2, and 3, as independent predictors of total postoperative hospital stay [7]. They concluded that a laparoscopic resection was an independent predictor of decreased length of stay, in accordance with the results of the earlier LAFA Trial, thus further validating the improvement in early recovery with the use of laparoscopy within an enhanced recovery protocol.

Zhuang et al., published an update to their prior meta-analysis regarding ERAS protocols within colorectal surgery versus traditional care with a more focused meta-analysis in 2015,evaluating laparoscopic versus open colorectal surgery within an enhanced recovery program [3, 14].Five randomized clinical trials encompassing 598 patients were included in the final analysis. The nature of their inclusion/exclusion criteria increased the strength of this meta-analysis. They included only RCTs and all studies must have had at least 7 enhanced recovery interventions. Laparoscopic colorectal surgery significantly reduced total hospital stay by 1.92 days (95 % confidence interval (CI): 2.61± 1.23 days; $p < 0.00001$) and number of complications (RR 0.78; 95 % CI 0.66–0.94; $p = 0.007$) compared with open surgery in the setting of enhanced recovery programs [3]. Unfortunately, the benefits of laparoscopic colorectal resection within optimal ERAS programs was not able to be determined. In part, this was due to the lack of high-quality primary studies. In addition, there were too few laparoscopic/standard versus laparoscopic/fast track comparisons.

The effect of the skill level of surgeons performing laparoscopy on final outcomes within an enhanced recovery protocol has also surfaced amongst these studies, as many of the prior studies proclaimed that the participating surgeons were well versed in the technique of laparoscopic colorectal surgery [13, 15]. Tiefenthal published a study in the summer of 2015 looking at laparoscopic versus open right-sided colonic resection within an ERAS protocol [5]. They attempted to avoid the bias introduced in previous laparoscopic research where laparoscopic specialists performed the surgery. They included surgery performed by low-volume surgeons and trainees. Their primary outcomes included postoperative recovery and morbidity, with secondary outcomes including preoperative variables that influenced the selection of patients for laparoscopic or open surgery [5]. The compliance with the enhanced recovery elements was very high compared to most studies at 87 %, and on multivariate analysis the authors reported earlier pain control and shorter hospi-

tal stay in the laparoscopic group (2.4 ± 3.2 days *vs*. 4.2 ± 5.9 $p = 0.016$; and 4 *vs*. 6 days ($p = 0.002$), respectively). The authors concluded that trainees and low-volume surgeons within a well-performed enhanced recovery protocol program might still produce the similar results as reported in prior studies.

The most recent evidence supporting laparoscopic colonic resection within an enhanced recovery protocol was a meta-analysis performed by Lei and colleagues in 2015, which supports the use of laparoscopic-assisted techniques [4]. This meta-analysis encompassed seven RCTs and a total of 714 patients: 373 undergoing laparoscopic colonic resections and 341 undergoing an open operation--all within an enhanced recovery program. The authors found the laparoscopic group demonstrated a significant decrease in postoperative hospital stay, total hospital stay, and overall complications when compared to the open operation [4]. The strengths of this meta-analysis include their inclusion of only RCTs, large number of patients, and studies only comparing laparoscopic with open colorectal resection within the setting of an established enhanced recovery program. The downside includes the lack of comparison evaluating the benefit of laparoscopic plus enhanced recovery versus simply laparoscopy alone. Despite this drawback, this analysis strongly supports our recommendation concerning the use of laparoscopic techniques within an enhanced recovery system in order to reduce the postoperative stay, total hospital stay, and overall complications without jeopardizing patient's safety.

Song and colleagues looked at randomized and clinical controlled trials from 2000–2012, and focused this analysis on laparoscopic cases only—identifying 13 trials and 1795 patients. Overall, time to time to passage of flatus (WMD = −1.37, 95 % CI: -1.55 ~ −1.19, P < 0.05), time to resumption of diet/drink (WMD = −2.62, 95 % CI: -2.69 ~ −2.55, P < 0.05), postoperative length of postoperative hospital stay (WMD = −1.63, 95 % CI: −1.92 ~ −1.34, P < 0.05) and the incidence of postoperative complications (OR = 0.52, 95 % CI: 0.41 ~ 0.67, P < 0.05) were all improved in the fast track cohort. The authors concluded that enhanced recovery does make a difference in improving outcomes, even for those patients undergoing a laparoscopic approach [16]. Taupyk and colleagues followed this in a small blinded controlled trial of 70 patients with colorectal cancer, all of who munder went conventional laparoscopic surgery and were then randomized to fast track versus conventional recovery [17]. The fast track protocol consisted of avoidance of bowel preparation, early postoperative feeding, and early ambulation. Total length of stay (5.9 vs. 10.9 days), post-operative stay (4.3 vs. 8.0 days), first flatus (1.6 vs. 2.5 days), defecation time (2.2 vs. 4.5 days), and time to resumption of solid diet (1.1 vs. 3.6 days) were all improved in the fast track cohort, as well as lower CRP levels. Although this was a "bare-bones" fast track system, it does highlight that even simple things can improve outcomes--even in patients undergoing laparoscopic surgery.

Improved length of stay with the addition of an enhanced recovery pathway for all patients undergoing laparoscopic colorectal surgery has also been shown by Haverkamp and associates. This retrospective chart review looked at those prior to (n = 77) and after (n = 109) implementation of a fast track program. Whereas they were unable to show any improvement in postoperative procedure-related complications, morbidity, readmission, reoperation, or mortality, length of stay was

improved in those with a fast track program (4 vs. 6 days) [18]. These same benefits with regards to hospital length of stay have been demonstrated in the setting of minimally invasive approaches for rectal cancer as well [19, 20].

Recommendations Based on the Data

A 2005 Cochrane review confirmed that laparoscopic colorectal resection resulted in better safety, decreased the postoperative pain, and lessened the duration of postoperative ileus than open surgery [21]. Around this time, enhanced care protocols came into the forefront of colorectal surgery, initially making their mark in open surgery [2]. We feel strongly that this same improvement can be witnessed when applied to laparoscopic colorectal surgery as well. This improvement in clinical outcomes seen when combing laparoscopic surgery with the enhanced recovery protocol may be due to simply combining the two modalities, which ultimately decreases postoperative stress, inflammatory response, and leads to a faster recovery. The literature discussed above only strengthens the recommendation stated in the Cochrane review: **the implementation of an enhanced recovery protocol to a minimally invasive approach for colorectal surgery should be performed in every possible instance**. This STRONG recommendation would be expected to result primarily in faster recovery times and decreased length of stay. The effect on decreasing complications, improving patient satisfaction, and cultivating overall patient safety remains to be determined, but the majority of the literature suggests (at a minimum) equivalent, and likely better outcomes with adding a fast track program.

Recommendations Based on the Data

1. Adding an enhanced recovery/fast track pathway to laparoscopic-assisted colorectal surgery is the preferred approach whenever feasible. (Strong recommendation based on moderate-high quality evidence)
2. Patients deemed at high-risk (*i.e.*, elderly, multiple comorbidities, high frailty index) may still benefit from individual components of an enhanced recovery/fast track pathway when undergoing laparoscopic colorectal surgery. (Weak recommendation based on low-quality evidence)

A Personal View of the Data

Our review of the data regarding the addition of an enhanced recovery/fast track pathway even in those well versed in laparoscopic-assisted techniques for colorectal surgery is that it will result in an improvement in outcomes. Anecdotally, this

has definitely been the senior author's experience. The data seems clear that adding a fast track pathway will result in shorter hospital stays. Although outcomes such as complications, readmission, quality of life, and reoperations are lower with fast track pathways when comparing open with laparoscopic approaches, the majority of data shows equivalent or more modest benefits when limited to laparoscopic cohorts alone. Part of this is obvious--the benefits of a minimally invasive technique (*i.e.*, laparoscopy) for emergent and elective colon and rectal procedures has been clearly evident based on relatively longstanding literature. Several meta-analyses have demonstrated not only the impact on decreased length of stay, morbidity and quality of life, but also improved pain control, earlier return of bowel function, and lower mortality with the laparoscopic approach. With such vast improvements in outcomes, the question remains that in the face of a technically sound laparoscopic approach, what is the impact of an enhanced recovery program to improve outcomes even further? On one hand, laparoscopic techniques are increasingly becoming a new "standard of care" within colorectal surgery, and many institutions have already implemented a majority of fast track tenets within their "traditional" care pathways. Therefore, many comparisons are "apples to apples". However, especially for those without a fast track pathway in place, laparoscopy with the addition of an enhanced recovery program will improve outcomes. We do need more and higher level data to solidify this recommendation. As such, we need to gear our future investigations to augment the paucity of literature evaluating outcomes following laparoscopic colorectal surgery in traditional postoperative recovery pathway versus outcomes following laparoscopic colorectal surgery in an enhanced recovery pathway. It seems likely that there is a symbiotic relationship that results in a meaningful improvement inpatient outcomes.

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Chapter 43
Quality Improvement: Enhanced Recovery Pathways for Open Surgery

W. Conan Mustain and Conor P. Delaney

Introduction

Patients undergoing open colectomy are frequently subjected to severe metabolic stress and dramatic alterations of their normal physiology during the perioperative period. These changes contribute to prolonged pain, immobility, and gut dysfunction which require extended hospitalization. In recent years efforts have been made to accelerate recovery, by minimizing stress, optimizing pain control, and shortening the time to resumption of normal activities, with the goal of returning patients to their normal lives and avoiding perioperative complications. The logical secondary benefit of decreasing length of stay and complications is a reduction in health care costs. The combination of multiple modalities to achieve this goal has been referred to as fast-track surgery, multimodal recovery, enhanced recovery pathways (ERP), or enhanced recovery after surgery (ERAS).

The general concept of ERP involves a protocol designed to avoid unnecessary stress, preserve organ function, and promote patient autonomy. This requires a series of targeted interventions in the preoperative, intraoperative, and immediate postoperative period. The principle areas of an effective ERP and the outlined in Table 43.1. The specific interventions within each realm that are required for an effective ERP are still open to debate. Over 20 different possible interventions have been described, with great variation in their use between institutions. A detailed analysis of the evidence behind each potential component of an ERP is beyond the scope of this review. For a

W.C. Mustain, MD
Division of Colon and Rectal Surgery, University of Arkansas for Medical Sciences, Little Rock, AR, USA

C.P. Delaney, MD, PhD (✉)
Digestive Disease Institute, Cleveland Clinic,
9500 Euclid Avenue, Cleveland, OH 44195, USA
e-mail: delanec@ccf.org

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Table 43.1 Components of an enhanced recovery pathway

Patient information
1. Preoperative information and counseling
2. Preset discharge criteria
3. Stoma marking and education if indicated
4. Optimization (home incentive spirometer, smoking cessation, prehab)
Preservation of bowel function
5. Clear liquids until 2 h before surgery
6. High-carbohydrate beverage morning of surgery
7. Alvimopan, chewing gum, laxatives
8. Early feeding post-operatively
Avoiding organ dysfunction
9. Selective use of bowel prep
10. Antimicrobial and thromboembolic prophylaxis
11. Avoid hypothermia
12. Balanced use of crystalloids to optimize cardiac output and avoid excess fluid
Optimizing pain control
13. Preemptive analgesia started before surgery
14. Local anesthetic, regional blocks, or epidurals
15. Laparoscopy or minimal access incisions
16. Scheduled use of non-opioid analgesics
Promotion of patient autonomy
17. Avoid long-acting sedative premedication
18. Avoid nasogastric tubes and drains
19. Enforced early mobilization
20. Early removal of urinary catheter and IV fluids

comprehensive analysis of the evidence supporting specific pathway components the reader is referred to the Guidelines for Perioperative Care in Elective Surgery: Enhanced Recovery After Surgery (ERAS®) Society Recommendations [1].

While the theoretical benefits of ERP are clear, it is necessary to ensure that the benefits outweigh any undesirable consequences caused by deviations from conventional management. Simply achieving an earlier discharge from the hospital is insufficient if there are resultant increases in complications from feeding patients too early, readmissions from sending them out too soon, or dissatisfaction from patients' feeling rushed out of the hospital. In this chapter we review the literature supporting ERP for open colectomy and provide an evidence-based endorsement for their routine application.

Methods

Following the GRADE approach we began by formulating an appropriate clinical question, defining the four critical components of patient population, intervention, comparison, and outcomes of interest, illustrated in a standard PICO table

Table 43.2 PICO table

P (patient population)	I (intervention)	C (comparator)	O (outcomes of interest)
Patients undergoing open colectomy	Enhanced recovery pathways (ERP)	Traditional care (TC)	Complications Readmissions Length of Stay Cost Quality of Life/ Satisfaction

(Table 43.2) [2]. The patient group of interest was those undergoing open colectomy, with the intervention of treatment by ERP as compared to traditional care (TC), with the intent to answer, "Should patients undergoing open colectomy be managed by ERP rather than TC?" The outcomes considered critical in this search were morbidity, mortality, and readmission rates, recognizing the principle of non-maleficence (do no harm) as paramount over any effects on hospital stay or costs. However, because beneficence (acting for the benefit of others), rather than simply avoidance of harm, should form the foundation of any clinical recommendation we also considered hospital length of stay (LOS), costs, and patient satisfaction or quality of life (QoL) as important outcomes. The quality of the evidence was graded for each outcome and the evidence was used to formulate a recommendation on the question of interest. The strength of our recommendation is based on our degree of confidence that the desirable effects outweigh the undesirable effects, as influenced by the magnitude of the differences between benefit and harm, the quality of the evidence, and the value placed on the outcomes of interest.

Search Strategy

A systematic search of the literature was conducted using MEDLINE, PubMed, Web of Science, and the Cochrane Collaborative to identify articles related to the topic of interest. The initial search included Medical Subject Headings terms, as well as entry terms for relevant interventions and outcomes. Key words included ["colectomy" OR "colon surgery" OR "colorectal surgery"] AND ["perioperative" OR "post-operative" OR "post-surgical" OR "rehabilitation"] AND ["enhanced recovery" OR "ERAS" OR "ERP" OR "fast-track" OR "multimodal"]. The search was conducted for all dates up to November 2015 and restricted to English language titles. No age limits were applied. Titles and abstracts were screened for inclusion based on relevance. In addition, reference lists of retrieved articles were screened for additional relevant studies. Randomized controlled trials, case control trials, retrospective cohorts, systematic reviews, meta-analyses, reviews, letters, and editorials were considered. Emphasis was placed on studies comparing ERP to TC after open colectomy, with priority given to randomized controlled trials and meta-analyses where data was available for specific outcomes. For less well-studied outcomes all sources were considered.

Results

We identified over 300 articles related to the topic of interest, including 15 meta-analyses and systematic reviews of trials comparing ERP to TC (Table 43.3). These reviews encompass a total of 32 different randomized controlled trials, controlled clinical trials, and retrospective reviews, and provide some insight in each of the outcomes of interest for our clinical question.

Complications

Several large meta-analyses of randomized controlled trials, including a Cochrane review, have examined morbidity and mortality after colectomy in patients manage by ERP versus TC (Table 43.3). Mortality is a rare event after colorectal surgery with consistent rates of around 1 % and no significant difference between ERP and TC in any series. The three largest and most recent meta-analyses to examine post-operative complications, by Greco [3], Yin [30], and Zhuang [31] respectively, all found a significant risk reduction for overall complications with ERP as compared to TC [Greco RR = 0.60 (95 % CI 0.46 – 0.76); Yin RR = 0.58 (95 % CI 0.43 – 0.77); Zhuang RR = 0.71 (95 % CI 0.58 – 0.86)]. Some reviews examined sub-categories of complications. Two studies found a significant decrease in non-surgical, but not surgical complications [3, 31] with ERP. The Cochrane review by Spanjersberg et al. found a significant reduction in overall complications with ERP [RR = 0.52 (95 % CI 0.38 – 0.71), though significance did not hold up when examining major complications or minor complications separately. The definition of complications and the way in which they were recorded is not constant and many studies fail to note whether complications occurring after discharge were measured; nonetheless, the findings remain consistent across multiple large studies and it is unlikely that major complications were missed.

Readmission

After assuring safety, the most obvious concern with implementing pathways designed to get patients home sooner, is if this makes them more likely to be readmitted to the hospital. In each of the studies cited above there was no difference in the rate of readmission among patients managed by ERP or TC [3, 30, 31, 41]. In the largest of these series, including over 1,600 patients, the overall readmission rate was 4 – 5 % in each group. This outcome is consistent and has very low heterogeneity in multiple meta-analyses. There is a risk of observational error if patients were readmitted to a different hospital, but there is no reason to suspect this phenomenon more frequently in one group versus the other.

Table 43.3 Meta-analyses and systematic reviews of enhanced recovery pathways vs. traditional care for colectomy

Author	Year	Studies	Inclusion criteria	Included studies	Primary outcomes	Secondary outcomes
Greco et al. [3]	2014	RCT	Open or laparoscopic Minimum 4 ERAS elements	Anderson [4], Delaney [5], Garcia-Botello [6], Gatt [7], Ionescu [8], Khoo [9], Lee [10], Muller [11], Ren [12], Serclova [13], Vlug [14], Wang [15], Wang [16], Wang [17], Wang [18], Yang [19]	Overall morbidity Surgical complications Nonsurgical complications	Primary LOS Readmission Mortality Ileus
Lee et al. [20]	2014	RCT CCT[a] RR[b]	Open or laparoscopic Minimum 5 ERAS elements Cost data included	Ren [12], Vlug [14], Archibald [21] [a], Bosio [22][a], Folkerson [23][a], Jurowich [24][a], Kariv [25][a], King [26][a], Sammour [27][a], Stephen [28][b]	Cost	N/A
Lemanu et al. [29]	2014	RCT CCT[a] RR[b]	Open or laparoscopic No minimum ERAS elements Cost data included	Ren [12], Vlug [14] Archibald [21][a], Kariv [25][a], King [26][a], Sammour [27][a], Stephen [28][b]	Cost	Primary LOS Readmission Morbidity

(continued)

Table 43.3 (continued)

Author	Year	Studies	Inclusion criteria	Included studies	Primary outcomes	Secondary outcomes
Yin et al. [30]	2014	RCT	Open or laparoscopic No minimum ERAS elements	Anderson [4], Gatt [7], Ionescu [8], Khoo [9], Muller [11], Serclova [13], Vlug [14], Wang [16], Yang [19]	Total LOS Readmission Morbidity Mortality GI function	
Zhuang et al. [31]	2013	RCT	Open or laparoscopic Minimum 7 ERAS elements	Anderson [4], Garcia-Botello [6], Gatt [7], Ionescu [8], Khoo [9], Muller [11], Ren [12], Serclova [13], Vlug [14], Wang [17], Wang [18], van Bree [32], Yang [19]	Primary LOS Total LOS Readmission Total complications Surgical complications Nonsurgical complications Mortality	Time to first flatus and stool Hospital costs
Lvet al. [33]	2012	RCT	Open surgery only No minimum ERAS elements	Anderson [4], Delaney [5], Gatt [7], Khoo [9], Muller [11], Serclova [13], Vlug [14]	Primary LOS	Readmission Morbidity Mortality

(continued)

Table 43.3 (continued)

Author	Year	Studies	Inclusion criteria	Included studies	Primary outcomes	Secondary outcomes
Adamina et al. [34]	2011	RCT	Open or laparoscopic Minimum 4 ERAS elements	Anderson [4], Delaney [5] Gatt [7], Khoo [9], Muller [11], Serclova [13]	Primary LOS Readmission Morbidity Mortality	N/A
Rawlinson et al. [35]	2011	RCT CCT[a] RR[b]	Open or laparoscopic Minimum 4 ERAS elements	Anderson [4], Delaney [5], Gatt [7], Khoo [9], Muller [11], Serclova [13] Basse [36][a], Kariv [25][a], Polle [37][a], Raue [38][a], Teeuwen [39][a], Wichmann [40][a], Stephen [28][b]	Primary LOS Total LOS Readmission Morbidity Mortality	N/A
Spanjersberg et al. [41]	2011	RCT	Open or laparoscopic Minimum 7 ERAS elements	Anderson [4], Gatt [7], Khoo [9], Serclova [13]	Mortality Total complications Major complications Minor complications	Operative time Economic impact QoL

(continued)

Table 43.3 (continued)

Author	Year	Studies	Inclusion criteria	Included studies	Primary outcomes	Secondary outcomes
Khan et al. [42]	2010	RCT CCT[a]	Open or laparoscopic No minimum ERAS elements QoL or satisfaction data included	Anderson [4], Delaney [5], Gatt [7], Henriksen [43], Basse [36][a], Jakobsen [44][a], King [26][a], Polle [37][a], Raue [38][a], Zargar [45][a]	QoL Patient satisfaction	
Varadhan et al. [46]	2010	RCT	Open surgery only Minimum 4 ERAS elements	Anderson [4], Delaney [5], Gatt [7], Khoo [9], Muller [11], Serclova [13]	Primary LOS	Readmission Morbidity Mortality
Eskicioglu et al. [47]	2009	RCT	Open or laparoscopic No minimum ERAS elements	Anderson [4], Delaney [5] Gatt [7], Khoo [9]	Primary LOS Total LOS	Readmission Morbidity Mortality
Gouvas et al. [48]	2009	RCT CCT[a] RR[b]	Open or laparoscopic No minimum ERAS elements	Anderson [4], Delaney [5], Gatt [7], Khoo [9] Basse [36][a], Bradshaw [49][a], Kariv [25][a], Polle [37][a], Raue [38][a], Wichmann [40][a], Stephen [28][b]	Primary LOS Total LOS Readmission Morbidity Mortality	NG required Lung function Pain, fatigue, quality of life scores

(continued)

Table 43.3 (continued)

Author	Year	Studies	Inclusion criteria	Included studies	Primary outcomes	Secondary outcomes
Walter et al. [50]	2009	RCT CCT[a]	Open or laparoscopic Minimum 5 ERAS elements	Anderson [4], Gatt [7] Basse [36][a], Raue [38][a]	Primary LOS	Total LOS Readmission Morbidity Mortality
Wind et al. [51]	2006	RCT CCT[a]	Open or laparoscopic Minimum 4 ERAS elements	Anderson [4], Delaney [5], Gatt [7] Basse [36][a], Bradshaw [49][a], Raue [38][a]	Primary LOS Total LOS Readmission Morbidity Mortality	N/A

[a]*CCT* controlled clinical trial
[b]*RR* retrospective review
RCT randomized controlled trial, *ERAS* enhanced recovery after surgery, *Primary LOS* initial postoperative length of stay, *Total LOS* primary LOS + readmission LOS, *QoL* quality of life, *NG* nasogastric tube

Length of Stay

Perhaps the most consistent positive finding in the literature regarding ERP after colectomy is a decrease in hospital LOS with ERP as compared to TC. There are likely differences in the definition of "traditional" care between hospitals, and especially between countries, as evidenced by the wide variation in mean LOS in the TC cohorts of many recent series, ranging from 7 to 12 days [11–13, 15, 19]. However, there is high quality evidence showing a consistent reduction in LOS of around 2 days with implementation of ERP [3, 30, 31, 34, 46]. There is a risk for observer bias in some studies where discharge criteria were less than explicit and were assessed by non-blinded investigators.

Cost

Economic and cost-effectiveness analyses of healthcare technologies and systems are frequently plagued by imprecise and unclear methodology [52]. This is the case for the limited data available to examine cost-effectiveness of ERP as compared with TC. In 2014, two systematic reviews [20, 29] on the economic impact of ERP in colorectal surgery were published encompassing a total of 10 studies, including two randomized controlled trials (Table 43.3). The authors found significant

heterogeneity in the methods used to the calculate costs and the types of factors considered. Most studies reported only direct hospital charges with few considering hospital overhead, cost of implementation of the ERP, or indirect costs such as loss of productivity by patients or caregivers. In total, eight of the 10 studies reported lower costs with ERP as compared to TC, including all four American studies [21, 22, 25, 28], two Australasian studies [12, 27], and two out of four European studies [14, 23, 24, 26]. Lee et al. were able to generate incremental cost-effectiveness ratios for five of the 10 studies, with all five showing ERP to be dominant (less costly and more effective) with regard to LOS [20]. Two studies published in 2015 reported cost data from retrospective comparisons of ERP and TC cohorts. Thiele et al. [53] reported a significant decrease of $7,129/patient in direct costs, while Ehrlich et al. [54] found a trend toward lower in-hospital costs with ERP that did not reach statistical significance.

Quality of Life

The impact of ERP on patient satisfaction and QoL remains unclear. It stands to reason that most patients place a high value on resuming normal activities and returning to their homes. On the other hand, some patients may have a negative perception of ERP if they feel rushed out of the hospital before they are ready. Unfortunately, it is difficult to objectively measure these perceptions and their relative importance to patients. A systematic review by Khan et al. examined the available evidence regarding QoL and patient satisfaction of colorectal surgery patients managed by ERP or TC [42]. The authors included four randomized controlled trials and six comparative cohort studies, with mostly small numbers of patients (Table 43.3). There was significant heterogeneity in the instruments used for assessment, the outcomes examined, and the timing of measurements. Only two studies used a validated global QoL index [5, 26] with neither finding a difference between ERP and TC at time of discharge or post-operative day (POD) 30.

Five studies compared pain scale values [4, 5, 7, 38, 43], though all at different time periods. Three of these found no difference between the groups in pain scores at any point [7, 38, 43]. One study found significantly increased pain in the TC group on POD 1 [4], while another found increased pain at discharge in the ERP group [5]. In the later study, the day of discharge was significantly earlier in the ERP group so the discharge pain scores were closer to the date of surgery. Neither study found a difference in pain scores between the groups at POD 7 or POD 30. Seven studies assessed fatigue levels between the two approaches, with three finding no difference at any time point [7, 36, 43] and another four finding increased fatigue in the TC groups at various points in the early postoperative period [4, 38, 44, 45]. A single included study reported patient satisfaction scores of ERP vs. TC patients. The authors reported similar scores (50.4 and 49.8 out of a potential 80; $p=0.84$) between ERP and TC patients on a 16 question satisfaction survey, with an 80%

Table 43.4 Summary of the evidence evaluating enhanced recovery pathways vs. traditional care for colectomy

Outcome	Summary	Quality of evidence	Comment
Complications	Consistently decreased with ERP in multiple meta-analyses of randomized trials	Low	Inconsistency Small magnitude of effect
Readmission	No increase with ERP in multiple meta-analyses of randomized trials	Moderate	Study quality Publication bias
Length of Stay	Consistently decreased with ERP in multiple meta-analyses of randomized trials	High	Imprecision
Cost	Consistently decreased with ERP in all available studies	Low	Study quality Inconsistency Imprecision Publication bias
Quality of Life/Patient Satisfaction	No decrease with ERP in any study; similar or slightly improved in most studies	Low	Study quality Inconsistency Small magnitude of effect

response rate in both groups. The Cochrane review concluded that more research is necessary to clarify the effect of ERP on QoL [41].

Wang et al. recently published the results of a prospective trial of ERP vs. TC after open colectomy for cancer [55]. Using validated, cancer-specific QoL instruments, the authors found significantly better scores in multiple domains including global QoL, physical and emotional functioning, pain, appetite, gastrointestinal symptoms, and financial difficulties in patients treated by ERP as compared to TC. The large, multicenter prospective trial by Vlug et al. examined QoL and patient satisfaction in a four-armed study comparing laparoscopic and open colectomy with or without ERP and found no differences in either outcome between the four groups [14]. An ongoing multicenter prospective trial comparing open colectomy plus TC, open colectomy plus ERP, and laparoscopic colectomy plus ERP aims to assess QoL as a secondary outcome and may provide additional information [56].

A summary of the findings and grading of the evidence for each outcome is presented in Table 43.4.

Recommendations Based on the Data

"Patients undergoing open colectomy should be managed by a standardized Enhanced Recovery Pathway designed to preserve preoperative function, minimize surgical stress, and hasten return to normal activities."

Strength of recommendation: strong

Quality of the evidence: low

The strength of this recommendation reflects our confidence that the desirable effects of ERP outweigh the undesirable effects, as influenced by the magnitude of the treatment effect, the quality of the evidence, and the value placed on the outcomes of interest, in accordance with the GRADE approach to developing guidelines [57]. We placed a high value on the avoidance of complications and readmission. While the quality of the evidence regarding complications is low, based on significant heterogeneity and a modest treatment effect, there is no data to suggest that ERP are unsafe or associated with any increase in harm. The safety of ERP is further supported by numerous trials demonstrating a lack of difference in readmission when patients are managed by ERP. This is a consistent finding with low heterogeneity, though there is a risk for observational error.

If there is no undesirable effect of ERP on patient safety, the question becomes if there is any improvement in either resource utilization or patient quality of life. There is abundant evidence that implementation of ERP leads to shorter LOS after colorectal surgery. Hospital LOS is a reliable, objective, and easy to measure outcome and the quality of the evidence supporting the positive effect of ERP is high. Whether this reduction in hospital stay is associated with a reliable decrease in resource utilization and healthcare system costs is less clear, for the reasons stated above. The quality of the evidence in this regard is poor, but no studies have suggested that overall expense is increased by the use of ERP, even when costs of implementing the program are considered [27]. The available literature suggests that there is no negative effect on QoL or patient satisfaction when patients are managed by ERP.

A Personal View of the Data

Despite the shortcomings of the available evidence, there is ample data that the institution of ERP is associated with a decrease in some postoperative complications and a reduction in hospital stay, without an increase in readmissions. There is no data to suggest that patients managed by ERP are dissatisfied with being fed earlier or allowed to return to their homes sooner. In fact, the limited evidence (and common sense) would suggest that QoL improves when complications are avoided and patients are able to return to their normal activities. While health system costs may be of minimal importance to individual patients, the impact on the practice of medicine and healthcare economics cannot be overlooked. In an era of diminishing resources, clinician efforts to be cost-effective are paramount to sustainability.

The concept of “enhanced recovery” and the specific components constituting a pathway is a moving target. It is frequently assumed that individual interventions, shown to be beneficial on their own, will have an additive effect when combined into multidimensional pathways. The inherent problem with this approach however is that it becomes very difficult to weigh the individual merits of a particular

intervention when multiple variables are instituted at once. This problem is further compounded by the fact that the literature on ERP rarely includes the degree of compliance to specific measures within pathways and infrequently uses blinded data collectors. Furthermore, the natural course of medicine is such that treatments or interventions which seem radical at first, such as avoiding NG tubes after colectomy, eventually become part of standard practice, thereby altering "traditional care" and blurring the lines between ERPs and modern surgical management.

We and others believe that a critical part of a successful ERP is the audit of one's own data and the willingness to adapt. For various reasons certain components of an ERP may cease to become efficient or cost-effective in a given setting. A perfect example in our practice is that of intravenous acetaminophen, which we abandoned in favor of the oral form when the price of the drug more than doubled. If epidurals are slow to be placed and poorly managed in a particular hospital, they are unlikely to have a benefit. Proper education of the staff and adherence to the protocol is paramount to success, and deviations from the pathway should be analyzed periodically.

How We Do It

Since 2000, we have managed patients according to a standardized ERP which has been modified and refined over time [58–62]. We use a similar protocol for open and laparoscopic colectomy, except where noted below. In the preoperative phase we focus on patient education, medical optimization, and avoiding physiologic derangements. Patients are counseled in the office about the details of their procedure and their anticipated post-operative course. They are provided with printed instructions for the days leading up to surgery as well as the expected course of recovery and rehabilitation. Patients with an anticipated need for a stoma are referred to a separate appointment with our certified enterostomal therapists for marking and education. Pre-anesthesia evaluation and testing is ordered based on the results of a standardized risk assessment form.

We prescribe gabapentin 300 mg 3 times daily for 3 days prior to surgery and 100 mg of diclofenac for the night before surgery. On the day of surgery patients are encouraged to drink clear liquids until 2 h before surgery. They are provided with a high carbohydrate beverage to be consumed on the way to the hospital. We use mechanical bowel preps selectively. We order mechanical and antibiotic bowel prep on all rectal cancer patients and in settings where a diverting ostomy is deemed likely. This is consistent with recommendations from the ERAS Group on rectal and pelvic surgery [63]. We avoid mechanical bowel prep for right colectomy when there is no anticipated need for intraoperative colonoscopy. We make a point to inform our anesthesiologists whether the patient has had mechanical bowel prep to help them gauge preoperative volume status.

In the preoperative holding area patients are ordered an additional 300 mg gabapentin, appropriate antibiotic and thromboembolic prophylaxis, and alvimopan

12 mg if the procedure is planned as open or has a high risk of conversion. In laparoscopic colectomy using our ERP, the typical LOS is the same or better than the published median for laparoscopic colectomy with alvimopan, so we have not appreciated a benefit in these patients [59, 64]. We avoid thoracic epidurals for pain control, having found no benefit to their use in randomized trials of laparoscopic and open colectomy [65, 66]. Intraoperatively patients are actively warmed and IV fluids are given judiciously as determined by our anesthesiologists familiarized with ERP principles. We routinely perform transversus abdominus plane (TAP) blocks at the conclusion of laparoscopic and open procedures [67–71]; we do not use NG tubes or drains after colectomy. Post-operatively patients are ordered IV patient controlled analgesia (PCA) plus 650 mg of oral acetaminophen every 4 h beginning immediately after surgery. Gabapentin 300 mg every 8 h and ketorolac 15 mg IV every 6 h are given for up to 72 h unless there is preexisting renal dysfunction or high risk of bleeding. Bisacodyl 10 mg daily is given beginning the following day. Patients are given noncarbonated liquids and chewing gum on the evening of surgery and are walked with the assistance of their nurse.

On post-op day 1, the PCA and Foley catheter are removed. Laparoscopic colectomy patients who have tolerated liquids are given a soft diet on post-op day 1 and their IV fluids are hep-locked. We continue liquid diets until day 2 after open procedures. Oral narcotics are offered in addition to the other analgesic modalities if needed. Patients are instructed to walk the halls (roughly 60 m) up to 5 times per day, sit in a chair between walks, and use an incentive spirometer at regular intervals. Before discharge patients must be passing flatus, tolerating solid food, comfortable on oral analgesia, and have adequate home support as assessed by the discharge planner on the hospital floor. Adherence to our protocol has been greatly facilitated by trying to keep our patients on a single hospital ward and the hiring of dedicated nurse practitioners who provide consistency in the face of frequently changing housestaff and fellows.

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Chapter 44
Quality Improvement: Preventing Readmission After Ileostomy Formation

Najjia N. Mahmoud and Emily Carter Paulson

Introduction

Readmission after surgery is a problem that is increasingly recognized by surgeons, patients, insurers, and hospitals. It exposes patients to additional risk and increases expense in a variety of predictable ways. Readmission can occur for a number of reasons but in colorectal surgery it falls into a few broad categories: complications related to the operative procedure, functional complications as a result of the procedure, and medical complications unrelated to the procedure but related to hospitalization, anesthesia, or patient comorbidities. Relatively common reasons for readmission following discharge after elective colorectal operation include surgical site infection (wound infection and anastomotic leak or intra-abdominal abscess), high ileostomy output and dehydration, and symptomatic venous thrombosis events. In recent years, a focus on quality metrics has highlighted deficiencies that are possible to target by planned interventions resulting in improvement in patient clinical outcomes as well as health system resource allocation. Surgical site infection and venous thrombosis prevention have been the subject of numerous studies. There are evidence-based guidelines and recommendations focused on creating pathways and specific interventions for these issues already and a chapter on evidence and recommendations could easily be written on each of these problems. Acceptable interventions for ileostomy dehydration are not as well studied and therefore consensus is more difficult.

Readmission following diverting ileostomy in colorectal surgery is a frequent occurrence and could serve as a target for future quality improvement programs. A recent retrospective review of over 75,000 patients undergoing colectomy with either primary

N.N. Mahmoud (✉) • E.C. Paulson
Department of Surgery, University of Pennsylvania, Philadelphia, PA, USA
e-mail: Najjia.Mahmoud@uphs.upenn.edu

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anastomosis, colostomy, or ileostomy revealed that ileostomy patients return to the hospital at a much more frequent rate than those patients who do not have an ileostomy [1]. In this group, almost 40 % of the ileostomy patients had a hospital-based acute care encounter within 30 days of their initial discharge. Over 17 % of these encounters were secondary to either renal failure and/or fluid and electrolyte disorders from dehydration. This result is consistent with many other studies published in the past 5 years regarding readmission following ileostomy [1–6]. In these studies, the overall readmission rate for patients with new ileostomies ranged from 17 % to over 40 %. Dehydration and/or renal failure accounted for up to 40 % of these readmissions.

Pre-operative stoma education with involvement of enterostomy nurses, including preoperative marking of the planned stoma site, have been advocated as a means to reduce stomal complications. Much of this discussion, however, has focused on prevention of mechanical stomal problems, such as leakage due to malposition, and on the psychosocial preparation required for adapting to life with an ostomy [7, 8]. There has been little published regarding interventions targeted at reducing the high rate of readmission following ileostomy, especially readmission due to the dehydration and electrolyte imbalances that can accompany high ileostomy output. The aim of this chapter is to identify and review the published literature regarding interventions aimed at reducing readmission following ileostomy formation.

Search Strategy

We searched the PubMed database from January 1, 2005-January 1, 2016 to identify studies (including meta-analyses, randomized controlled trials, and retrospective cohort studies) relevant to readmission following ileostomy formation. The search terms were: “ostomy” or “ileostomy” or “stoma” and “readmission” or “dehydration” or “renal failure”. The articles were screened by title and abstract by both authors. English-only articles were included if they evaluated a specific ostomy-focused intervention at the time of stoma creation (pre- or post- creation) and reported on the outcome of interest--readmission.

Patient population	Intervention	Comparator	Outcomes studied
Patients undergoing ileostomy	Patient education; stoma teaching	Traditional management	Readmission

Results

Only three articles were identified that specifically discussed stoma-related interventions and readmission (Table 44.1) [9–11]. The quality of evidence of these studies is rated as low.

Table 44.1 Studies of Ileostomies and Readmission Rates

Study	Study design	Patients	Outcome of interest	Traditional management	Enhanced education	Quality of evidence
Nagle [9] (2012)	Uncontrolled before and after	203 Loop or end ileostomy	Readmission rates	35.4 %	21.4 %	Low
Younis [10] (2012)	Uncontrolled before and after	240 Loop or end ileostomy	Readmission rates	2.5 %	0 %	Low
Phatak [11] (2014)	Systematic Review	NA	Readmission rates	NA	NA	Low

In 2012, Nagel et al. published the results of a non-randomized before-and-after trial examining the impact of a well-defined ileostomy pathway on readmission following formation of a new ileostomy [9]. Their pathway included preoperative education, standardized ileostomy teaching materials, in-hospital teaching including direct patient engagement with their ileostomy, and strict post-discharge tracking of fluid input and output.. The authors compared readmission rate for new ileostomy patients over the 7 months after implementation of the pathway ($n=42$) to the rate for new ileostomy patients for the 4 years prior ($n=161$). The overall readmission rate dropped from 35.4 to 21.4 % after the pathway was initiated, but this was not statistically significant ($p=0.28$). The readmission rate for dehydration, however, dropped from 15.5 to 0.0 % with adoption of the ileostomy pathway ($p=0.02$). These authors conclude that their overall decrease in readmissions was almost exclusively "due to preemptive management of potential diarrhea and dehydration by patient's self-management of their input and output."

In 2012, Younis et al. published the results of a non-randomized trial evaluating the impact of focused preoperative patient stoma education on post-ileostomy outcomes [10]. In this study, the stoma intervention was included as part of a larger enhanced recovery program (ERP) being evaluated. Patients in their ERP received a stoma instructional DVD and a "practice pack" to allow them to practice ileostomy care preoperatively. Prior to ERP, the patients at their institution had only received routine information and counselling at their surgical preoperative visit. The authors compared 120 patients who underwent ileostomy after institution of the ERP to 120 patients who underwent ileostomy in the 2 years prior to ERP. They found that delay in hospital discharge caused by delay in independent stoma management was reduced from 17.5 % in the pre-ERP group to 0.8 % in the ERP group ($p<0.001$). Their readmission rate was very low compared to almost all other published studies. Only 2.5 % of the pre-ERP patients were readmitted, compared to 0 % of the ERP group, although this was not a statistically significant difference ($p=0.001$)

Finally, in 2014, Phatak et al. published a systematic review of educational interventions for ostomates [11].This group only identified 3 articles, two of which are discussed above, that reported rates of readmission following new ostomy from a total of 7 articles that evaluated any stoma education intervention. They conclude that the quality of evidence regarding educational interventions and readmission following ostomy surgery is low. Of note, the third article identified in this review was a randomized-trial published by Delaney et al. in 2003 evaluating the impact of a postoperative care pathway using controlled rehabilitation with early ambulation and diet (CREAD) on outcome after intestinal resection. Upon review of this article, there is no clear description of specific stoma-related interventions. The authors do mention that CREAD patients received "supporting written information documenting the expected post-operative milestones." As such, it is hard to draw any conclusions related to stoma-specific interventions and readmission from this trial, which is why it is not included in our review.

Recommendations Based on the Data

It should be quite obvious that the data related to specific ileostomy pathways for prevention of readmission, and specifically readmission for dehydration, is quite sparse. Furthermore, the data that is available is low quality. Even so, there are many institutions that have implemented ad hoc ileostomy counseling and have encouraged pathway development in an effort to prevent the well-known complication of post-discharge dehydration and readmission.

There is good reason to believe from the study by Nagle et al., that an appropriately powered, prospective study would likely show that a programmatic approach to providing specific counselling to prevent dehydration results in a reduction of readmissions. But there are also compelling reason to believe that the additional benefits of counselling new ostomates obviates the need for level 1 data In reality, stoma interventions including pre- and post-operative counselling and education and patient-driven pathways to track and balance post-discharge fluid management pose minimal risk to new ostomates. The benefits, however, can improve quality of life and decrease readmission and cost of care. Our practice includes, when possible, preoperative stoma site marking and counselling with an enterostomal therapist, in-hospital counselling and education, and post-discharge visiting nursing.

Preoperative ileostomy marking can ensure that the planned ileostomy is in a position that enables the avoidance of leakage, skin excoriation, and facilitates patent self-care. It is also an opportunity to counsel, educate, and reassure. New ostomates desire and require preoperative education to set expectations and alleviate anxiety. They need to know what to expect both in the hospital and afterwards. Data in the field of education supports the fact that repetitive exposure to the same set of educational objectives reinforces desirable behaviors and, in this case, helps compliance. The patient should be reassured that they will receive stoma education

again prior to discharge and be helped and supervised in the care of their own ostomy prior to discharge.

Personal Recommendations Based on the Data

While published data is scarce, the basics of post-discharge ileostomy management is actually quite simple. In our practice, prior to hospital discharge, patients should be able to:

1. Change their own appliance.
2. Make daily measurements of output and record 24 h totals until the first office visit.
3. Be aware of dietary restrictions.
4. Be familiar with 2–3 interventions for reducing output.
5. Have recourse to contact help if confused or ill.

Specific interventions include:

1. An ileostomy checklist reviewed, point-by-point, with a caregiver prior to discharge. Review with both patient and family members can help reinforce compliance.
2. A 24 h chart for documenting output.
3. Ensuring that the patient can participate in his or her own care by viewing a change of appliance in the hospital.
4. A list of foods to avoid in the post-operative period.
5. A graduated measuring vessel and a specific 24 h total ileostomy output to target.
6. A list of interventions and medications to try if output exceeds the target.
7. A reliable call-in number for the patient to reach out to the office in the event of questions or concerns that will be answered within several hours.

Other interventions that may be offered that are quite valuable and improve patient satisfaction include routine and automatic referral to visiting nurse services for new ostomates, calls from the office in the early discharge period to reinforce checklist, measurement, and dietary compliance, and reminder texts and emails via secure medical portals to ensure that directions are followed.

Although it seems logical that program like this should reduce readmissions, it is also likely that overall institutional and practitioner compliance is poor. Improvement in our ability to administer complex pathways is dependent upon diffusion of knowledge of goals of care to all members of the team including floor nurses and social workers and home nurses, and empowerment of ancillary providers to provide counselling and materials for ileostomy care postoperatively. A pathway such as the one outlined is not difficult to organize, it is simply hard to routinely administer. Providing alternative means (data pushed out via electronic medical records and secure portals) and empowering personnel (floor nurses, advanced practitioners,

stoma therapists, social workers) may allow us to improve the efficacy of these pathways in the future.

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Part VIII
Technique

Chapter 45
Trans-anal Endoscopic Surgery vs. Conventional Transanal Surgery

Theodore J. Saclarides

The treatment of rectal cancer has evolved substantially over the years. Treatment options available to the patient and surgeon over the years have been determined by available instrumentation and technology as well as the ability to care for the sick patient in terms of anesthetic techniques and knowledge of critical care medicine and antisepsis. Prior to 1908, transanal and posterior approaches dominated and, by today's standards, these choices were oncologically inadequate. In 1908, Sir Ernest Miles published his report of an operation which now bears his name and with his technique; radical removal not only of the tumor bearing segment of bowel was performed, but also the regional lymphatics of the rectum.

Although radical resection remains the oncologic standard for the treatment of patients with rectal cancer, there is substantial morbidity due to both the pelvic dissection and the stoma when necessary. Complications related to the former include genitourinary dysfunction (e.g., impotence and urinary retention) and to the latter include hernias and skin issues. It has been questioned whether taking on this morbidity is justified for very early tumors where possibly more conservative surgery could achieve similar oncologic outcomes, but without the higher morbidity and mortality. This has been debated for decades and the debate will continue. Further, many patients are not medically fit for radical surgery; consequently alternative surgical methods have been sought and even combined with adjuvant therapy in some instances. As such, transanal resection of rectal cancer remains an important aspect of the surgeon's armamentarium.

Conventional transanal resection involves using a variety of hand held or self retaining retractors to gain exposure. The patient is usually positioned in the exaggerated prone jack-knife position and the overhead lights are directed into the

T.J. Saclarides, MD
The Section of Colon and Rectal Surgery, Loyola University School of Medicine, Maywood, IL, USA
e-mail: thsaclarides@lumc.edu

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rectum; the surgeon may also wear a headlight for illuminating the surgical field. Standard surgical instruments are the norm. The lesion is visualized, surrounding tissue is grasped, and stay sutures are placed around the lesion in order to bring it down into view. The lesion is removed while attempting to avoid fragmentation of the specimen, obtain negative margins, and to handle complications that arise such as bleeding or entry into the peritoneal cavity or vagina. Limited upward reach and poor exposure have restricted the surgeon to the distal-most rectal lesions. Yet for even such tumors, being able to remove the lesion in one piece with negative margins has remained a challenge. Reported recurrence rates as high as 30 % have restricted wholesale acceptance of transanal excision of rectal cancers [1].

In order to circumvent the limitations posed by conventional instruments, Professor Gerhard Buess pioneered and developed Transanal Endoscopic Microsurgery (TEM) in the mid 1980's during the dawn of the era of minimally invasive surgery. His equipment utilizes a closed, air-tight system that insufflates carbon dioxide into the rectum where it is retained and distends the rectal vault. Visibility is obtained through a fiberoptic scope that has an extended field of view relative to standard laparoscopes. The scope is inserted through a rigid rectoscope which is 40 cm in diameter and sealed with an airtight face piece. The scope may be connected to an adapter to enable viewing on a video screen. This "pneumorectum", combined with the high definition optics and the long shafted instruments, has extended the application of transanal surgery to larger and more proximal lesions. The instruments are inserted through working ports in the sealed facepiece and are manipulated in parallel. The most important component of the system is the endosurgical unit which regulates four different functions at once: carbon dioxide insufflation, irrigation, suction, and monitoring of the intrarectal pressure. Once the system is setup and the surgeon verifies there is no air leak within the system, cautery points are placed around the lesion such that at least a one centimeter margin of normal tissue is obtained surrounding the lesion. The tumor is removed by dissecting either within the submucosal plane or by traversing the full thickness of the rectal wall into the perirectal fat. Most surgeons routinely close the rectal wall in a transverse fashion. The specimen is submitted for histologic analysis and decisions are made whether or not additional therapy is needed. Occasionally, the treating physicians decide that radical surgery is needed because of the presence of unfavorable features. Complications include bleeding, wound dehiscence, entry into the peritoneal cavity, rectovaginal fistula, and fecal soilage, which is short lived and temporary in the majority of cases.

Recently, industry has entered the fray and a variety of different platforms are available for the surgeon who wishes to practice Transanal Endoscopic Surgery (TES). There are distinct differences in the systems, yet they all share certain unifying features. First, this surgery is an endoscopic, intraluminal operation aided by the insufflation of carbon dioxide. Secondly, visibility is obtained with the use of fiberoptic laparoscopes or scopes specifically designed for this purpose instead of direct vision as with conventional transanal surgery. Thirdly, long shafted instruments allow excision of lesions beyond the reach of conventional instruments. Many reports describe being able to remove lesions beyond 15 cm from the anal canal. Fourth, TES is technically demanding and advanced training is required, although a skilled

laparoscopist can master TES in a short time. Lastly, because of the extended utility of this type of surgery, many of the lesions referred for excision are the recurrent or persistent tumors that failed successful management with conventional instruments.

Publications describing TEM appeared sparsely in the medical literature in the 1980's. In fact, most of the papers were written by Buess himself. Over the next three decades, more manuscripts were written and range in character from small series describing a novel application of the technology to large meta-analyses. It is difficult to compare TEM/TES with other conservative operations for rectal cancer not only for the reasons mentioned above, but also because once surgeons master the technique, they cannot resort to older methods simply for the sake of a comparative research study. This is certainly the case for this author. Nevertheless, it will be the focus of this chapter to review the literature comparing TES platforms with other methods. The specific factors that will be assessed are whether TES is more likely to obtain negative margins, cause less tissue fragmentation, produce fewer complications, and yield better outcomes with respect to tumor recurrence. The articles chosen for this review were found using a PubMed computer search using the terms "transanal excision" and "transanal endoscopic microsurgery" from 2003 to 2016. Alternative methods to TES include conventional transanal excision, posterior approaches such as the Kraske operation, and endoscopic mucosal (EMS) and submucosal dissection (ESD). Table 45.1 outlines the objectives of the study.

Results

Table 45.2 summarizes the literature. The table is organized to reflect those factors for which TEM/TES (collectively referred to as TES) has advantages to, is equal to, or is disadvantageous compared to the alternative techniques. Overall there is a paucity of manuscripts comparing these techniques with the other methods of local excision. As stated above, a randomized prospective study is not likely to appear because once the technique is mastered, some form of TES will become the preferred approach for surgeons. There is only one prospective, randomized study and excision of only adenomas is considered. [2] Of the remaining studies, there are 3 meta-analyses, [3–5] one systematic review, [6] and several retrospective series [7–14] where the control groups are within the same institution, other institutions, or literature based. Study designs are generally flawed.

Table 45.1 PICO Table

P (patients)	I (intervention)	C (comparator)	O (outcomes)
Patients undergoing transanal endoscopic surgery (TES)	TES	Patients undergoing conventional transanal excision, posterior approach, or endoscopic submucosal or mucosal resection (alternative methods)	Negative margins, tumor fragmentation, recurrence rates, perioperative outcomes

Table 45.2 Analyzed studies

Author (year)	Study type	Level of evidence	Patients	Results		
				TES > alternative[a]	TES=alternative	Alternative > TES[b]
Clancy (2015) [4]	Systematic review		492 TES, 435 conventional transanal excision	Negative margins Less tissue fragmentation Recurrence rate	Complication rate	
Moore (2008) [9]	Retrospective		82 TES, 89 conventional	Negative margins Less fragmentation Recurrence rate	Complications	
Winde (1996) [2]	Prospective randomized		90 TEX, 98 conventional; adenomas only	Local recurrence		
Sgourakis (2011) [3]	Meta-analysis		TES vs conventional for T_1 and T_2 cancers	Negative margins Disease free survival		
Han (2012) [8]	Case controlled		53 TES, 76 conventional	Local recurrence Distance from anus		Operative time
de Graaf (2010) [7]	Case controlled		216 TES, 43 conventional; all adenomas	Operative time complications Negative margins Less fragmentation Local recurrence		
Lebedyev (2009) [10]	Retrospective		24 TES, 18 conventional; all T_1 cancer		Negative margins complications recurrence	
Christoforidis (2009) [1]	Retrospective		42 TES, 129 conventional; postoperative adjuvant therapy	Negative margins fragmentation	Disease free survival for tumors ≥ 5 cm	

Langer (2003) [11]	Retrospective		79 TES, 76 conventional; T_1 and T_2 cancers and adenomas	Local recurrence	2 year survival	
Nakagoe (2003) [12]	Case controlled		45 TES, 26 posterior approach; adenomas and cancer	Operative time, blood loss, length of stay analgesic need complications		
Hitzler (2015) [6]	Systematic review		TES vs Endoscopic Submucosal Dissection. European and Japanese Literature	In European literature: Negative margins Fragmentation Complications		
Lin (2006) [13]	Retrospective		31 TEM, 51 Posterior Approach different hospitals, benign and malignant	Length of stay Time to oral intake Analgesic need	Mortality Resection margins Recurrence	
Arezzo (2014) [5]	Systematic review		1407 TEM, 490 ESD benign and malignanty	En bloc resection RO resection	Complications Recurrence rate for adenoma	
Kawaguti (2014) [14]	Retrospective review		13 TEM, 11 ESD		En bloc resection Operative time Hospital stay	

[a]Advantage in favor of TES
[b]Alternative methods superior to TES

Regarding complications, there are no differences when comparing TES with conventional transanal excision; however TES generally has fewer complications when compared to the posterior approach [12] and in Hitzler's study of patients undergoing ESD [6]. Compared to conventional transanal surgery, TES is associated with longer operative times but this may be due to the time required for patient positioning, equipment set up, and troubleshooting carbon dioxide leaks when they occur [8]. Other potential disadvantages include the need for advanced training, mastering the learning curve and the cost of the equipment, but no comparative studies exist regarding these issues. Because of these factors, combined with the technical difficulty of performing TES, it is not likely that TES will be performed by the surgeon whose practice has a low volume of patients with suitable lesions.

TES has definite advantages compared to conventional transanal resection, and these are consistently noted in the manuscripts. TES is superior with respect to being able to obtain negative margins surrounding the lesion [1, 3, 4, 7, 9], and being able to remove the lesion en bloc, intact and without fragmentation [1, 4, 7, 9]. These advantages are directly related to improved visibility because of the pneumorectum and the high definition optics. The end result is being able to provide the pathologist with a better specimen to study, and since this often drives decisions regarding whether or not additional treatment is necessary, this is extremely important. In the meta-analysis provided by Clancy et al., a lower recurrence rate with TES was noted, along with a lower incidence of positive margins and tumor fragmentation [4]. In the meta-analysis of patients with T1 and T2 cancers by Sgourakis et al., an improved disease free survival was noted [3]. A lower incidence of positive resection margins and tumor fragmentation was noted in the majority of the retrospective series as well.

There has been debate as to who "owns" the rectal adenoma or the superficial cancer; the surgeon or the gastroenterologist. If the lesion is persistent or recurrent following endoscopic resection (ESD), the patient should be referred to a TES surgeon after one attempt. All too often, patients are referred only after multiple polypectomies, laser or argon plasma coagulations, or ESD have been performed and such practices can render the subsequent TES operation more technically difficult and/or make it harder to close the wound. Certainly, if the lesion has a central ulceration or depression or does not lift well with saline injection, consideration should be given to prompt referral to a TES surgeon without attempting to remove it with alternative endoscopic methods.

Author's View of the Data

TES and alternative methods of local excision are different operations and it is incorrect to compare the two. TES requires advanced training, the equipment is more expensive, the learning curve must be mastered, and surgeon volume must support maintaining skills. Having said that, TES is the preferred method of local excision because it enhances our ability to obtain negative margins and remove the lesion without fragmentation. In some series, this leads to a lower recurrence rate,

however, the strength of the data is suspect. The debate will continue and will not likely be answered with an adequately powered, prospective randomized study in the future.

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Chapter 46
Laparoscopic Versus Robotic Versus Open Surgery for Rectal Cancer

Campbell S. Roxburgh and Martin R. Weiser

Clinical Scenario A 64-year-old male completed neo-adjuvant chemo-radiotherapy for a cT3bN+ adenocarcinoma at 11 cm from the anal verge 5 weeks ago. Repeat MRI demonstrates tumor downsizing. He is aware that surgery involves open or minimally invasive approaches. He wants to return to work as soon as possible but above all wants surgery with the highest chance of "cure."

Question Which of the surgical approaches for rectal cancer resection (open vs. laparoscopic vs. robotic) results in the best outcomes?

Background When choosing among operative approaches, outcome measures fall into two broad categories: (1) those related to short and long-term sequelae of the radical resection (surgical morbidity, return to function, and quality of life), and (2) those related to the disease process (recurrence, disease-free and overall survival). Both open and minimally invasive (laparoscopic and robotic) techniques may be employed to perform total mesorectal excision (TME) for rectal cancer. Here we aim to review outcomes for each approach to aid decision making.

We make two comparisons:

A. Compared with open surgery, does laparoscopic surgery result in better outcomes after rectal cancer treatment? (Table 46.1a)
B. Compared with laparoscopic surgery, does robotic-assisted surgery result in better outcomes after rectal cancer treatment? (Table 46.1b)

C.S. Roxburgh
Memorial Sloan Kettering Cancer Center, New York, NY, USA

M.R. Weiser, MD (✉)
Colorectal Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA
e-mail: weiser1@mskcc.org

N. Hyman, K. Umanskiy (eds.), *Difficult Decisions in Colorectal Surgery*,
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Table 46.1 (a) Laparoscopic versus open surgery for rectal cancer and (b) robotic versus laparoscopic surgery for rectal cancer – PICO tables

(a)	Patient population	Intervention	Comparator	Outcomes studied
	Rectal cancer, post neoadjuvant chemo-radiotherapy	Laparoscopically performed TME	Open TME	**Procedure related morbidity** Length of stay, complications – grade 3/4/5, anastomotic leak, reoperation
				Oncologic CRM involvement, distal resection margin involvement, distance to CRM, distance to distal resection margin, LN yield, completeness of TME Disease specific survival, overall survival, local recurrence
(b)	**Patient population**	**Intervention**	**Comparator**	**Outcomes studied**
	Rectal cancer, post neoadjuvant chemo-radiotherapy	Robotically performed TME	Laparoscopically performed TME	**Procedure related** Length of stay, complications – grade 3/4/5, anastomotic leak, reoperation, cost, open conversion
				Oncologic CRM involvement, distal resection margin involvement, distance to CRM, distance to distal resection margin, LN yield, completeness of TME Disease specific survival, overall survival, local recurrence

Methods/Search Strategy Studies reporting short- and long-term results for rectal cancer surgery in which a proportion of patients received neoadjuvant treatment were reviewed. Rectal cancer was defined as a tumor 15 cm or less from the anal verge. Laparoscopic surgery was defined as completion of the pelvic dissection using laparoscopic instruments. Non-conventional laparoscopic techniques were excluded (e.g., hand-assisted or single-port surgery). Robotic surgery was defined as completion of the pelvic dissection using a robotic platform. PubMed, Ovid, Web of Science and Cochrane databases were searched using terms “rectal cancer”, “laparoscopy”, “open”, “robot”, and “robotic” for studies up to December 1, 2015. We sought to review the highest quality evidence with emphasis on Level 1/2 data. For

comparison (A), five multicenter RCTs have reported data pertinent to this question and therefore the meta-analysis focused on their results. For comparison (B), no prospective randomized data is available. If multiple reports were published from one institution, the most recent series was evaluated.

Results: (A): Laparoscopic Surgery Versus Open Surgery for Rectal Cancer

Description of Studies Five multicenter RCTs have been undertaken to evaluate laparoscopic surgery versus open surgery in rectal cancer: the CLASICC, COREAN, COLOR II, ACOSOG Z6051 and ALaCaRT trials [1–5]. Trial characteristics and results are summarized in Table 46.2. Long-term outcomes are reported by CLASICC, COREAN and COLOR II. Each trial was designed with a slightly different rationale for power calculation and outcome reporting. CLASICC recruited 413 colon and 381 rectal cancer patients and was powered not by an outcome assessment; but on the need to evaluate laparoscopic colorectal surgery in a trial setting by examining differences between treatment arms for a range of endpoints [1]. The COREAN trial recruited 170 patients per arm with tumors ≤10 cm from the anal verge after neoadjuvant chemoradiotherapy [2]. The trial assessed non-inferiority of laparoscopic surgery based on 3-year disease-free recurrence. COLOR II recruited 1044 patients (699 laparoscopic vs. 345 open) with tumors ≤15 cm from the anal verge to assess non-inferiority of laparoscopic surgery based on 3-year local recurrence rates [3]. ACOSOG Z6051 recruited 462 patients (240 laparoscopic vs. 222 open) with tumors ≤12 cm from the anal verge after neoadjuvant treatment [4]. The trial was powered to detect non-inferiority of laparoscopic surgery based on a composite pathological endpoint: completeness of TME, negative circumferential margin (CRM) and negative distal resection margin (DRM). ALaCaRT had a similar design, recruiting 475 patients (238 laparoscopic vs. 237 open) with tumors ≤15 cm from the anal verge to assess non-inferiority of laparoscopic surgery based on a composite pathological endpoint [5].

Short Term Outcomes

Length of hospital stay (LOS) No differences in LOS were seen in the COREAN, ACOSOG Z6051, or ALaCaRT trials. In contrast, CLASICC and COLOR II reported lower LOS in the laparoscopic group (CLASICC: 11 vs. 13 days; COLOR II: 8 vs. 9 days). The COREAN trial demonstrated a trend towards reduced LOS in the laparoscopic arm (8 vs. 9 days $P = 0.056$), but unlike ALaCaRT and ACOSOG Z6051, consistently better short-term outcomes were also observed for the laparoscopic group (e.g. earlier passing of flatus, earlier defecation, and resumption of normal diet). The equivocal short-term outcomes for treatment groups in ACOSOG

Table 46.2 Perioperative and oncologic outcomes from published multicenter randomized controlled trials comparing laparoscopic versus open surgery for rectal cancer (laparoscopic/open)

Trial	CLASICC (Rectal cancers)		COREAN		COLOR II		ACOZOG Z6051		ALaCaRT	
Design	Phase 3 multicenter RCT		Non-inferiority phase 3 multicenter RCT		Non-inferiority phase 3 multicenter RCT		Non-inferiority phase 3 multicenter RCT		Non-inferiority phase 3 multicenter RCT	
Number of centers	27		3		30		35		24	
Location	United Kingdom		South Korea		Europe		North America		Australia and NZ	
Number (lap/open)	253/128 (ITT) 160/132 (ATG)		170/170		699/345		240[a]/222		238/235	
Time period	1996–2002		2006–2009		2004–2010		2008–2013		2010–2014	
Site of tumors			Mid-low rectum <10 cm from AV		≤15 cm of AV		≤12 cm from AV		Within 15 cm of AV	
Treatment group	**Lap**	**Open**	**Lap**	**Open**	**Lap**	**Open**	**Lap**	**Open**	**Lap**	**Open**
% receiving neoadjuvant treatment	58	60	100	100	59	58	100	100	50	49
BMI median (mean[b])	26	25[b]	24.1	24.1	26.1	26.5[b]	26.4	26.8[b]	27	26
Perioperative outcomes										
Conversion	34		1		16		11		9	
LOS (days)	11	13	8	9	8	9	7.3	7.0	8	8[b]
Mean operative time (min)			244	197	240	188	266	220	210	190[b]
Complications Grade 3/4 (%) Grade 5 (%)			0.0	0.0	1.1	1.7	21.7 0.8	21.1 0.9	18.5 0.4	26.4 0.8
Anastomotic leak (%)	10	7	1.2	0	13	10	2.1	2.3	3	3
Reoperation (%)			1.8	1.8	6	6	5	2.3		
Oncological outcomes										
CRM negative ≤1 mm (%)	84	86	97.1	95.9	93	91	87.9	92.3	93	97
DRM negative (%)	No difference						98.3	98.2	99	99

Complete/nearly complete TME (%)			91.8	88.2	97	98	92.1	95.1	97	99
Composite endpoint							82	87	82	89
Mean LN yield			17	18	13	14	17.9	16.5		
Distance DRM (mm)			20	20	30	30[b]	32	31[b]	26	30
Distance to CRM (mm)			9	8	10	10[b]	10.5	12.8[b]	10	12
3 year DFS OS LR	70.9 74.6 9.7	70.4 66.7 10.1	79.2 91.7 2.6	72.5 90.4 4.9	74.8 86.7 5.0	70.8 83.6 5.0				

Data presented as median unless otherwise stated

RCT randomized controlled trial, *NZ* New Zealand, *TME* total mesorectal excision, *AV* anal verge, *BMI* body mass index, *LOS* length of stay, *ITT* intention to treat, *ATG* actual treatment group, *CRM* circumferential resection margin, *DRM* distal resection margin, *LN* lymph node, *DFS* disease free survival, *OS* overall survival, *LR* local recurrence

[a]Includes 34 Robot assisted procedures

[b]Mean

Z6051 and ALaCaRT may relate to the use of hybrid approaches permitted in the open arms.

Complications, Anastomotic Leak and Reoperation Rates Clavien-Dindo grade 3/4/5 complication were comparable for open and laparoscopic surgery in the ACOSOG Z6051 and ALaCaRT trials. The COREAN and COLOR II trials reported similar rates of infectious and noninfectious complications and short-term mortality in each trial arm. CLASICC reported higher perioperative morbidity and mortality in patients converted from laparoscopic to open surgery. Complication rates for laparoscopic, open and converted rectal cancer operations were 32 %, 37 % and 59 %, respectively. No trial reported a difference in anastomotic leak or reoperation rates.

Short Term Outcomes Summary Mean LOS after rectal cancer surgery ranged from 7 to 9 days across the treatment arms. Although two trials reported reduced LOS with laparoscopic surgery, we conclude that LOS is comparable for each approach. Rates of complications, anastomotic leaks and reoperation are also equivocal.

Conclusion
The assessed short-term outcomes are comparable for laparoscopic and open surgery.
GRADE: HIGH QUALITY

Oncologic Outcomes

Circumferential resection margin involvement Excepting CLASICC, all trials reported non-involved CRM rates in excess of 87 %, underlining the technical skills of the surgeons participating in this study. No trial was powered based solely on CRM assessment. Clear CRM rates were comparable in all five trials (Table 46.2). In a subgroup analysis of anterior resections, CLASICC reported a nonsignificant trend towards higher CRM involvement for laparoscopy (12 % vs. 6 % based on 16 positive CRMs in 129 laparoscopic versus 4 positive CRMs in 64 open resections). Distance to CRM was comparable in COREAN, COLOR II and ALaCaRT. However, ACOSOG Z6051 reported reduced distance to CRM with laparoscopy (10.8 vs. 12.8 mm, $P = 0.03$).

Distal margin DRM involvement was low (1–2 %) and incidence was equivalent where it was reported (Table 46.2) [1, 4, 5].

Complete/nearly complete TME No differences in rates of complete/nearly complete TME were reported where this outcome was assessed (Table 46.2) [1–5].

Composite pathological outcomes Both ACOSOG Z6051 and the ALaCaRT trials used a composite pathological assessment as their primary outcome measure. Both trials were powered based on the assumption that 90 % of rectal cancer resections are oncologically complete (CRM negative, DRM negative, and complete/nearly complete TME). ACOSOG Z6051 stated non-inferiority would be declared if the lower border of the 95 % CI for difference between groups was >6 %. ALaCaRT set a similar non-inferiority threshold of >8 %. In ACOSOG Z6051, a complete specimen was achieved in 81.7 % of laparoscopic versus 86.9 % of open resections (5.2 % difference, lower bound 95 %, CI −10.8). For ALaCaRT, a complete specimen was achieved in 82 % of laparoscopic versus 89 % of open resections (7.0 % difference, lower bound 95 %, CI −12.4). For each trial, non-inferiority was not established.

Lymph node (LN) yield No trial reported a difference in number of LNs retrieved between treatment arms for laparoscopic versus open surgery (Table 46.2).

Long-term oncologic outcomes Three trials (CLASICC, COREAN, COLOR II) published long-term outcomes [6–9]. CLASICC reported a trend towards increased CRM involvement with laparoscopic surgery but this failed to translate into detectable difference in terms of local recurrence (LR) (9.7 % vs. 10.1 %), disease-free survival (DFS) (70.9 % vs. 70.4 %) and overall survival (OS) (74.6 % vs. 66.7 %) at 3 years. CLASICC also reported a non-significant trend towards improved OS and DFS in Stage I rectal cancer in the laparoscopic arm. The COREAN trial reported 3-year DFS rates of 79.2 % vs. 72.5 % (6.7 % difference, 95 % CI −15.8 to 2.4). Laparoscopic surgery therefore was deemed non-inferior. No differences were reported between groups for 3-year OS or LR rates (Table 46.2). COLOR II reported no difference in 3-year LR (5 % vs. 5 %), concluding laparoscopy is non-inferior. However, the results favored slightly improved outcomes for laparoscopic surgery in terms of 3-year DFS (74.8 % vs. 70.8 %) and OS (86.7 % vs. 83.6 %). The most pronounced difference between groups was seen in Stage III disease (DFS 64.9 % vs. 52 %).

Oncologic Outcomes Summary No trial has demonstrated a statistically meaningful difference between techniques for CRM and DRM involvement, TME completeness or LN yield. ACOSOG Z6051 reported reduced distance to CRM with laparoscopic surgery, an observation not repeated elsewhere. Using a composite pathological assessment, two trials reported open surgery had higher rates of "oncologically complete" resections. Results from three trials demonstrated comparable long-term oncologic outcomes.

Conclusion
The assessed oncologic and long term outcomes are comparable for laparoscopic and open surgery.
GRADE: HIGH QUALITY

Results: Robotic Surgery Versus Laparoscopic Surgery for Rectal Cancer

Description of Studies We identified 43 studies in which outcomes for both robotic and laparoscopic surgery were reported between 2006 and 12/1/15, 28 of which were published in the last 3 years, with 17 published in 2015 alone. Most studies originated in Korea (19) and the United States (10), followed by Italy (3) Spain (2), Japan (2), Taiwan (2) Turkey (2), Switzerland (1), Romania (1) and Canada (1). No prospective randomized trials have been published evaluating the role of robotic surgery versus laparoscopic surgery for rectal cancer. Three early studies were small, randomized pilot series which aimed to evaluate feasibility of robotic surgery (Baik et al., 2008, n = 18 and Patriti et al., 2009, n = 29, Jimenez Rodriguez et al., 2010, n = 6) [10–12]. Two studies report audit outcomes from the American College of Surgeons (ACS) National Cancer Database (NCDB) [13, 14]. The remainder (38 studies) are single/multicenter case series, the majority of which (n = 26) analyze outcomes from <50 robotic cases. Of 12 series in which ≥50 robotic cases are reported, several originate from the same center, reported at different time points. Outcomes from the six largest series are presented in Table 46.2 [15–20]. Finally, seven meta-analyses have reviewed between 7 and 17 studies to assess robotic versus laparoscopic surgery for rectal cancer [21–27].

Short Term Outcomes

Length of hospital stay Based on pooled data from published meta-analyses in addition to reported data from the ACS NCDB, LOS is comparable for robotic and laparoscopic surgery for rectal cancer [13, 14, 21, 22, 24, 26, 27].

Complications, anastomotic leak and reoperation rates Published meta-analyses report no differences in complications rates between the techniques [21–24, 26, 27]. Furthermore, rates of anastomotic leak or reoperation are comparable. ACSNCDB data also report comparable Grade III/IV complications and short-term mortality after robotic (n = 1217) and laparoscopic (n = 4700) resections [14].

Cost Robotic surgery is more expensive in comparison to laparoscopic surgery. Park et al. reported the cost of robotic rectal cancer surgery was 2.4 times that of laparoscopic surgery per patient episode [28]. Other recent reports suggest the disparity in cost is not as great; Ramji et al. (n = 70) reported costs of $18,273 for robotic vs. $11,493 for laparoscopic rectal surgery per episode [29], and Kim et al. reported costs of $15,965 vs. $11,933 per hospital episode [30].

Conversion Meta-analyses report consistently lower rates of conversion to open surgery for robotic (1.1–3 %) versus laparoscopic (6–7.5 %) surgery [22, 24, 26,

27]. The odds ratios for the reduction in risk of conversion using robotic versus laparoscopic surgery were 0.26 (95 % CI 0.12–0.57, $P < 0.001$) reported by Trastulli (2011) and 0.23 (95 % CI 0.10–0.52, $P < 0.001$) reported by Xiong in 2013 [21, 26].

Short Term Outcomes Summary Based on meta-analyses of non-randomized studies and audit series, short-term outcomes are equivalent for robotic and laparoscopic surgery. Robotic surgery has lower rates of conversion to open and is considerably more expensive.

Conclusion
The assessed short-term outcomes are comparable for robotic and laparoscopic surgery.
GRADE: LOW QUALITY

Oncologic Outcomes

CRM involvement Across the six larger series reviewed, low rates of CRM involvement were reported, ranging from 0 to 8 % for robotic surgery and 1–12 % for laparoscopic surgery. No series demonstrated a statistically lower rate of CRM involvement with robotic surgery, consistent with pooled results from meta-analyses [21–24]. ACSNCDB data also report equivalent rates for CRM involvement (5 %) [13, 14]. However, one meta-analysis of eight studies, published in 2014, reported lower CRM involvement with robotic surgery (2.7 % vs. 5.8 %) [25].

DRM involvement One meta-analysis published in 2011 reported lower rates of DRM involvement with robotic surgery [24], but later meta-analyses published in 2012 and 2014 reported no difference [21, 23, 25]. Equivalent DRM rates were seen in the six larger series detailed in Table 46.3 [15–20]. ACS NCDB data also reported equivalent rates for DRM involvement (5 %) with both techniques [14].

Complete/nearly complete TME One small study by Baik reported higher rates of complete/nearly complete TME after robotic surgery [31].

Lymph node yield No differences in lymph node yield in resection specimens were reported in meta-analyses [21, 23, 24, 26, 27] or ACS NCDB reports [13, 14].

Long-term oncologic outcomes Two large case series from Korea reported data on long-term outcomes at 3 and 5 years, revealing comparable OS, DFS and LR rates for the two techniques [15, 18]. Using ACS NCDB data, Sun et al. observed comparable OS at 3 years (1217 robotic vs. 4700 laparoscopic resections) [14].

Oncologic Outcomes Summary Based on meta-analyses of non-randomized studies and audit studies, measures of pathological quality and long-term outcomes

appear to be comparable for both robotic and laparoscopic surgery for rectal cancer.

Conclusion
The assessed long-term outcomes are comparable for robotic and laparoscopic surgery.
GRADE: LOW QUALITY

Recommendations

A. After neoadjuvant treatment, patients with non-margin-threatening rectal cancer may be managed by either open or laparoscopic TME as long-term outcomes for each technique appear comparable (**Evidence Strong; strong recommendation**).
B. Although data from prospective, randomized studies is awaited, robotic surgery does not appear to be inferior to laparoscopic surgery for TME in terms of short and long-term outcomes (**Evidence Weak, weak recommendation**)

Personal View The implementation of MIS in colorectal cancer treatment has brought with it reduced surgical trauma and stress with a more rapid return to function and is widely regarded as the major development in colorectal surgery in the past 20 years. Rectal cancer surgery requires technical competence and outcomes are improved by surgical specialization and increased case volume [32]. This is especially critical for TME performed using MIS techniques. To date, equivalent long-term oncologic outcomes are reported with both laparoscopic and open TME; some subgroup analyses suggesting improved outcomes with the laparoscopic technique. Questions over the oncologic adequacy for laparoscopic TME have arisen from analyses of surrogate pathological endpoints. This is the case in the ALaCaRT and ACOSOG Z6051 studies, which employed a novel composite pathological assessment. The endpoint was based on retrospective studies correlating these pathological characteristics with recurrence. Interestingly, no differences between the individual components of the composite score (CRM and DRM clearance and completeness of TME) were seen between the treatment groups in each study. This composite has not been validated to date as a risk assessment for recurrence, but was employed by these studies to enable early analysis. Long-term results with recurrence data are ultimately required to draw final conclusions on its prognostic importance. This is especially relevant given CLASICC initially reported higher CRM involvement after laparoscopic TME, a finding that failed to translate into a meaningful difference in long-term oncologic outcome beyond 5 years [7].

Colorectal surgeons are faced with several RCTs which draw somewhat conflicting conclusions. The most mature data demonstrates no difference in long-term outcomes and significant weighting should be afforded to these studies. Nonetheless,

Table 46.3 Perioperative and oncologic outcomes from largest published studies comparing robotic versus laparoscopic surgery for rectal cancer (robotic/laparoscopic)

Study	Park JS (2011)		D'Annibale (2013)		Ielpo (2015)		Cho MS (2015)		Park JS (2015)		Yamaguchi (2015)	
Design	Retrospective case series comparison		Retrospective case series comparison		Retrospective case series comparison		Case matched retrospective		Multicenter case matched retrospective		Prospective case series comparison	
Number of centers	1		1		1		1		7		1	
Location	South Korea		Italy		Spain		South Korea		South Korea		Japan	
Time period	2007–2009		2004–2012		2012–2013		2007–2011		2008–2011		2010–2015	
Site of tumors	≤15 cm from AV		Patients undergoing TME		≤15 cm from AV		Patients undergoing TME		Patients undergoing ISS with CAA		Transection below peritoneal refection	
Treatment group	**Rob**	**Lap**	**Rob**	**Lap**	**Rob**	**Lap**	**Rob**	**Lap**	**Rob**	**Lap**	**Rob**	**Lap**
Number	52	123	50	50	56	87	278	278	106	106	203	239
% neoadjuvant treatment	23.1	8.1	68	56	82	81	67.3	78.8	64.2	56.6	0.5	0
BMI median	23.7	23.6			22.8	23.7	23.5	23.5	24.3	23.8	23.4	23.1
Perioperative outcomes												
Conversion (%)	0	0	0	6	1.8	9.2	0.7	0.4	0.9	1.9	0	1.8
LOS (days)	10.4	9.8	8/10	10	13	10	10.4	10.7	9.9/	1.7	7.3	9.3
Mean operative time (min)	233	158	270	280	309	252	361	272	271	232	232	227
Complications 30 days Grade 3/4 (%) Grade 5 (%)	7.7 0	4.9 0			7.1 0	5.7 0	12.2 0	12.2 0.4	6.6 0	11.3 0	0	0

(continued)

Table 46.3 (continued)

Study	Park JS (2011)		D'Annibale (2013)		Ielpo (2015)		Cho MS (2015)		Park JS (2015)		Yamaguchi (2015)	
Anastomotic leak (%)	9.6	5.6	10	14	9.5	4.5	10.4	10.8	3.8	5.7	1.5	2.9
Reoperation (%)					5.3	3.4						
Oncologic outcomes												
CRM ≥1 mm (%)	98.1	97.6	100	88	96.4	97.7	95.0	95.3	92	91	100	99
DRM negative (%)					100	100	99	97	98.8	98.8	100	100
Mean LN yield	19.4	15.9	16.5	13.8	10	9	15.2	16	13.2	15.2	30	29
Distance to DRM (mm)	28	32	30	30			20	22	12	12	28	32
Distance to CRM (mm)	7.9	8.2							6.9	7.2		
3 year DFS OS LR							5 year 81.8 92.2 5.9	5 year 79.6 93.1 3.9	89.6 93.8 6.7	90.5 94.8 5.7		

Data presented as median unless otherwise stated

TME total mesorectal excision, *AV* anal verge, *ISS* intesphincteric dissection, *CAA* coloanal anastomosis, *BMI* body mass index, *LOS* length of stay, *CRM* circumferential resection margin, *DRM* distal resection margin, *LN* lymph node, *DFS* disease free survival, *OS* overall survival, *LR* local recurrence

CRM <2 mm

surgeons should be prepared to make treatment decisions and recommendations based on both patient and tumor characteristics, respecting the patient's own informed choices. To conclude, no data exists to suggest that long term outcomes are worse with laparoscopy. Providing the surgeon is competent to perform the laparoscopic TME, both open and laparoscopic techniques can be offered based on individual treatment considerations.

Robotic rectal cancer surgery is evolving and to date, meta-analyses suggest equivocal short-term outcomes to laparoscopic techniques. The UK MRC ROLARR trial is the first multicenter RCT examining robotic surgery compared with laparoscopic surgery for rectal cancer and outcomes are eagerly awaited [33]. No published results are available but preliminary data presented at the American Society of Colon and Rectal Surgeons Annual Meeting in 2015 reported low CRM involvement (5 %) and a complete/near complete TME in 89 % in the robotic arm. If confirmed in the final report, this data is comparable to published data for laparoscopic surgery. The published literature consistently demonstrates lower rates of open conversion with robotic surgery, suggesting robotic platforms may enhance ability to complete more challenging cases with minimally invasive techniques (e.g. high BMI; narrow pelvis; low, locally advanced tumor).

We favor the use of the robotic platform for MIS in rectal cancer. This stance is based on the perceived benefits of robotic surgery, improved visualization and increased dexterity of the instruments. These benefits in our view enable the operator to perform a more precise and detailed dissection with greater ease than conventional laparoscopic surgery alone.

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Chapter 47
Reservoir Construction After Low Anterior Resection: Who and What?

David A. Liska and Matthew F. Kalady

Introduction

The two key major outcomes after surgical treatment of rectal cancer are oncologic and functional. Improved understanding of tumor biology and advanced surgical techniques have led to improved oncologic results and also increased rates of sphincter-preserving procedures for low rectal cancers. This trend, however, has brought to light the functional consequences following low anterior resection (LAR) with total mesorectal excision (TME) and coloanal anastomosis (CAA). Many patients who have undergone sphincter-preserving low or ultra-low anterior resections with a straight CAA experience defecatory symptoms that can include frequency, urgency, clustering, incomplete evacuation, constipation, diarrhea, and incontinence [1]. This collection of symptoms, also known as low anterior resection syndrome (LARS),is partially attributable to the loss of the reservoir function of the rectum.

In an attempt to improve functional outcomes, different surgical techniques have been devised for the creation of a neo-rectal reservoir in lieu of a straight CAA. Lazorthes et al. [2] and Parc et al. [3]initially described a neo-rectal reservoir creation in the form of a colonic J pouch in 1986. Due to anatomic constraints in some patients (especially obese male patients with a narrow pelvis), a low anastomosis with a J-pouch is sometimes not technically feasible. Therefore, other reservoir options in addition to the colonic J pouch have been described and evaluated, including transverse coloplasty, and side-to-end CAA. Each of these options has its distinct advantages and disadvantages when compared to a straight CAA. This chapter reviews the literature on this topic comparing the different types of reservoir

D.A. Liska, MD • M.F. Kalady, MD (✉)
Department of Colorectal Surgery, Cleveland Clinic, Cleveland, OH, USA
e-mail: KALADYM@ccf.org

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Table 47.1 Structure of the analysis performed to evaluate different techniques of reservoir construction

Patient population	Intervention	Comparators	Outcomes studied
Rectal cancer patients undergoing low anterior resection with coloanal anastomosis	Colonic reservoir creation: J-pouch, transverse coloplasty, or side-to-end anastomosis	Straight coloanal anastomosis	Postoperative morbidity and functional outcomes

construction and formulates clinical recommendations. A summary of the structure of this analysis is provided in Table 47.1

Search Strategy

A systematic literature search was conducted in the following bibliographic databases: MEDLINE (using PubMed) and the Cochrane Library since the inception of the databases until October 2015. In addition, reference lists of published systematic reviews were searched manually. Publications not written in English were excluded. Given the availability of multiple randomized controlled trials (RCTs), non-randomized trials were excluded. Only trials comparing two reconstructive procedures were included for review. Studies reporting on results with less than 6 months follow up were excluded with regards to functional outcomes. No restrictions were applied with regard to publication date. Titles and abstracts of retrieved studies were screened for relevance and eligibility. Results from the most recent meta-analyses were also included in this review. Full texts of all eligible studies were retrieved and reviewed.

Results

Our literature search retrieved 20 RCTs that prospectively compared outcomes with a straight CAA to one of the colonic reservoirs or compared outcomes between different types of colonic reservoirs (Table 47.2). We reviewed ten RCTs comparing a straight anastomosis (SA) to a colonic J pouch (JP), six studies comparing a JP to a transverse coloplasty (CP), four studies comparing a JP to a side-to-end anastomosis (STE), and one study comparing a SA to a CP. The vast majority of studies used a circular stapled technique for the coloanal anastomosis. The largest published RCT, by Fazio et al. [18],randomized patients in whom a JP was technically feasible to receive either a JP or a CP, and if a JP was not feasible to receive either a SA or a CP. For clarity sake, this study was treated as two separate studies in Table 47.2. Our review also included one well-designed, recently published meta-analysis [25] and the most recent Cochrane systematic review published in 2008 [26].

Table 47.2 Summary of randomized controlled trials included in this review

Study	N		Anastomotic leak		Follow-up (months)	BM/24 h		Continence		Urgency	
	SA	JP	SA	JP		SA	JP	SA	JP	SA	JP
Straight coloanal (SA) vs. colonic J pouch (JP)											
Seow Chen (1995) [4]	20	20	0	0	6	4	2*				
					12	2	2	–	+*	–	+
Ortiz (1995) [5]	19	19	2	2	12	11[a]	5[a]*	–	+	–	+
Hallbook (1996) [6]	52	45	8	1*	2	6.4	2*	–	+*	–	+*
					12	3.5	2*	–	+*	–	+*
Lazorthes (1997) [7]	19	18	2	1	3	~5	~2*	–	+	–	+*
					12	~4.5	~2*	–	+	–	+
					24	~3.5	~2*	=	=	+	–
Ho (2000, 2001) [8, 9]	19	16	0	0	6	15[b]	6[b]*	–	+*	=	=
					12	7.1	4.6*	–	+	+	–
					24	7[b]	3[b]	–	+	=	=
Furst (2002) [10]	37	37	3	3	6	4.7	2.5*	–	+*	–	+
Oya (2002) [11]	21	20	0	0	6	4	3	–	+	=	=
					12	3	2.5	–	+	=	=
Sailer (2002) [12]	32	32	4	3	3	1.2[c]	1.2[c]	–	+*	=	=
					12	1.3 [c]	1.3 [c]	=	=	=	=
Park (2005) [13]	26	24	0	0	3	~11	~5*	–	+*		
					12	~6	~5	–	+*		
Liang (2007) [14]	24	24	0	0	3	7	4*	–	+	+	–
					6	6.5	4*	–	+	+	–
Colonic J pouch (JP) vs. transverse coloplasty (CP)											
Ho (2002) [15]	44	44	0	7*	4	4.5	4.6	–	+*	–	+*
					12	3	3.4	–	+	=	=
Pimentel (2003) [16]	15	15	1	2	3	4.1	3.9	+	–	–	+
					6	3.4	3.1	+	–	–	+
					12	2.8	2.1	+	–	=	=
Furst (2003) [17]	15	20	=	=	6	2.75	2	–	+	–	+
Fazio (2007) [18]	137	131	4	6	4	3	4*	+	–*	+	–
					12	3	3*	+	–	+	–
					24	2	3*	+	–*	+	–
Ulrich (2008) [19]	68	76	6	6	1						
Biondo (2013) [20]	54	52	1	1	6	29[b]	31[b]	=	=	=	=
					36	9[b]	10[b]	=	=	+	–

(continued)

Table 47.2 (continued)

Study	N		Anastomotic leak		Follow-up (months)	BM/24 h		Continence		Urgency	
	SA	JP	SA	JP		SA	JP	SA	JP	SA	JP
Straight coloanal (SA) vs. transverse coloplasty (CP)											
Fazio (2007) [18]	49	47	5	4	4	6	5.5	–	+*	–	+
					12	4	4	=	=	–	+
					24	3	2.5	=	=	–	+
Colonic J pouch (JP) vs. side-to-end (STE)											
Huber (1999) [21]	29	30	3	2	3	2.2	5.4*	+	–	+	–
					6	2.2	3.1*	=	=	+	–
Machado (2003) [22]	50	50	4	5	6	3.4	3.4	=	=	+	–
					12	3.1	3.0	=	=	+	–
Jiang (2005) [23]	24	24	0	0	3	4	4	=	=	=	=
					12	2.3	1.9	=	=	=	=
					24	1.9	2	=	=	=	=
Doeksen (2011) [24]	55	52	10	9	4	28	42[d]	+	–*		
					12	21	30[d]	+	–*		

+ Indicates better function (i.e., better continence and less urgency)
*$p < 0.05$
[a]Number of patients with >3 BM per day
[b]Number of patients with >4 BM per day
[c]Mean result of two point score > 5 BM = 0, 3–5 BM = 1, 1–2 BM = 0
[d]Mean of transformed score (0–100) with higher scores indicating worse bowel function

There were some design shortcomings and risks for bias in many of the included studies. Due to the nature of these trials, a double-blinded design—including blinding of the surgeon—is not feasible. However, it is unfortunate that the majority of trials do not clearly state if the patients and other study personnel were blinded. Considering that functional outcomes depend on self reported variables, non-blinding of patients can lead to significant bias. The majority, but not all of the included trials, describe appropriate randomization and allocation methods. Attrition and losses to follow-up were relatively low in most studies. Most of the studies did not specifically address the experience of the participating surgeons and, as such, allow for some element of bias. In all trials, randomization achieved groups that were well-matched in terms of important preoperative variables that could affect outcomes such as gender, preoperative bowel function, height of the tumor, and neoadjuvant chemoradiation. Overall, despite the relatively small number of patients enrolled in each study and the mentioned design shortcomings, the reviewed RCTs and meta-analyses provide us with moderate to high quality evidence with relatively low risk of bias [25].

The outcomes reported in the reviewed trials generally include surgical outcomes in terms of perioperative morbidity and mortality and specifically those related to anastomotic dehiscence. Some trials supply further, more detailed, perioperative variables in terms of morbidity, operative times, and length of stay. Except for the study by Ulrich et al. [19], which only reports short-term perioperative outcomes, all studies included report outcomes with regards to bowel function. Bowel function

is longitudinally assessed at different time points, which in patients with diverting ostomies is measured following restoration of intestinal continuity. There is significant variability among the different trials in the time points chosen at which bowel function is assessed. Furthermore, there is great heterogeneity among the different trials in terms of the specific functional parameters evaluated, questionnaires used to collect data, and scoring systems used to report outcomes such as incontinence and urgency. This variability makes it difficult to directly compare results from one trial to the other. Future research would greatly benefit from the uniform use of a validated scoring system at defined time points to assess post-operative function in rectal cancer patients [27].

While all trials assessing functional outcomes document self-reported variables such as bowel frequency, continence, and urgency, a significant number of trials also report data from anorectal physiologic assessments conducted in these patients. Interestingly, differences between the reconstructive options in terms of functional parameters such as bowel frequency, urgency, and incontinence did often not correlate with anorectal manometric or volumetric measurements. The explanation for this finding proposed by Furst et al. [10]is that a colonic reservoir such as a J pouch does not improve function by providing a more capacious reservoir, but is predominantly related to decreased propulsive motility in the pouch. This theory has gained widespread acceptance as many investigators have noted minimal or no correlation between differences in anorectal physiologic measurements and functional outcomes.

Perioperative Outcomes

Straight CAA Versus Colonic J Pouch

When comparing perioperative complications between a straight CAA and a colonic J pouch, there was a statistically non-significant trend towards fewer complications with a colonic J pouch. With regards to anastomotic leaks, only the study by Hallbook et al. [6] had a significant difference in postoperative complications, with a reduced rate of anastomotic leaks in patients with a JP compared to patients with a SA (2 % vs. 15 %, $p = 0.03$). It is noteworthy that the 15 % leak rate is higher than most reports in the literature and could account for the statistical difference. The trial by Jiang et al. [23], in which all procedures were done by laparoscopic-assisted technique, had similar perioperative outcomes between the JP and SA groups, but significantly longer operative times for the JP group (274.4 ± 34.0 vs. 202.0 ± 28.0 min, $p < 0.001$). The other studies reported no significant difference in operative times. On pooled analyses there was no statistically significant difference with regards to anastomotic leaks or overall complications between patients with a JP reconstruction versus a straight anastomosis. It is hypothesized that despite the additional staple lines required for a colonic JP, the risk for leaks is actually lower in the JP due to better blood supply to the anastomosis and reduced “dead space” in the pelvic cavity [13].

Colonic J Pouch Versus Transverse Coloplasty

When comparing perioperative outcomes between colonic J pouch and transverse coloplasty patients, only the study by Ho et al. [15]showed a statistically significant difference in the incidence of anastomotic leaks. In that study, seven patients (15.9 %) in the CP group developed anastomotic leaks compared to zero patients in the JP group. All leaks in this study developed at the anterior portion of the stapled coloanal anastomosis below the site of the coloplasty which was made 4 cm proximal to the anastomosis. In subsequent RCTs, the leak rate in CP patients ranged from 1.9 to 13 %, without any statistically significant differences when compared to JP patients. Of note, in the study by Fazio et al., comparing CP to a straight CAA reconstruction, there was also no difference in anastomotic leak rates. It is possible that the increased leak rate with the CP reservoir found by Ho et al. [15]was due to the contributing surgeons still being early on the learning curve for this procedure. On meta-analysis there was no significant increase in leak rates with a transverse CP reconstruction [25].

Side-to-End Versus Colonic J Pouch

In trials comparing STE anastomoses to colonic JP reconstruction, there was no statistically significant difference in overall complications or anastomotic leaks. The study by Huber et al. [21] showed significantly shorter operative times for STE patients compared to JP patients (149 vs. 167 min, $p < 0.05$), with similar trends in other trials. On meta-analysis there was again no significant difference with STE reconstruction in terms of perioperative complications.

In summary, there is no significant difference in perioperative outcomes between the different reconstructive options assessed by the included trials. There is a trend towards decreased anastomotic leaks with a colonic JP and STE anastomoses compared to transverse CP and straight CAA that does not reach statistical significance [25].

Functional Outcomes

Straight CAA Versus Colonic J Pouch

When comparing the functional results following a straight CAA versus a colonic JP reconstruction, most studies show significantly improved results with a JP, especially in the first 6–12 months after restoration of intestinal continuity. When specifically assessing bowel frequency, eight of the ten included RCTs showed significantly decreased bowel frequency with the JP. In trials assessing functional outcomes at 12 months, the majority of studies still found significantly reduced bowel frequency with a JP reconstruction. In the study by Lazorthes et al. [7] this held true even at 2 years post restoration of intestinal continuity. However, the study by Ho et al. [8]

demonstrated that at 2 years, in patients with a straight CAA, there was colonic conduit adaptation and marked reduction of bowel frequency, so that there was no longer a significant difference compared to patients with a JP. In terms of functional outcomes related to continence and urgency, the majority of trials demonstrated significantly better function with a JP. These benefits however were less pronounced and usually not significantly different when assessed at 12 months and beyond. On meta-analysis of the data amenable to pooling, bowel frequency was significantly lower with a JP at early and intermediate time points, while other measures of bowel function were not significantly different between the groups [25].

Colonic J Pouch Versus Tranverse Coloplasty

Functional outcomes following a transverse (CP) compare well to those observed with a JP in most studies. However, the study with the largest number of patients, by Fazio et al. [18], demonstrated that patients with a JP had significantly lower bowel frequency and better continence (as measured by the Fecal Incontinence Severity Index) in the early postoperative months and at 2 years. In that study, 27 % of patients were ineligible for a JP and were randomized to either a CP or straight anastomosis. Except for improved continence with a CP in the early postoperative period, there were no significant functional differences between the CP and the SA groups. This study was excluded from the meta-analysis due to unclear patient numbers at the different follow-up points. The remaining studies comparing a JP versus CP reconstruction that were included in the meta-analysis did not show any significant functional differences [25].

Side-to-End Versus Colonic J Pouch

There are only few RCTs comparing functional outcomes of a STE anastomosis with colonic JP reconstruction. Only the study by Huber et al. [21]showed significantly decreased bowel frequency with a JP, with the longest follow-up being only 6 months. The more recent study by Doeksen et al. [24] found better continence scores with a JP at 4 and 12 months but similar results with respect to other functional parameters. The other studies and data included in the meta-analysis showed that functional results following a STE compare well with those of a JP.

Summary of Comparisons

In summary, functional results after a colonic JP are significantly improved when compared to a straight anastomosis. These benefits are most pronounced in the early postoperative months, and according to some studies are still apparent at 2 years

following restoration of intestinal continuity. While there is no high-quality data directly comparing a side-to-end anastomosis to a straight anastomosis, the reviewed studies demonstrate that functional results following a STE compare relatively well to those seen with a JP. We therefore would expect a STE anastomosis to provide better function than a SA. Most studies also suggest that a transverse coloplasty provides functional benefits similar to a JP. However the transverse coloplasty study with the largest number of patients, demonstrated significantly better function with a JP and minimal benefit when comparing TC to a straight anastomosis.

Recommendations Based on the Data

For rectal cancer patients treated by low anterior resection and restoration of the gastrointestinal tract via CAA, a colonic J pouch should be constructed for the anastomosis as opposed to a straight CAA. There is no difference in perioperative morbidity between the two techniques, but the J pouch reconstruction results in improved postoperative functional outcomes. This is a strong recommendation based on high quality evidence. In patients with anatomy not suitable for a colonic J pouch, reconstruction with a side-to-end anastomosis or transverse coloplasty should be considered instead of a straight coloanal anastomosis due to improved functional results As there is limited direct evidence comparing straight coloanal anastomosis to side-to-end anastomosis or coloplasty, this is a conditional recommendation based on moderate data.

Personal View of the Data

In our opinion, there is strong evidence based on randomized controlled trials supporting the use of a colonic JP for coloanal anastomosis after low anterior resection for rectal cancer. This should be the default option for reconstruction as opposed to a straight coloanal anastomosis. Although there is some bias in the randomized trials, the total body of work overwhelmingly supports this recommendation. We recognize that there are some clinical situations where creation of a colonic J pouch for reconstruction is not technically feasible due to the patients anatomy; e.g., an obese male with a narrow pelvis may not be able to accommodate a colonic J pouch reservoir. In these situations, a side-to-end coloanal anastomosis or a transverse coloplasty are preferred reconstructions compared to a straight coloanal anastomosis. Although data directly comparing these latter techniques to a straight coloanal anastomosis are limited, the literature supports similar functional outcomes when directly comparing colonic J pouch, side-to-end, or transverse coloplasty anastomoses. Therefore, it is logical to expect superior functional outcomes with these techniques as compared to a straight coloanal anastomosis. Therefore in clinical practice, the authors primarily use a colonic J pouch, but have no reservations using a

side-to-end anastomosis if a colonic J pouch is not feasible. Although a transverse coloplasty is acceptable, it is not routinely used in our practice.

Abstract of Recommendation

Patients with rectal cancer treated by proctectomy with restoration of bowel continuity via coloanal anastomosis should receive a colonic J pouch reservoir reconstruction if technically feasible (strong recommendation; high quality evidence). If a colonic J pouch to anal anastomosis is not possible, then a side-to-end anastomosis or transverse coloplasty should be performed (conditional recommendation, moderate quality evidence).

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Chapter 48
Conventional vs Single Port Approaches to Laparoscopic Colectomy

H. Hande Aydinli and Meg Costedio

Introduction

Multiple multicentered randomized clinical trials confirming the safety, efficacy and benefits of laparoscopy have arguably made minimally invasive surgery the new standard of care for colon resection. Both European and American multicenter randomized clinical trials (RCT) demonstrate improved short-term and comparable long-term outcomes with laparoscopic versus open colon resection [1–7].

It is now established that laparoscopic colorectal resection is associated with less intraoperative blood loss (EBL) despite a longer operating time, less postoperative narcotic use, earlier return of bowel function and equal or shorter hospital stay (LOS) when compared with open surgery [2, 3]. In the early stages of laparoscopy, skepticism existed about whether laparoscopic colon resection was safe for oncologic procedures, both technically as well as the possibility of cancer seeding from carbon dioxide insufflation. Studies show no difference in the lymph node yield or the length of resected bowel between laparoscopic and open surgery. The 3 and 5 year follow up publications of RCT's demonstrate comparable outcomes with resection margins, mean number of lymph nodes harvested, overall survival, disease-free survival, and local and distant recurrence [5–7].

As most studies show a longer operative time and an increased cost associated with laparoscopy, it was initially hypothesized that laparoscopy would not be cost effective when compared to an open surgical procedure. Multiple RCT's and a case-matched study confirm that the total cost, including the treatment of postoperative complica-

H. Hande Aydinli, MD • M. Costedio, MD
Department of Colorectal Surgery, Digestive Disease Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: costedm@ccf.org

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tions and additional hospital stay, are comparable to open surgery [1, 8–12]. Long term hernia rates were also found to be comparable or lower when laparoscopy was performed [8, 11, 13]. The cosmetic benefits of laparoscopy have never been in question.

As surgeons and technology have advanced, laparoscopy is being attempted in more complex situations and surgeons are using less ports and advanced instrumentation. Multiple new techniques are being introduced to further minimize trauma to the patient as well as increase minimally invasive options for complex procedures. The single incision laparoscopic surgery (SILS) technique for colectomy was first described by Remzi et al. in 2008, and minimizes the incision solely to the extraction site, sparing multiple laparoscopic port sites. Since colorectal surgeons almost uniformly have at least 2–3 cm specimen or are creating a stoma, SILS is particularly applicable to colorectal surgery. Considerable clinical experience has been accumulated with SILS, but this technique has been scrutinized for many of the same concerns that were conveyed with conventional laparoscopy (CL) [14].

The aim of this evidence-based chapter is to discuss and answer questions related to the following issues; (a) what is the evidence regarding safety and feasibility of SILS in patients who are undergoing laparoscopic colorectal resection and (b) is there a difference in perioperative complications, cost, postoperative pain, cosmetic outcomes, hernia formation, or oncological outcomes between SILS and conventional laparoscopy.

Patient population	Intervention	Comparator	Outcomes studied
Patients undergoing minimally invasive colorectal resection	SILS	'Conventional laparoscopy'	Perioperative outcomes, cost, pain, cosmetic outcomes, hernia formation, oncological outcomes

Search Strategy

PubMed was queried using Medical Subject Headings (MESH); "Colon/surgery", "Rectum/surgery", "laparoscopy", and search terms; "single site", "single incision", "single port" in combination with the Boolean operators AND or OR. English language, adult: 19+ years and humans filters were used. Relevant articles' references were also reviewed.

Results

Among the 23 papers reviewed from the literature, there was only one RCT comparing the outcomes between SILS and CL in colorectal surgery to our knowledge, and this study was limited by sample size. One systematic review (SR), four propensity

score-matched (PSM) studies, and four case-matched (CM) studies with adequate sample sizes compared and reported the short-term, long-term and oncological outcomes between the patients underwent SILS and CL in the context of colorectal surgery. Eight retrospective cohort (RC), three case–control (CC), and two case-series (CS) were also reviewed, and the results were added to the study (Table 48.1).

Perioperative Outcomes

Multiple case-matched and case series studies demonstrate that the perioperative outcomes after SILS colectomy appear to be at least equal to CL [15, 16, 18–30, 32, 34–37]. Katsuno et al. compared 107 patients who underwent SILS colectomy with 107 patients who underwent CL in a propensity score-matched study design and no differences were found in operative time, EBL, LOS or postoperative complications [15]. In the largest case-matched study to date comparing 318 CL cases with 308 SILS cases, no significant differences were found in terms of elective or emergent status, operative time, or conversion to laparotomy. This study did show a significant decrease in EBL in favor of the SILS group. This study also demonstrated a significant decrease in superficial surgical site infections, 11.3% vs. 5.8% in the SILS group with a similar LOS between the groups [29].

Of the 23 studies reviewed, 21 report on LOS. 13 of the studies (3 PSM, 3 CM, 2 CC and 5 RC studies) show a comparable LOS between groups. The other 8 papers (1 RCT, 1 SR, 1 PSM, 1 CM, 1 CC and 3 RC studies) report a shorter LOS favoring SILS.

Overall 20 papers reported on operative time, 13 of these (4 PSM, 1 RCT and SR, 2 CM, 3 RC and 2 CC studies) report no significant difference in terms of operative time between SILS and CL. In one PSM study where they compared 61 patients who underwent SILS with 61 patients who underwent CL for colon cancer, they distinguished total operation time from net operation time (procedure time). The total operation time was significantly shorter in SILS group but the total procedure time was not statistically different. This indicates that port placement and closure are likely to be quicker in SILS [35].

A total of ten papers reported on EBL. Seven studies found a comparable EBL after SILS and CL (3 PSM, 3 CM, and 1 RCT), while three studies found decreased EBL after SILS.

Cost

Stewart et al. evaluated the cost in patients undergoing laparoscopic surgery in four groups including CL converted to open and SILS converted to open groups. This study included 149 CL and 111 SILS cases. As expected, patients who were

Table 48.1 Study size, type, nature of disease, summary of outcomes, and quality of evidence summarized for all studies

Study	Patient	Benign/malign/mixed	Study type[a]	Results'			Quality of evidence
				SILS > CL[b]	SILS = CL[b]	CL > SILS[b]	
Katsuno (2015) [15]	SILS (n = 107), CL (n = 107), pts w CRC	Malign	PSM	Pain, Incision length	Op time, EBL, LOS, complication, 5-year DFS and OS, LN		Moderate
Lee (2011) [16]	SILS (n = 46), CL (n = 46)	Mixed	CM	Cosmesis	Op time, LOS, incision length, body image score, complication		Moderate
Markar (2014) [17]	SILS (n = 1312), CL (n = 1862)	Mixed	SR	EBL, LOS	Op time, Complication, mortality, Hernia, LN		Moderate
Poon (2012) [18]	SILS (n = 25), CL (n = 25)	Mixed	RCT	LOS, pain	Op time, EBL, complications, LN, narcotic		Moderate
Takemasa (2014) [19]	SILS (n = 150), CL (n = 150)	Malign	PSM	Pain	Op time, EBL, LN, hernia, mortality, LOS		Moderate
Champagne (2012) [20]	SILS (n = 165), CL (n = 165)	Mixed	CC	EBL, pain	Op time, LOS, complication		Low
Chew (2013) [21]	SILS (n = 40), CL (n = 40)	Mixed	RC		Op time, Complication, LN, incision length, pain, narcotic, LOS		Low
D'Hondt (2014) [22]	SILS (n = 20), CL (n = 40), Sigmoidectomy for diverticulitis	Benign	CM	Pain, cosmesis	EBL, LOS, hernia	Op time, cost	Low

Keshava (2013) [23]	SILS (n = 75), CL (n = 74), pts underwent R hemi-colectomy	Mixed	RC	LOS, incision length	Complication		Low
Kim (2011) [24]	SILS (n = 73), CL (n = 106)	Malign	RC	Narcotic, LOS	Complication, LN,	Op time	Low
Kim (2015) [25]	SILS (n = 120), CL (n = 120), pts w sigmoid tm	Malign	PSM	Incision length, pain	Op time, EBL, LOS, complication, LN, 3-year DFS and OS		Low
Osborne (2013) [26]	SILS (n = 55), CL (n = 327)	Mixed	RC	Op time, LOS, LN	Complication, pain, hernia		Low
Papaconstantinou (2011) [27]	SILS (n = 39), HALS (n = 39), CL (n = 39), pts undergoing Right colectomy	Mixed	CM	Pain, LOS	Op time, EBL, incision length, complication,		Low
Rosati (2013) [28]	SILS (n = 50), CL (n = 50), pts undergoing Right colectomy	Mixed	CC	LOS	Op time, complication, LN		Low
Sangster (2015) [29]	SILS (n = 308), CL (n = 318)	Mixed	RC	EBL, LN, complication	Op time, LOS, hernia, mortality		Low
Stewart (2014) [30]	SILS (n = 111), CL (n = 149)	Mixed	RC	Op time	LOS, cost		Low
Sulu (2014) [31]	SILS (n = 95), CL (n = 90)	Mixed	CM	Op time	EBL, LOS, cost, complication		Low

(continued)

Table 48.1 (continued)

Study	Patient	Benign/malign/mixed	Study type[a]	Results'			Quality of evidence
				SILS > CL[b]	SILS = CL[b]	CL > SILS[b]	
Velthuis (2012) [32]	SILS (n = 50), CL (n = 50), pts undergoing Right colectomy	Mixed	CC	Op time	Complication, LOS, LN, hernia		Low
Waters (2012) [33]	SILS (n = 100), pts underwent Right hemi-colectomy	Mixed	CS		Short term outcomes, oncological outcomes		Low
Yun (2013) [34]	SILS (n = 66), CL (n = 99), pts underwent Right hemi-colectomy	Malign	RC		Op time, LOS, complication, LN		Low
Yun (2015) [35]	SILS (n = 61), CL (n = 61)	Malign	PSM	LOS, total op time	Net procedure time, complication, LN, DFS, OS		Low
Kanakala (2012) [36]	SILS (n = 40), CL (n = 78)	Mixed	RC	LN	Op time, LOS, complication		Very low
Vestweber (2013) [37]	SILS (n = 224)	Benign	CS		Short term outcomes		Very low

DFS disease free survival, *OS* overall survival, *LN* number of lymph node cleared, *Pain* postoperative complaining frequency of pain, *Narcotic* postoperative narcotic use

[a]CC: Case-controlled study, CM: Case-matched study, CS: Case-series, RC: Retrospective cohort study, PSM: Propensity score-matched study, SR: Systemic review

[b]SILS ≥ CL: Variables with a better outcome in SILS group, SILS = CL: Comparable outcomes, CL ≥ SILS: Variables with a better outcome in CL group

converted to open were found to have a higher cost but no significant difference was found between patients who underwent CL and SILS in terms of total cost [30]. Sulu et al. found total cost including operating room, nursing, pharmacy, radiology, professional and pathology/laboratory costs to be comparable in patients undergoing SILS (n = 90) and CL (n = 90) colorectal resections in a case-matched study design. The anesthesia costs were significantly lower in the SILS group ($p = 0.003$) which was related to the significantly longer operating time in the CL group ($p < 0.001$) [31]. On the other hand, D'Hondt et al. reported a higher total disposable cost (2599.02 ± 127.28 vs. 2320.13 ± 116.40, $p < .0001$) in a case-matched study where they compared 20 SILS patients with 40 CL patients who underwent sigmoidectomy for diverticulitis. Since the cost they reported did not include the hospital stay and complication costs, the results are limited in terms of the applicability [22].

Pain

Lesser postoperative pain is a theoretical advantage of SILS that should lead to a decrease in narcotic use, and in turn, decreased length of stay. There are many case-matched studies showing that patients who underwent SILS colectomy had better postoperative pain control with less frequent use of parenteral narcotics [15, 18–20, 22, 24, 25, 27]. Papaconstantinou et al. compared SILS with CL as well as hand assisted laparoscopy in patients undergoing laparoscopic right colectomy. Twenty nine patients were included in each group and the maximum pain scores on postoperative day 1 and 2 were significantly lower in the SILS group compared with both CL and the hand assist group. Since adequate pain control is a widely accepted discharge criteria, LOS was found to be one day shorter in SILS group when compared to CL in this study [27]. In a retrospective cohort study by Kim et al., they evaluated the short-term outcomes in 179 patients (SILS n = 106, CL n = 73) with colorectal cancer. Results showed a significantly decreased use of parenteral narcotics; accompanied by a significantly shorter LOS (9.6 ± 9.6 vs 15.5 ± 9.8 days, $p = 0.000$) favoring the SILS group [24].

Cosmetic Outcomes

Another obvious benefit of SILS over CL is cosmesis. This has proven to be a difficult outcome to measure as patients are unaware of the cosmetic results of other procedures, and are often pleased with their cosmetic result. As expected, studies do not always show a significant difference in the length of incision between SILS and CL as often the length of incision is based on the size of the specimen [27]. Keshava et al. reports the mean length of extraction incision to be less than 1 cm smaller ($p < 0.001$),when comparing 75 patients who underwent SILS right hemi-colectomy

vs. 74 patients with CL [23]. Lee et al. compared the body image and cosmesis scores 3 months from the surgery in a case-matched study of 92 patients, where they found the incision was 1 cm shorter in the SILS group. The body image scale measured the patients' perception of and satisfaction with their own body; the cosmetic scale on the other hand assessed the degree of satisfaction of patients in terms of the physical appearance of the scar. While the body image score was found to be comparable between groups, there was a significant difference in the cosmetic score favoring the SILS group [16]. D'Hondt et al. measured an overall satisfaction and a cosmetic result evaluation on a scale ranging from 0 to 10 in 60 case-matched patients underwent sigmoidectomy for diverticulitis. They reported comparable overall satisfaction rates but an improved cosmetic results for SILS group [22]. The incision length was reported to be 4 cm (3.3 ± 0.6 vs 7.7 ± 0.7 cm) longer in CL group when they compared 180 patients with sigmoid colon cancer (SILS N = 60, CL N = 120) in a propensity score-matching setting [25].

Hernia Formation

In the 23 studies reviewed, 6 reported a hernia rate separate from the overall complication rates. Neither the definition, criteria for diagnosis of hernia nor the follow up time until diagnosis, was were clear in four of the studies. Sangter et al. reported comparable 60-day incisional hernia rates according to the clinicians' judgment, but they excluded 40 patients with a stoma due to the increased risk for hernia [29]. Markar et al. reported comparable 30-day port site hernia rates [17]. There was no consistency in the literature in terms of types of the hernias reported (2 'hernia', 2 'incisional hernia', 2 'port site hernia' terms were used). The data does not support a difference in hernia rates between SILS and CL [17, 19, 22, 26, 29, 32].

Oncologic Outcomes

Fourteen papers reported the number of lymph nodes in the specimen and 10 papers commented on the comparable safety and feasibility of the SILS in cancer cases (1 RCT, SR, CC, CS, 4 PSM and 2RC studies) [15, 17–19, 24, 25, 28, 33–35]. The number of harvested lymph nodes was comparable between SILS and CL for colorectal cancers in a RCT and multiple CM/PSM studies [15, 18, 19, 35]. There were no significant differences in terms of overall survival rates (one study 24 months 3-year and 5- year) or disease free survival rates (one study 24 months, 3-year and 5- year) [15, 25, 34]. Long-term results are still pending, as this technique has only been described for colorectal procedures for approximately 7 years.

Recommendations

Single incision surgery is still evolving, and high quality comparative evidence is still lacking. These studies are likely affected by selection bias, where patients with optimal anatomy and BMI would be chosen for SILS over CL. This could lead to results skewed towards the SILS group with regards to perioperative outcomes. It is a common finding that operative time is shorter in the SILS group and this is likely a combination of decreased port insertion and closure times as well as the fact that the many advanced laparoscopic surgeons choose to perform SILS. Overall, based on the available literature, SILS is operatively and oncologically safe and feasible in advanced laparoscopic hands for selected patients. If the surgeon feels that they can perform the operation using the SILS technique the same way they perform it using CL, then it is appropriate for the patient. Cosmetic outcomes and pain scores are improved with SILS. But prolonged oncologic and hernia outcomes need to be assessed with well-designed trials. Data are lacking to demonstrate a benefit of SILS over CL and large well-designed RCT's are needed.

Personal View of the Data

Our personal view is that SILS colectomy is comparable to CL in experienced hands. Cosmesis is improved, which is particularly beneficial in young patients. It is difficult to obtain adequate traction/counter traction required for rectal cancer surgery and the authors choose not to use SILS for this indication. A common misconception is that conversion to multiport laparoscopy is a failure of the SILS technique. The authors would counter that starting with the extraction site allows the surgeon to inspect intraabdominal adhesive disease early and make decisions about the need for added ports or conversion to open prior to unnecessary adhesiolysis solely for port placement. So whether the surgeon utilizes the pure SILS technique or a reduced port technique, this potentially saves time intraoperatively while making the procedure safer.

Recommendations

- If the surgeon feels that they can perform the operation using the SILS technique the same way they perform it using CL, then it is safe and feasible for the patient. (Evidence quality is moderate, weak strength)
- Overall based on the available literature SILS is operatively and oncologically safe and feasible in advanced laparoscopic hands in selected patients. Cosmetic outcomes are improved with SILS and pain scores are decreased. (Evidence quality low; weak strength).
- Prolonged oncologic and hernia outcomes need to be assessed with well-designed trials. Data is lacking to demonstrate a benefit of SILS over CL. (Evidence quality low; no recommendation)

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Chapter 49
Anastomotic Leak Management Following Low Anterior Resections

Nathan R. Smallwood and James W. Fleshman

Introduction

Anastomotic leaks commonly occur after low anterior resections (LAR) and are among the most feared complications encountered by surgeons. Although, overall mortality rates remain low (~2%) following LAR, one-third of all postoperative deaths occur in patients with anastomotic leak [1] Anastomotic leaks also result in increased rates of patient morbidity, permanent stomas, as well as poor bowel function and incontinence in those patients managed without a permanent stoma [2–4]. Despite an extensive amount of literature addressing risk factors and methods of prevention, the number of anastomotic leaks following low anterior resections has remained the same for the last 40 years [5].

The creation of standardized treatment strategies to manage anastomotic leaks are commonly built on expert opinion and consensus, as there are only a limited number of studies focusing on anastomotic leak management [6, 7]. As a result, these prior treatment strategies are largely empiric and based upon very little evidence. Further, recommended options are often broken down according to the site of the anastomosis (intraperitoneal vs. extraperitoneal) or size of the anastomotic defect (minor vs. major),and typically result in an overly complex treatment algorithm [6].

N.R. Smallwood, MD
Division of Colon and Rectal Surgery, Baylor University Medical Center, Dallas, TX, USA

J.W. Fleshman, MD (✉)
Department of Surgery, Baylor University Medical Center, Dallas, TX, USA

Texas A&M Healthsciences, Dallas, TX, USA
e-mail: James.Fleshman@baylorhealth.edu

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The appropriate management of anastomotic leaks following LAR is best simplified by focusing on two primary questions:

1. ***What is needed to obtain source control****?* Specifically, what intervention is needed that will provide effective drainage and eradication of the infectious source while also preventing recurrence of local sepsis?
2. ***What interventions/measures can be performed to help reestablish intestinal continuity****?*

PICO table

Patient population	Intervention	Comparator	
Patients with anastomotic leak following LAR	Anastomotic salvage	Anastomotic takedown and end stoma	Morbidity, mortality, functional outcomes

Search Strategy

Relevant studies published between January 2000 and December 2016 were identified from the search of the Medline databases and Cochrane databases. The following search terms were used: rectal, rectum, proctectomy and leakage, failure, integrity, insufficiency, breakdown, defect, separation, dehiscence. Further articles were then selected based upon a review of the citations found in selected papers from the first search. All English language publications which primarily focused on the management of anastomotic leaks following low anterior resections were selected. Exclusion criteria included: (1) studies primarily focusing on risk factors, prevention, recurrence, or the treatment of other types of complications; (2) studies in which the majority of leaks were not involving a rectal anastomosis (ileo-colic, colo-colonic, ileo-anal); (3) non-English papers; (4) animal or laboratory studies. To avoid redundant studies, all of the authors and organizations, community of patients and study dates were routinely checked. When a study reporting the same patient cohort was included in several publications, only the most recent or complete study was selected.

The patients that are the most in need of infectious source control are those with generalized peritonitis and/or sepsis. Most surgeons would agree on the need for fluid resuscitation, antibiotics and operative intervention to drain and divert. However, aside from gross ischemia or complete dehiscence, there continues to be controversy over whether the anastomosis should be taken down or salvaged. We specifically wanted to know whether or not anastomotic salvage leads to inferior source control and therefore higher mortality rates as compared to anastomotic takedown. Also, as has been suggested in prior studies, does anastomotic salvage provide any benefits over takedown in terms of the ability to re-establish intestinal continuity and prevent the number of permanent stomas?

There is very little consensus regarding the best methods for preserving or reestablishing intestinal continuity. Despite the high rates of permanent stomas and poor

rectal function in patients with anastomotic leak, many surgeons continue to rely on a wait and see approach. Definitive treatment to allow for complete closure is therefore delayed in the hopes of spontaneous healing. Ultimately, this approach has been and will continue to be challenged by the emergence of active therapies to treat anastomotic leaks.

At our institution we have used endoluminal vacuum (E-Vac) therapy in the treatment of anastomotic leaks. While this therapy is not commonly utilized in the US, it has been used primarily in Germany since around 2002 [8]. Without any established gold standard for comparison, we decided to create PICO tables that compared E-Vac therapy to redo surgery, and conservative management (including the "wait and see approach,"). Other methods such as endoscopic stent placement will be less formally reviewed as it was anticipated that available studies concerning these methods would be limited.

A manual search was also performed focusing on the search terms endoluminal vacuum therapy, endoscopic vacuum therapy, endo-SPONGE, endosponge, endo sponge, and endoluminal negative pressure therapy. Additional articles were found using a Google Scholar search using the same search terms as well as from a review of the citations of selected articles. All studies evaluating the use of E-Vac therapy were reviewed and assessed for treatment related complications. Only studies including ten or more patients treated with E-Vac therapy were used in comparing outcomes between interventions. One final manual search was performed for a better evaluation of the baseline risk of permanent stoma in patients with and without anastomotic leak. Keywords used were "permanent stoma," "definitive stoma," "permanent ostomy", "definitive ostomy."

Recommendations Based on the Data

Traditionally the treatment of choice for a leaking colorectal anastomosis has been resection with end colostomy. This is despite the limited evidence to support this practice (Table 49.1a, b). In fact, one of the commonly referenced studies which emphasized the need for anastomotic takedown contained only three patients so treated [13]. More recently, the need for anastomotic takedown has been questioned and the trend continues to be moving away from this approach and towards performing anastomotic salvage.

Comparisons between anastomotic takedown and salvage were limited to four studies reporting on two of the four important outcomes. Patients treated with anastomotic salvage had statistically significant fewer postoperative deaths [9] and permanent stomas [9, 12] compared to patients treated with anastomotic takedown. Patients treated with anastomotic takedown as compared to anastomotic salvage also had more episodes of recurrent sepsis [22.7 % (5/22) vs. 0 % (0/10)] [12] and underwent an additional laparotomy more often [18.5 % (10/54) vs. 7.7 % (3/39)] [9], respectively.

Table 49.1 Outcomes following anastomotic takedown compared to anastomotic salvage for the treatment of anastomotic leak

(**a**) **Mortality**					
№ of participants (studies)	Risk of bias	Publication bias	Outcome		Overall quality of evidence
			Anastomotic salvage	Anastomosis takedown	
125 (1 observational study) [9]	Very serious[a]	Very strong association. Residual confounding would reduce demonstrated effect.	15.4 %[b] (6/39 patients)	37.0 % (20/54 patients)	Very low
(**b**) **Need for permanent soma**					
134 (4 observational studies) [9, 10, 11, 12]	Very serious[a]	Very strong association. Residual confounding would reduce demonstrated effect.	5.6 %[c] (4/71)	61.9 % (39/63)	Low

[a]In the selected studies, the choice between anastomotic takedown or salvage was not randomized or controlled

[b]Statistically significant $p < 0.05$

[c]All four studies showed reduced number of permanent stomas in patients treated with anastomotic salvage. Only two of four studies assessed for statistical significance with both showing a statistically significant decrease ($p < 0.05$) in permanent stomas in patients treated with anastomotic salvage

These differences must be analyzed with caution based upon the overall quality of the studies (low to very low). Treatment bias may result in severe leakage (larger defects, colon necrosis etc.) being treated with anastomotic takedown, but remains unlikely account for differences in outcomes.

Surgical Management of Anastomotic Leakage Following LAR in Patients with Generalized Peritonitis and/or Sepsis

1. In the absence of bowel ischemia/necrosis and/or major dehiscence, patients should be managed without resection or takedown the anastomosis and given a proximal diverting stoma. (Strong recommendation based upon low or very low-quality evidence)

The authors of all four included studies reported favoring the use of anastomotic salvage [9, 10, 12, 11]. In three of the four studies, anastomotic takedown with

Table 49.2 Outcomes of re-do surgery compared to endoluminal vacuum therapy in restoring intestinal continuity

(**a**) **Permanent stoma**					
№ of participants (studies)	Risk of bias	Publication bias	Need for permanent stoma		Overall quality of evidence
			Redo surgery	E-vac therapy	
349 (12 observational studies) 1 [15–22, 8, 23, 22]	Serious[a]	Publication bias strongly suspected	15.0 % (21/140)	18.9 % (18/95) ≤ 6 weeks 15.9 % (10/63) + diversion 7.70 % (1/13)	Very low
(**b**) **Complete closure**					
№ of participants (studies)	Risk of bias	Publication bias	Complete closure		Overall quality of evidence
			Redo surgery	E-vac therapy	
293 (11 observational studies; 8 E-Vac, 3 Redo) [20, 22, 19, 17, 21, 16, 15, 24, 23, 8, 18]	Serious[a]	Publication bias strongly suspected. Residual confounding would reduce the demonstrated effect	77.1 % (91/118)	85.7 % (150/175) ≤ 6 weeks 92.1 % (70/76) + diversion 93.8 % (75/80)	Very low
(**c**) **Rectal function**					
№ of participants (studies)	Risk of bias	Publication bias	Rectal function		Overall quality of evidence
			Redo surgery	E-vac therapy	
160 (4 observational studies; 4 Redo) [14, 17, 16, 15]	Serious[a]	Publication bias strongly suspected	No incontinence 78 % (60/77) LARS Score 22 ± 9 (n = 17 patients) Wexner score 8 (0–17) (n = 43 patients)	Not reported	Very low

[a]Risk of bias secondary to study design and no control group

creation of an end stoma was only favored in the management of anastomoses with ≥ 50–100 % dehiscence or in the presence of bowel ischemia or necrosis [9, 11, 12]. In the absence of the above criteria, diverting ostomy and salvage of the anastomosis is an effective method of controlling peritoneal sepsis resulting from leakage of both intraperitoneal and extraperitoneal rectal anastomoses. Anastomotic salvage and diversion is also the favored approach when anastomoses are inaccessible or poorly visualized as a result of significant inflammation, exudate, and/or adhesions.

Reestablishing Intestinal Continuity in Patients with Symptomatic Anastomotic Leakage Following LAR

1. E-Vac therapy is an effective early treatment option for anastomotic leaks with an associated abscess cavity, with or without diverting stomas. (Table 49.2). Strong recommendation based upon low or very low-quality evidence.

Only studies reporting ≥ 10 patients treated with E-Vac therapy were included. Studies were excluded (Keskin et al.) if the described method of E-Vac therapy differed greatly from the original description by Weidenhagen et. al. [25, 26]. The study by von Koperen et al. was excluded because delay in starting of E-Vac led to worse outcomes [27]. In the majority of studies, E-Vac therapy was the treatment of choice for anastomotic leaks involving the rectum, associated with a cavity in patients without generalized peritonitis. E-Vac therapy resulted in very high complete closure rates and low permanent stoma rates. The highest closure rates and lowest permanent stoma rates could be seen in the subgroup of patients with proximal diverting stomas and/or early treatment (<6 weeks). No deaths related to E-Vac therapy or anastomotic leak occurred following the start of therapy. Only a limited number of complications thought to be related to E-Vac therapy occurred (recurrent abscesses, fistulas, bleeding).

Compared to E-Vac therapy, redo surgery resulted in slightly lower permanent stoma rates despite decreased complete closure rates. No postoperative deaths occurred following redo surgery despite major intraoperative complications and postoperative morbidity requiring further surgery in 10.3 % of patients. Redo surgery is technically demanding, often requiring adjunctive surgical methods including advanced colon mobilization and anastomotic techniques. Authors of these studies recommend redo surgery only in patients with minimal to no comorbidities and after multiple other measures have failed.

E-Vac therapy can safely and effectively close anastomotic leaks ultimately allowing for intestinal continuity to be reestablished in the majority of patients, especially in patients treated early and those who have a diverting stoma. E-Vac therapy can be performed in the endoscopy suite, intensive care unit or operating room, does not require general anesthesia, and in some patients, continued on an outpatient basis. However, patients should be counseled and informed on the expected number of endoscopic sponge changes [7–11] and treatment duration (18–34 days) needed to allow for leak closure. A diverting stoma should be considered in patients being treated with E-Vac therapy since it is associated with increased ease of use and higher anastomotic leak closure rates.

Unfortunately, a number of important barriers exist which may severely limit the feasibility of implementing E-Vac therapy in the US. Due to the inaccessibility and increased cost seen with the Endosponge device, E-Vac therapy requires adaptation of current negative pressure devices. Adoption of this new method by surgeons will likely be slow and challenging at the present time until the collective experience increases.

2. Reoperative surgery is a treatment option in patients with chronic leaks, minimal to no comorbidities, and in whom other less invasive methods have failed. (Weak recommendation based upon low or very low-quality evidence)

Patients with a failed colorectal anastomosis from anastomotic leaks or fistulas who have failed other therapies can successfully be treated with reoperative or "redo" surgery. Redo surgery in this setting is highly demanding procedure and associated with high intraoperative and postoperative morbidity. Therefore, reoperative surgery should only be considered in patients with minor comorbidities and a very low risk of postoperative mortality. Pelvic recurrence must be excluded in patients whose primary surgery was for cancer. Patients must also be counseled on the increased risk of complications that could occur and the potential need for further interventions, including the need for further surgery. Patients must also understand that even with a successful redo surgery, their functional result may be poor. Finally surgeons who are considering performing redo surgery must have experience with advanced techniques that often are needed for colon mobilization and anastomotic creation.

3. E-Vac therapy should be considered in selected patients who are highly committed to having their stoma closed. (Strong recommendation based upon low or very low-quality evidence)

Despite the low level of evidence, we believed a strong recommendation was warranted based upon a number of factors. The desire to avoid a permanent stoma is important to most patients. There is likely to be a moderate to large reduction in permanent stoma rates with the use of E-Vac therapy as compared to conservative management. The undesirable effects associated with the use of E-Vac therapy are likely to be minimal. The present logistic barriers to usage are not likely to be permanent, but do require a surgeon or endoscopist experienced in its use.

A Personal View of the Data

The first recommendation for a patient with an anastomotic leak from non-diverted anastomosis, is that they should be given a diverting ostomy. Proximal diversion limits the flow of stool into the pelvis/abdomen, limits inflammation around the anastomosis and greatly enhances the ability to employ other adjunctive treatment methods. Even in the setting of peritonitis, the anastomosis does not typically need to be resected.

Most patients with a leak will have been given a diverting stoma at the time of their index operation. Assuming that the leak can be controlled and the patient does not have diffuse peritonitis and/or septic shock, the first step is usually to perform a CT of the pelvis with rectal contrast. Imaging indicates the size of the leak, the extent of potential spread (contained or not), the distance of the separated ends of the

colon and rectal stump, any involvement of the surrounding organs (rectovaginal fistula, colovesical fistula, coloenteric fistula) and the potential burden of contamination associated with the defective anastomosis. Each of these must be considered as the plan is made for treatment. Endoscopic evaluation of the anastomosis demonstrates the size of the defect, position of the leak along the circumference of the circular stapleline, the condition of the tissue at the anastomotic site (viable or ischemic or ragged), the volume of the extraluminal abscess cavity, the pliability of the tissue on each side of the stapleline and the distance of the defect from the anal verge.

The options for the treatment can now be considered and critically compared. Complete disruption of the anastomosis is generally the worst situation, but on rare occasions be temporized with a covered stent placed across the defect combined with external drainage of the pelvis. There must be a landing zone for the distal end of the stent above the anal sphincter to avoid severe tenesmus and erosion of the stent into the anal mucosa. The likelihood of successful healing of an intact functioning anastomosis is low, but the stent may buy valuable time so a definitive transabdominal repair can be done later under elective conditions in the setting of a clean pelvis.

Partial disruption of the anastomosis, with greater than 50 % of the circumference intact, has a better chance of local repair when the anastomosis is within the reach of an anoscope. Once again the external component of the leak must be managed with a percutaneous drain or endosponge placed through the separation in the anastomosis. Clearing the abscess cavity of fecal and purulent material is critical to eventual anastomotic healing and the functionality of the pelvic floor. As the cavity contracts and the area becomes clean, consideration can be given to either placing full thickness sutures across the defect to close the opening, or endoscopic clips can be placed to pull the lateral edges together and reduce the opening to a smaller diameter. The expense of the clips makes this approach less attractive. Suture placement can be facilitated by endoluminal suturing techniques borrowed from laparoscopy and transanal endoscopic microsurgery. The endosponge is then placed within the lumen of the bowel at the anastomosis to enhance healing at the sutureline. The vacuum created by the suction applied to the sponge collapses the lumen of the rectum and seals at the anus without extra maneuvers. The vacuum acts to remove bacteria, mucus and debris, encourage blood flow into the tissue and reduce edema of the adjacent tissue.

An alternative to suture repair of the anastomosis is to place the endosponge through the opening in the anastomosis to fill the external cavity. As the cavity shrinks, the sponge can be shaped to fit the cavity and over time is withdrawn from the cavity during subsequent sponge changes. The last phase involves leaving the sponge in the lumen of the bowel to completely obliterate the external cavity and draw the edges of the defect together.

E-Vac therapy requires patience on the part of the surgeon and compliance on the part of the patient. Numerous endoscopic changes will be required under sedation, and at times under general anesthesia. The sponges that are used to contract the pelvic abscess cavity must be changed more frequently to avoid in-growth of the

tissue and excessive bleeding during removal of the sponge. In addition, the endosponge loses its suctioning power and effectiveness overtime due to a buildup of secretions. Generally, endoscopic changes are done every 3–4 days, but can safely be extended up to 7 days, especially if the sponge is placed only within the lumen. Several months of treatment may be required depending on the extent of disruption of the anastomosis. However, if the leak can be diagnosed and treated earlier, leaks healing times may be much quicker [28]. As with all low rectal anastomoses, a final check of healing with an endoscopy and contrast enema prior to closure of the diverting loop ileostomy is prudent [29].

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Chapter 50
Management of the Unhealed Perineal Wound After Proctectomy

Jesse Moore and Sean Wrenn

Introduction

Abdominoperineal resection is the surgical standard for low rectal cancers when sphincter salvage is not possible, and has proven to be a life-saving procedure for patients who need it. Otherindications for abdominoperineal resection include inflammatory bowel disease (IBD), and salvage surgery for persistent or recurrentanal cancer [1]. An unhealed perineal wound after oncologic surgery was first described by Miles in 1908 and it remains an ongoing issue for patients to this day [2]. As surgical approaches have become more aggressive, i.e., extralevator abdominoperineal excision of the rectum to reduce positive circumferential margins, patients have become more susceptible to wound complications. The increased use of perioperative chemoradiation further impairs local healing. For these reasons the unhealed perineal wound is a common complication following proctectomy [3]. The presence of an unhealed perineal wound can delay adjuvant chemotherapy or radiation therapy. It can also result in severely diminished quality of life following the operation owing to frequent outpatient visits, prolonged hospital stays, frequent dressing changes, further operations, and increased healthcare costs [1, 4].

An unhealed perineal wound is classified as a persistent perineal sinus (PPS) if it persists for greater than 6 months following surgery [5]. The incidence of PPS is up to 30 % of patients after abdominoperineal resection (APR) for low rectal cancer, and after surgery for inflammatory bowel disease can be as high as 70 % [5] As many as 33 % of cases of PPS have not healed by 1 year, and chronic PPS becomes increasingly unlikely to heal spontaneously without aggressive intervention [6].

J. Moore, MD, FACS, FASCRS (✉) • S. Wrenn, MD
University of Vermont Medical Center, University of Vermont College of Medicine, Burlington, VT, USA
e-mail: Jesse.Moore@uvmhealth.org

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In the case of PPS, the sizeof the defect may dictate whether conservative or aggressive treatment strategies will be more appropriate.

Patients with inflammatory bowel disease, particularly Crohn's disease, are particularly susceptibile to perineal wound related complications [7]. Diabetes mellitus, tobacco use, malnutrition, and obesity are also well-recognized risk factors for inadequate perineal wound healing [8]. It is important to evaluate, address and control all patient risk factors (ideally prior to the initial operation) in order to maximize wound healing potential. In the setting of proctectomy for perineal Crohn's Disease, one should assess for the presence of any new or ongoing enteric fistulas that could prohibit local wound healing [9]. One should also rule out foreign body reaction and recurrent or *de novo* carcinoma in these chronic wounds [8].

In order to determine optimal treatment for unhealed perineal wounds and PPS, it is important to understand the anatomical predisposition created following pelvic exenteration and radical extirpations of the anorectum. The pelvic cavity is bound anteriorly by the urogenital organs (in the female the uterus, cervix and vagina, and in the male the prostate, seminal vesicles, and bladder [10]), posterolaterally by the coccyx, sacrum, and the two ischia, and superiorly by the pelvic peritoneum [5]. These well defined landmarks are generally immobile, except for downward migration of pelvic peritoneum. The postoperative vacancy leads to an intrinsic susceptibility for postoperative fluid collections. Bacterial contamination can result in secondary infection of this fluid, abscesses, inflammation, and fibrosis. These processes actively hinder further healing and can progress to perineal sepsis.

Several of the most effective treatment strategies have addressed the anatomical defect left following proctectomy, and have utilized tissue autografts or implants to further close the pelvic space. Historically it was observed that closure of the peritoneum resulted in higher incidence of PPS, likely due to the fact that closure inhibited bowel passively filling into the defect [1]. However the filling of the defect with bowel can prove to be problematic due to an unacceptably high incidence of adhesions and resultant bowel obstructions [11]. This chapter will review the alternative methods utilized to promote healing and closure of the perineal sinus.

PICO/clinical question	
Patient population	Patients with unhealed perineal wounds/PPS following proctectomy
Intervention	Surgical advancement flap
Comparator	Non-operative strategy/local wound care
Outcome	Primary perineal wound healing

Literature Search Strategy

All studies evaluating the management of perineal wounds following proctectomy were considered for inclusion. Inclusion was not restricted to study design, and all types of studies (retrospective vs. prospective, randomized vs. non-randomized, observational, etc.) were eligible for consideration. Studies were identified via search

of the Pubmed database (1991–2015) with the following MeSH terms: "postoperative complications", "perineum", and "wound healing". The results were then evaluated for relevancy to the topic, and citation lists of relevant papers were reviewed for further references. All papers were evaluated for the quality of their evidence and recommendations via the GRADE approach (Grades of Recommendation, Assessment, Development, and Evaluation). Papers were classified in quality as high, moderate, low, or very low based on multiple factors including methodology, consistency, precision of results, and directness of the evidence given [12, 13].

Non-operative Strategies

Conservative approaches for the management of the unhealed perineal wound include local wound care, topical medications and antibiotics, chemical debridement agents, fibrin glue, and negative pressure wound therapy [5]. Perineal wounds allowed to heal by secondary intention, which was the historical standard prior to the adoption of primary closure, can often result in a prolonged healing course [14]. Important factors to consider for optimizing wound healing include nutritional status, blood supply, and immune function. Ongoing infection within the wound will impair the healing process, as will devitalized tissue such as necrotic material or fibrinous exudate. The removal of such devitalized tissues via surgical debridement and control of any localized sepsis has been shown to accelerate healing.

Debridement

Debridement refers to the surgical removal of devitalized tissue, with the goal to promote the growth of the underlying healthy tissue. Various forms of debridement include sharp debridement, biosurgical debridement, chemical debridement, mechanical debridement, enzymatic debridement, and autolytic debridement [14]. Sharp debridement, typically using either a scalpel or scissors, can be performed either in the operating room or at the bedside, depending on the extent of the wound debridement and patient pain control. The wet to dry dressing, frequently applied within the realm of postsurgical care, utilizes both mechanical and autolytic debridement. Comparisons of modern dressings (alginates, hydrocolloids, polyurethane foam, silicone foam) to traditional gauze dressings seem to suggest a modest improvement in wound healing with modern dressings, though these studies have been criticized for small sample sizes and methodological flaws [14].

Local Antibiotic Agents

As ongoing perineal sepsis is a risk factor for PPS and a major cause of delayed wound healing, many agents have been developed to target local pathogenic

bacterial populations with the goal of preventing deep space infection and promoting healing. There are multiple delivery agents for local antibiotics, including sponges, fleeces, injections, and beads. Some agents appear to confer some benefit due to their space filling potential, with decreased seroma incidence and improved hemostasis [15]. A prospective trial found that gentamicin absorbable fleeces used following APR reduced postoperative wound infection to 6 % compared to 21 % of controls, but this did not translate into a statistically significant improvement in rates of wound healing [16]. A large multicenter randomized control trial comparing gentamicin-collagen fleeces following APR to standard care failed to demonstrate any reduction in perineal wound complications [17]. Due to the lack of consistent evidence demonstrating benefit, we do not recommend the routine use of local antibiotic agents. This advice is consistent with a large systemic review on the use of local gentamicin which did not support its use following APR [15].

Negative Pressure Wound Therapy

Vacuum assisted closure (VAC) is typically performed with foam wound dressings (either packed or at the skin surface) under negative pressure, and has become an increasingly common tool used for difficult surgical wounds to expedite the secondary intention healing process [18]. Its proposed mechanism decreases bacterial colonization within the wound, as well as tissue edema and wound tension, while increasing blood flow to the wound area [19]. Further, the device may confer benefit by creating a mechanical stimulus at the wound site, stimulating neo-angiogenesis, and enhancing granulation tissue production [20]. The tight seal associated with the VAC equipment additionally prevents exogenous contamination between dressings. Some frequent issues with these devices include their high costs, bulky size (which prevents patient mobility), and increased expertise required for dressing changes and device management [20]. It also should be avoided in patients susceptible to fistula formation [21]. Maintaining the necessary tight seal of the appliance may also be difficult due to the contours of the perineal space [22]. Recent improvements in technology including smaller, battery-operated vacuum canisters that have allowed increased patient mobility and more frequent use in the outpatient setting [22].

While there is considerable literature on negative pressure therapy, there is little data on the use in persistent perineal wounds other than a few small case series [19, 22]. Fujino et al. reported four cases, two to prevent and two to treat perineal wounds following proctectomy. All of these cases were successful without noted complication [19]. Yousaf et al. reported a single case of a large PPS (extending up to S2 via sinogram) following proctocolecotmy for IBD, which healed successfully with VAC therapy after 15 days [22]. This therapy has proven to be a safe and effective modality for wound healing and has shown promise in both the prevention and closure of complex perineal wounds [18].

Endoscopic Approaches: Sinusoscopy

The use of an endoscope to visualize and washout the perineal sinus cavity is a novel technique described by Al-Sheikh et al. [21]. They describe successful closure of three perineal sinus cavities, between 55 and 655 days old, with a technique that involves introduction of a pediatric gastroscope into the perineal sinus cavity. The gastroscope is used to irrigate the cavity with a hydrogen peroxide and saline mixture under direction visualization followed by endoscopic breakdown of loculations and curettage. This has the added benefit of allowing for monitoring for cancer recurrence with biopsies. This procedure is not recommended unless the perineal sinus is well developed, and may have the risk of causing sepsis or intraperitoneal air. There is little evidence on the safety of this technique and no additional studies to validate its efficacy.

Hyperbaric Oxygen Therapy

The use of hyperbaric oxygen therapy has demonstrated efficacy in improving healing in difficult, chronic wounds such as diabetic foot ulcers [6]. A small case series featuring IBD patients with persistent "extreme" PPS following proctectomy showed complete healing in all four patients with preoperative hyperbaric oxygen (25–30 sessions, 2.2–2.4 atm) combined with rectus abdominus muscle (RAM) flap, despite having previously failed multiple surgical interventions [6]. While this paper showed promising results with rapid wound healing of severe and chronic sinuses, further large and prospective studies are required to investigate any potential role of hyperbaric oxygen in the setting of perineal wounds.

Operative Strategies

The goals of reconstruction of the perineum following APR, as suggested by Sinna et al., include: avoid tumor recurrence, fill the dead space, and obtain skin healing [1]. The decision to reconstructa perineal wound, either immediately following APR or after development of PPS, is complex and multifactorial. The available evidence for the most common approaches will be outlined below. Prior to any additional operative intervention it is critical to evaluate patient anatomy, patient surgical risk factors, and patient care goals.

Omental Pedicle Grafts

The significant anatomical vacancy left following proctectomy leaves a space that can fill with fluid and become infected. One strategy is the use of omental pedicle grafts to fill the defect. Technically this can be accomplished via creation of a vascular pedicle

(typically based off the right or left gastro-epiploicvessels), with pelvic delivery via either a retrocolic or paracolic approach [20]. This graft can typically be performed with a laparoscopic approach, and is not as time-intensive or invasive as other autologous tissue grafts. A systemic review of omental pedicle flaps evaluated 14 studies including 891 patients. Primary perineal wound healing was 67% with an average time of 24 days for patients receivingo mental pedicle flaps compared to 50% with an average time of 79 days for patients without omental pedicle flap. Importantly, operating time was only minimally increased and there were few reported complications to the procedure [20]. One disadvantage to this technique in the setting of an unhealed perineal wound is the necessity of an additional major abdominal operation [23]. It is for this reason that the majority of such omental pedicle grafts are performed as immediate reconstructions during the abdominal portion of APR or proctocolectomy.

Wide Excision and Split Thickness Skin Grafts

The use of wide excision of the sinus followed by split thickness skin grafting of the perineum is an operative intervention that has the advantage of less donor site morbidity and ease of procurement of the graft compared to a muscle flap or omental flap. McLeod et al. reported healing in five of nine patients with this technique in a small case series [24]. Due to a difficult wound environment in the perineum, with high levels of sheering forces, the split thickness skin graft is now rarely utilized in perineal wounds when other grafts are available [8].

Gracilis Muscle Flap

The gracilis muscle flap is performed with a longitudinal incision in the medial thigh to harvest a gracilis muscle vascular pedicle (from the medial circumflex femoral artery), and subsequently transposing the pedicle to the perineal defect [3]. The loss of gracilis muscle, either unilaterally or bilaterally, does not cause significant functional limitations. This advancement flap is most successful when the sinus to be filled is relatively narrow, and is less ideal when there is an extensive pelvic space for which it may be less than sufficient [3]. The gracilis flap has a high partial skin necrosis rate which may compromise the flap and cause further morbidity [25].

Rectus Abdominus Myocutaneous Flap

The rectus abdominus muscle (RAM) flap can be harvested in various configurations with a pedicle derived from the superior or inferior epigastric arteries [26]. This can be performed with multiple variations at the donor site including a vertical

harvest (VRAM), transverse approach (TRAM), and oblique orientation (Taylor's Flap) [27]. Noted advantages to this flap include its availability within the operative field, ability to be harvested extraperitoneally, and its reliability. It can provide substantial bulk when a large pelvic defect needs to be closed. However as laparoscopic approaches become more common for the abdominal portion of the operation, the RAM may create unwanted abdominal sequelae such as increased postoperative pain and pulmonary complications [27]. Additionally a major potential drawback with the use of the rectus abdominus muscle in the setting of colorectal surgery is the loss of potential sites for ostomy creation [3]. Other potential donor site morbidity include the possibility of ventral hernias at the donor site due to weakening of the abdominal wall, which may be ameliorated with propylene mesh placement at the procurement site [26]. Other variations intended to decrease the donor site morbidity include the muscle sparing VRAM (ms-VRAM), the deep inferior epigastric perforator flap, as well as fascial-sparing techniques [27].

Intervention	References	Study design	GRADE of evidence	Summary of recommendations
Debridement and curettage	Lewis et al. (2001) [14]	Review and metanalysis	Moderate	Some modern dressings (i.e., hydrocolloid, alginate, and foam dressings) may improve secondary intention wound healing compared to traditional gauze, however many trails suffered from methodological flaws and may be prone to bias.
Local antibiotic agents	Collin et al. (2013) [17]	Multicenter RCT (7 hospitals, n = 102)	High	No significant differences in perineal wound healing were noted between those who received local gentamicin-collagen and those who did not.
Negative pressure (VAC) wound therapy	Fujino et al. (2015) [19]	Case series (n = 4)	Very low	VAC therapy appears to be a useful adjunct to speed perineal wound healing by secondary intention.
Endoscopic approaches	Al-sheikh et al. (2015) [21]	Case series (n = 3)	Very low	Patients tolerate the procedure safely without serious complication, and exhibited perineal wound healing. Further evidence is needed with larger trials prior to further recommendation.
Hyperbaric oxygen	Chan et al. (2014) [6]	Case series (n = 4)	Very low	Hyperbaric oxygen therapy, followed by PPS excision and RAM flap, led to complete wound healing in all patients in study. Appears to be a safe treatment modality for extreme and persistent perineal wounds

Intervention	References	Study design	GRADE of evidence	Summary of recommendations
Omental pedicle grafts	Killeen et al. (2013) [20]	Review and metanalysis (14 studies)	Moderate	Omental mobilization, transfer, and buttressing of primary perineal repair following protectomy reduces perineal wound morbidity with minimal additional operating time or flap-associated morbidity. Studies
Gracilis muscle flap	Menon et al. (2005) [10]	Case series (n = 17)	Low	A gracilis transposition is relatively simple operation with minimal morbidity useful for superficial sinuses not requiring much bulk.
Rectus Abdominus Muscle (RAM) flap	Chessin et al. (2005) [28]	Prospective cohort	Moderate	RAM flaps, when compared to primary closure alone, had a significantly lower rate of perineal wound complications, relative to the control group. Donor site morbidity should be taken into account when using the RAM flap.
Pudendal flap	Bodinet al. (2015) [25]	Case series (n = 6)	Very low	Advantages to this flap include less donor site morbidity, rich blood supply, immediate proximity to wound, and complete supra-fascial procurement.
Gluteus maximus flap	Haapamaki et al. (2011) [29]	Prospective cohort (n = 19)	Moderate	There are significant functional limitations following gluteus maximus flap. Functional deficits should be discussed with the patient and be taken into account prior to use.
Biologic mesh implants	Foster et al. (2012) [30]	Review and metanalysis	Moderate	There was no significant difference in the rates of perineal wound complications of perineal hernia formation when comparing biological mesh repair to flap repair.

Pudendal Flaps

Flaps derived from branches of the internal pudendal artery have been reported with success in the literature, under various names such as pudendal flaps, lotus flaps, gluteal fold flaps, and Singapore flaps [27]. These reconstructive approaches have been used frequently in the gynecologic surgery realm for pelvic reconstruction following pelvic exenteration [25].

One example is the supra-fascial lotus petal flap, named for the lotus petal shape of the resected donor sites. Advantages include effective coverage and healing without muscle harvesting or decrease in function, the option for unilateral or bilateral flaps, and improved cosmesis (as the flaps are procured from within the gluteal fold). When APR is performed in the prone position, no repositioning is required. Further, the flaps benefit from a rich blood supply derived from terminal branches of the internal pudendal arteries. The flap remains innervated from pudendal nerves and can be released safely without the underlying fascia. A small case series of six patients with chronic perineal wounds (four after APR) demonstrated no wound complications and a mean wound healing time of 35 days [25].

Gluteus Maximus Flap

The gluteus maximus flap is a local flap which provides ample tissue for filling the desired defect, and can be performed in either a bilateral or unilateral fashion [31]. This strategy provides a bulky and reliable flap immediate adjacent to the wound site, and avoids the abdomen entirely. A case series by Baird et al. demonstrated 50 % (8/16 patients) uncomplicated healing rates with this technique [32]. Unfortunately, the loss of gluteus maximus function cannot be understated. As a major hip extensor, the gluteus maximus plays an important role in posture, gait, and balance [1]. One study investigating performance status in patients who had undergone proctectomy with gluteal flap coverage found significantly decreased function with gait and balance, and high levels of pain while seated [29].

Similar to the RAM flap, various alterations of this flap have been devised to decrease the donor morbidity (and in this case functional impairment) of the donor site. Perforator flaps designed to spare the underlying gluteus maximus muscle such as the VY-perforator flap, the inferior gluteal artery perforator flap, and the superior gluteal artery perforator flap [27]. These adapted flaps are more technically challenging and are smaller tissue flaps than a full gluteus flap.

Meshes and Biological Implants

To avoid the morbidity of the previously mentioned myocutaneous flaps (or in centers with limited access to reconstructive plastic surgery expertise) while still expediting natural closure of the sinus cavity, one can turn to various meshes and biological scaffolds. Human acellular dermal matrix has been proposed for reconstruction as it is more biologically compatible than synthetic meshes, and was shown in a small case series to have excellent primary healing rates, with 11 of 12 patients achieving complete primary perineal wound healing at 2 weeks post surgery. The most common complications noted after this procedure were seroma formation and chronic perineal pain, occurring in 8 % and 33 % of the patients in this series respectively [33].

Harries et al. (2014) examined the immediate use of a similar porcine collagen implant (Permacol) following extralevator APR and also noted high rates of primary wound healing (73.9 % at 4 weeks, 90.9 % at 6 months) [15]. There is little data to date on the use of these scaffolds for chronic wounds. A review comparing evidence for immediate reconstruction with myocutaneous flaps versus prophylactic biological mesh showed no significant differences in perineal healing rates, however these studies were criticized for methodological flaws and small sample sizes [30]. A large multicenter randomized controlled trial comparing biologic mesh closure to primary perineal closure is currently underway to further investigate mesh perineal closure following extralevator APR [34].

While some synthetic meshes have been suggested to promote adhesion formation with higher incidence of bowel obstruction, Kusunoki et al. demonstrated that the use of hyaluronic acid impregnated (Seprafilm®) absorbable mesh to reconstruct the perineum may prevent adhesions [11].

Conclusions

The persistent perineal wound after proctectomy is a complex problem that results in morbidity for patients following surgery. The treatment strategies available to these patients range greatly in their complexity and cost. There are many patient and disease specific factors that must be considered when determining which approach to take. It is important to assess the impact of the unhealed wound on the patient's quality of life to determine the most appropriate treatment. We recommend evaluating the patient's wound healing capacity and optimizing all augmentable factors. Nutrition should be optimized, serum glucose should be under control and all efforts to stop smoking should be made. Infection and sepsis should be treated appropriately and fluid collections drained appropriately. The patient's anatomy should be clearly delineated by physical examination, intraoperative evaluation, and with relevant imaging modalities.

For small wounds with a minimal impact on the patient we recommend debridement of any devitalized tissue as needed. Depending on the size of the remaining defect, local wound care and healing by secondary intention may be all that is necessary. Negative pressure wound therapy is a useful adjunct to speed secondary intention healing. Additional novel and emerging therapies, including hyperbaric oxygen, and sinusoscopy lack sufficient evidence for recommendation.

For large sinuses, excision with an autograft may be necessary to close the space. Multiple factors must be taken into account when choosing a flap for your patient, and collaboration with a plastic surgeon may be beneficial [35]. The required volume of tissue necessary to fill the defect, the presence of absence of a rectus abdominus stoma, a patient's functional and performance status, patient cosmetic concerns, and presence of vascular disease should all be considered when selecting the ideal flap.

Prophylactic measures can be taken at the time of initial proctectomy to minimize the risk of perineal wound complication. Extralevator APR, or any rectal

excisions that leave large perineal cavities, remain at particularly high risk for potential wound complication. Strong consideration should therefore be taken to immediate reconstruction with either a flap or mesh approach.

Finally, evaluation of the current evidence makes it clear there are many promising and innovative therapies in this field with only minimal evidence to support. There is a need for high quality, large randomized trials to improve the strength of current recommendations. Until that time, controversies in treatment strategy will remain and management based on anectodal evidence.

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Erratum to: Difficult Decisions in Colorectal Surgery

Neil Hyman and Konstantin Umanskiy

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In the original version of chapters 24, 29, 37 the co-author names and their affiliations were missing. The names of the author should be read:

Chapter 24: Management of the Abnormal Pap Smear in HIV Positive Patients

Brad Champagne and Andrew J. Russ

Chapter 29: Who Needs Elective Surgery for Recurrent Diverticulitis?

Janice Rafferty and Bobby Lynn Johnson III

Chapter 37: Which Patients with Fecal Incontinence Require Physiologic Workup?

Tracy Hull and Nouf Y. Akeel

The above mentioned corrections are updated in Table of Contents. Also, the affiliations of the co-authors are updated in the respective chapter opening pages.

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Index

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